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University of Southampton

FACULTY OF ENVIRONMENTAL AND LIFE SCIENCES

SCHOOL OF HEALTH SCIENCES

**The Effectiveness of Nerve Conduction and Transcutaneous Oxygen Devices Against
Existing Methods in the Assessment of Neuroischaemia in the Feet of Adult
Participants With Type 2 Diabetes in the Community**

by

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Thesis for the degree of DOCTOR OF PHILOSOPHY

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Abstract

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Doctor of Philosophy

The Effectiveness of Nerve Conduction and Transcutaneous Oxygen Devices Against Existing Methods in the Assessment of Neuroischaemia in the Feet of Adult Participants With Type 2 Diabetes in the Community.

by

Simbarashe Richard TANYANYIWA

NICE NG19 (2015) guides the early identification of neuroischaemia to help prevent diabetes foot complications, but these largely subjective assessments are not standardised. The aim of this doctoral thesis was to explore the concept that new technological devices (DPNCheck® and Medicap) could give a picture that is clearer and closer to that truth of underlying neuroischaemia, than existing NICE NG19 methods (10g monofilament and TBI).

To achieve this, a series of cross-sectional observational investigations were undertaken to establish the reliability, validity and clinical effectiveness of the DPNCheck® against the 10g monofilament in the assessment of sensory neuropathy, and the Medicap against the TBI in the assessment of ischaemia, in adults with type 2 diabetes. Experimental Study 1 investigated DPNCheck® reliability in 21 healthy participants, and found $ICC(2,1)_{velocity} = 0.97$ (95% CI = 0.91- 0.99), and $ICC(2,1)_{amplitude}$ between 0.76 – 0.96 (95% CI = 0.63 – 0.99). Medicap validity was investigated against a TCM400 amongst healthy (Experimental Study 2) and low risk diabetes (Experimental Study 3) participants. The Medicap demonstrated criterion validity, but overestimated $TcPO_2$ by a mean of 24.8 (± 18.4) mmHg. Experimental Study 4 found TBI intrarater reliability $ICC(2,2)$ ranging from 0.79 – 0.99 (SEM = 0.03; 95% CI; 0.68 – 0.99), and interrater reliability with $ICC(2,2)$ between 0.81 – 0.98 (SEM 0.03; 95% CI; 0.65 – 0.99) ; and overall $ICC(2,3) = 0.96$ (95% CI; 0.93 – 0.98). Experimental study 5 investigated the intrarater reliability of the TBI, DPNCheck®, Medicap and 10g monofilament in people with diabetes, and found $ICC(3,1)_{TBI} = 0.97$ (95% CI = 0.84-0.99), and for $ICC(3,1)_{DPNCheck}$ velocity and amplitude = 0.96 ((95% CI = 0.87-0.99); $ICC(3,1)_{Medicap} = 0.66$ (95% CI = 0.24 – 0.87), and $ICC(3,1)_{10g\ monofilament} = 0.38$ (95% CI = -0.08 – 0.73). In Experimental Study 6, from 92 participants with diabetes, the DPNCheck® suspected 45 participants of having neuropathy, against 21 by the 10g monofilament which had a false negative rate of 35.2%, a sensitivity of 44.4% (95% CI = 30.9 – 58.8%), specificity of 97.9% (95% CI = 88.9 -99.6%) and $\kappa = 0.43$ (95% CI: 0.26 - 0.54; $p < 0.001$). In Experimental Study 7, both the TBI and Medicap each suspected 10 participants of ischaemia, but did not agree on any cases. Against the TBI, Medicap sensitivity was 0% (95% CI = 0 – 30.9%); specificity 86.6% (95% CI = 77.3- 93.1%), and $\kappa = -0.12$ ($p = 0.24$).

The Medicap demonstrated criterion validity and fair reliability, whilst the DPNCheck® demonstrated and excellent reliability. The DPNCheck® was more effective at assessing sensory neuropathy than the 10g monofilament, whilst the Medicap and the TBI were poorly comparable in the assessment of ischaemia. Findings from these thesis investigations point to a new clinical paradigm for earlier detection of peripheral neuropathy in which the quality and quantity components of neuroischaemia assessment could be combined. The implications for this would be in the detection of neuropathy at the stage where interventions have the potential to change the course of tissue damage and thus prevent diabetes related foot ulceration and amputation.

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List of Accompanying Materials

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Research Thesis: Declaration of Authorship

Print name: Simbarashe Richard TANYANYIWA

Title of thesis: **The Effectiveness of Nerve Conduction and Transcutaneous Oxygen Devices Against Existing Methods in The assessment of Neuroischaemia in the Feet of Adult Participants With Type 2 Diabetes in the Community.**

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission

Signature: Date: 7th March 2021

{Important note:

The completed signed and dated copy of this form should be included in your print thesis.

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Definitions and Abbreviations

ABI	Ankle Brachial Index
AGE	Advanced Glycation End products
AUC	Area Under Curve
BMI	Body Mass Index
CCM	Corneal Confocal Microscopy
CI	Confidence Interval
CNCS	Centred Nerve Conduction Score
CNS	Central Nervous System
CT	Computerised Tomography
DCCT	Diabetes Control and Complications Trial
DPN	Diabetes Peripheral Neuropathy
DPNCheck®	the NC-stat® DPNCheck® by Neurometrix ®, Woburn, MA
DRG	Dorsal Root Ganglion
DSA	Digital Subtraction Angiography
ERGO	Ethics and Research Governance Online
GOAL A1c	Glycaemic Optimization with Algorithms and Labs at Point of Care
HbA1c	Glycated Haemoglobin
IENFD	Intraepidermal Nerve Fibre Density
IQR	Inter Quartile Range
IRAS	Integrated Research Application System
Medicap	the Medicap Précise 8001, provided by Moor Instruments, Axminster
MNSI	Michigan Neuropathy Assessment Instrument
NCS	Nerve Conduction Study

NDS.....	Neuropathy Disability Score
NICE.....	National Institute of Health and Care Excellence
NPV.....	Negative Predictive Value
NSF	National Service Framework
NSS	Neuropathy Symptom Score
PKC	Protein Kinase C
PPV	Positive Predictive Value
PVD.....	Peripheral Vascular Disease
QOF	Quality Outcomes Framework
QST	Quantitative Sensory Testing
REC	Research Ethics Committee
ROS.....	Reactive Oxygen Species
RR	Risk Ratio
SPSS.....	Statistical Package for the Social Sciences
TBI	Toe Brachial Index
TcPO ₂	Transcutaneous Oxygen Partial Pressure
UK.....	United Kingdom
VIF	Variance Inflation Factor
VPT	Vibration Perception Threshold

Chapter 1 INTRODUCTION

1.1 Background

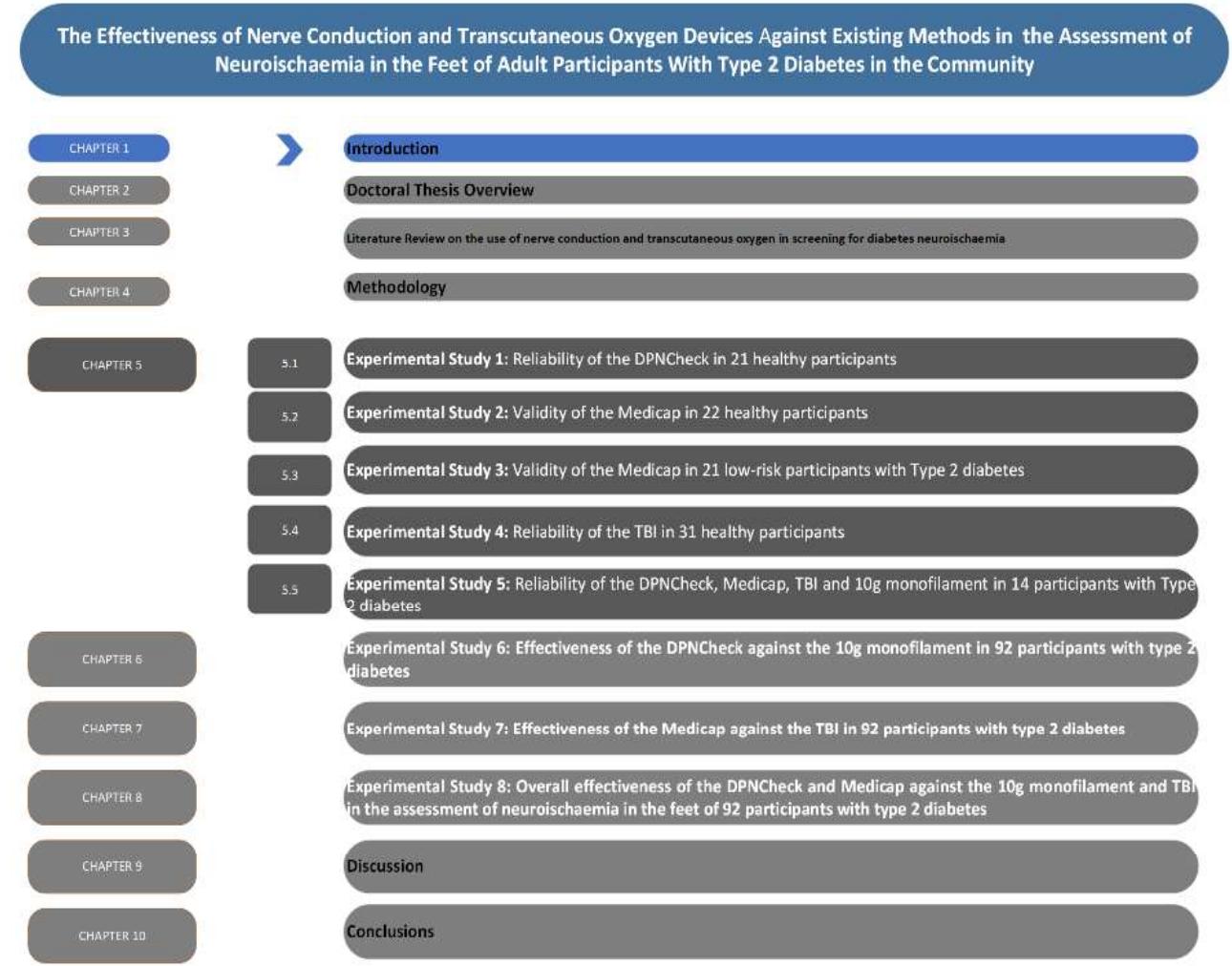
Diabetes is a chronic condition which impacts on the health and quality of life resulting in significant mortality for patients (Jupiter et al., 2015). Type 2 represents the most prevalent form of diabetes, affecting about 90% of the UK's total diabetes population (Diabetes UK, 2019; Jeffcoate, 2019). About 3.2 million adults (6.2%) of the UK population have been diagnosed with Type 2 diabetes, and this is projected to exceed 9% by 2030 (Hex et al., 2012). Overall, direct diabetes costs account for 10% (£9.8 billion) of total healthcare expenditure, and these are expected to eclipse 17% (£16.9 billion) within 25 years at current trends, presenting a significant growing challenge for public health services (Hex et al., 2012). It is estimated that up to 25% of the people diagnosed with diabetes go on to develop a foot ulcer (Armstrong, Boulton and Bus, 2017), and treating these extracts an additional £650 million from the healthcare budget (Ahmad et al., 2014; Kerr, 2017). In addition, diabetes disproportionately affects those from ethnic minorities (Davis, 2008) and those in areas of social deprivation, with consequent effects on ulcerations, amputations and deaths (Tillin et al., 2013). These populations also face delayed access to interventions (Mathur et al., 2020), which overall adds to the variation in diabetes care and outcomes. In an effort to improve standards and reduce disparities in care, the National Institute of Health and Clinical Excellence (NICE) as it was known then, was set up in 1999. Following this, the National Service Framework (NSF) for diabetes (2002) was set up to establish standards to detect and manage long term complications, and these were incorporated into the Quality Outcomes Framework (QOF) in 2004. Altogether these aimed to establish standards of care including the assessment and early detection of complications (NSF) and act as an incentive to reward those in primary care who met those standards (QOF), which would then meet the objectives of NICE in improving standards and reducing healthcare variation.

In its modern form, NICE (National Institute of Health and Care Excellence since 2013) issues

national guidance on managing various diseases, and since 2015, has for diabetes set the methods to screen for neuropathy and ischaemia as risk factors for ulceration under the National Institute of Health and Care Excellence National Guidance 19 (NICE NG19 (2015)). Yet the National Diabetes Footcare Audit (2019) still identifies disparities in prevalence and management of diabetes related complications between regions (Jeffcoate, 2019). This could at least in part be down to the suggested assessment approaches from NICE NG19 (2015), such as the 10g monofilament and doppler ultrasound pulses, whose subjective nature and non-standardised protocols leaves them open to regional interpretation, with consequent variations in assessment standards (Alavi et al., 2014a, 2014b; Amin and Doupis, 2016; Tehan, Bray and Chuter, 2016). Despite aiming to detect early neuropathy and ischaemia, due to the insidious nature of diabetes, by the time the current recommended clinical methods are able to detect changes it is often too late to implement measures capable of preventing further complications (Pecoraro et al., 1991; Alavi et al., 2014a; Samuel and Appel, 2016; Won and Park, 2016). Consequently, it has been suggested that the current clinical guidance is limited in reliably assessment neuroischaemia, and with different approaches under the same guidance it is difficult to standardise clinical practice. Improved quantitative technologies such as nerve conduction (Burke, Skuse and Lethlean, 1974) and transcutaneous oxygen (Dean T Williams, Price and Harding, 2006) have been proposed over the past decades as possible ways of assessment early neuroischaemic changes in people with diabetes following a uniform approach. However, these have proved difficult to adopt as mainstream clinical assessment methods and often seen as yet more additions to a plethora of tools, and thus existing subjective methods with their inherent shortcomings continue to be used (Shapiro and Nouvong, 2011; Malik, 2014; Vas and Edmonds, 2016; Won and Park, 2016). The late identification of neuroischaemia could potentially perpetuate the continued high prevalence of diabetic foot ulcerations, amputations and related deaths, which are expected to increase by 2030, exerting further demands on a constrained health service (Rowley et al., 2017). The situation could be improved if early identification of neuroischaemia could be introduced to enable timely intervention including lifestyle changes that would prevent or delay the onset of ulceration. Within this introductory chapter an account is given on diabetes neuroischaemic effects on

the foot, the respective features of neuropathy and ischaemia, the different neuroischaemic assessment methods and the importance of their early detection. There are highlights on guidelines aimed at the early detection of diabetes neuroischaemic changes (NICE NG19 (2015)), and a discussion on the extent to which the different assessment methods meet these. This chapter concludes by outlining the problem statement on the need to improve the assessment of diabetes neuroischaemia, and suggests the use of nerve conduction and transcutaneous oxygen as part of the diabetes foot assessments. An outline of where this chapter sits within the context of the thesis as a whole, is shown in Figure 1.1.

Figure 1.1: Showing Chapter 1 within the context of the thesis.



1.2 Diabetes Neuroischaemic Effects on The Foot

Diabetes exerts several intrinsic and extrinsic effects on the foot, including changes to the skin, foot posture as well as neuroischaemic manifestations that place the foot at greater risk of ulceration (Alavi *et al.*, 2014a). This section will focus on the neuroischaemic effects of diabetes on the foot, and will discuss the various metabolic processes thought to precipitate neuroischaemic damage, shown in Figure 1.2.1.

Figure 1.2.1: Showing diabetes pathways leading to neuroischaemia

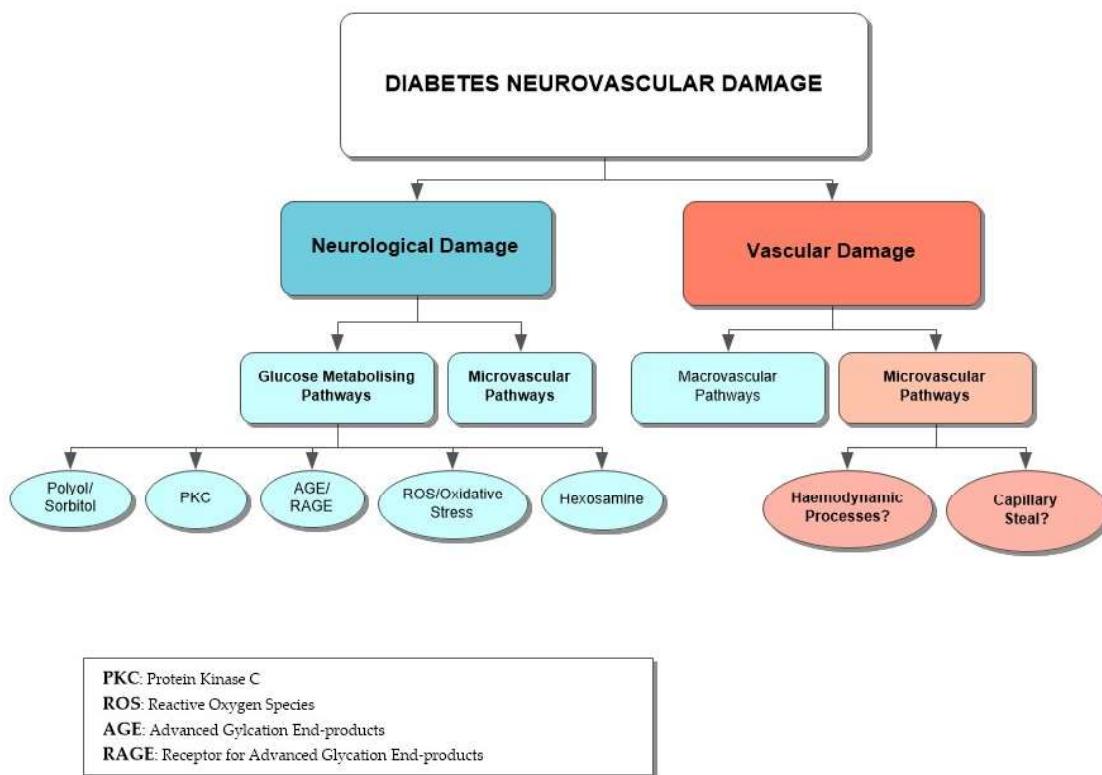
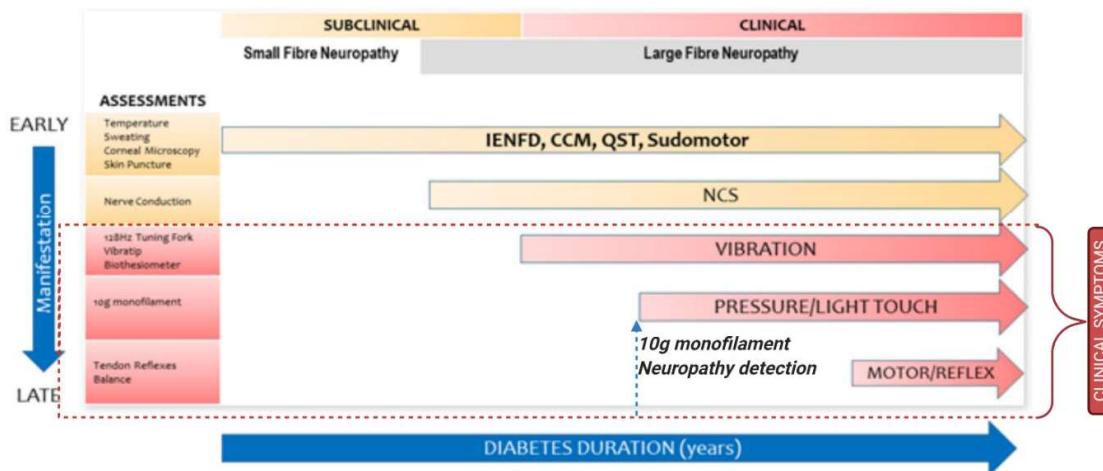


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1.3 Diabetes Neuropathy

Diabetes neuropathy can be defined as the nerve dysfunction induced by chronic hyperglycaemia to the different components of the nervous system, and appears in multiple clinical and subclinical forms affecting every part of the body. A clinical manifestation is one that is readily detectable and quantifiable by common clinical assessment methods, in contrast to a subclinical symptom which often cannot be detected or quantified. In the foot, a key manifestation of diabetic complications is polyneuropathy, which is a combination of one or more of sensory, motor and autonomic dysfunction, and is one of the strongest predictors of foot ulceration (Monteiro-Soares *et al.*, 2012). Initially, it often presents with distal peripheral manifestations leading to its further classification as diabetic peripheral neuropathy (DPN). As shown in Figure 1.3.1, diabetes progression has different neuropathic manifestations, and each stage requires different methods and tools for neuropathy diagnosis (Petropoulos *et al.*, 2018).

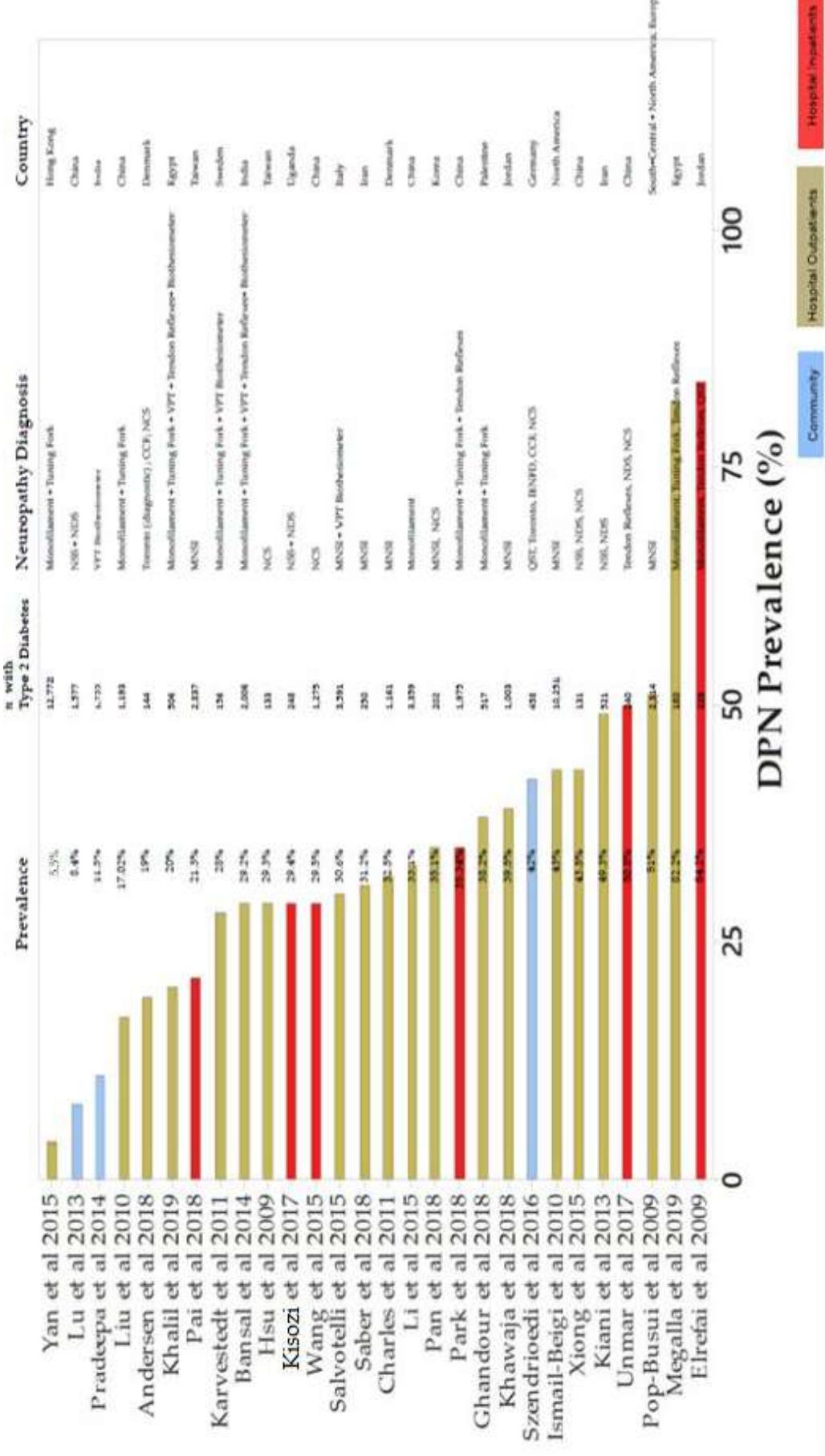
Figure 1.3.1: Showing The Diabetes Neuropathy Detection Methods Based on Diabetes Staging (adapted from Jin and Park, 2015)



The main challenge in diagnosing DPN lies in objectively detecting the different forms of nerve dysfunction, from what is generally a subjective symptom with several diverse manifestations. Despite this, it is generally agreed that morphological nerve changes, which can be detected by nerve conduction evaluation, occur before the manifestation of clinical

symptoms (Brown *et al.*, 2017). Historically, the diversity of symptoms and difficulties in diagnosing neuropathy have led to a wide plethora of tools, protocols and classifications, resulting in varied reports on its prevalence, as shown in Figure 1.3.2 (page 7). Prevalence of DPN amongst people with type 2 diabetes was estimated following a literature search of major databases (PubMed, Science Direct and SCOPUS) on studies published between 2009 – 2019, that measured DPN in people who had type 2 diabetes, and published their findings in English, for which full text was available. Figure 1.3.2 was derived from the acquired studies following the literature search. This shows there is wide reported prevalence estimates for DPN which range between 4.5% - 84.2%, and it is postulated that this disparity could be attributed to different target symptoms, tools, protocols, interpretation and participant health status, which form the basis for the DPN prevalence discussions in sections 1.3.1 – 1.3.3.

Figure 1.3.2: Showing Studies on DPN Prevalence Amongst Type 2 Diabetes Participants



CCF Corneal Confocal Microscopy IENFD Intraepidermal Nerve Fibre Density
 NCS Nerve Conduction Study NDS Neuropathy Disability Score;
 QST Quantitative Sensory Testing; Toronto Clinical Neuropathy Score

MNSI Michigan Neuropathy Scoring Instrument;
 NSS Neuropathy Symptom Score;
 VPT Vibration Perception Threshold

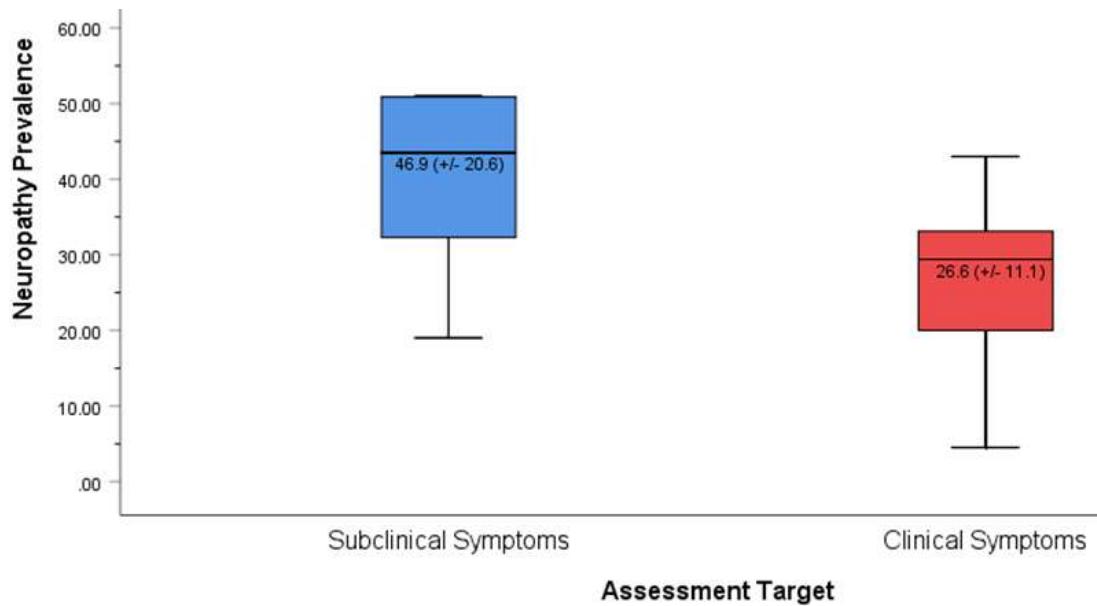
1.3.1. Prevalence based on clinical and subclinical symptoms.

Different tools and assessments could give different prevalence estimates depending on whether they target clinical or subclinical symptoms as part of their diagnostic criteria. As shown in Figure 1.3.1 (Chapter 1, page 5), the early stages of DPN commonly present with subclinical symptoms such as tingling or pain, mainly due to small nerve fibre dysfunction. Diagnosing DPN at this early stage relies heavily on the participant's medical history and their description of symptoms. As diabetes progresses, DPN transitions to involve the large sensory nerve fibres with clinical manifestations, in a sequence that progresses from vibration perception, pressure and light touch, proprioception and, in the later stages, the motor nerve fibres. Following Figure 1.3.1 (page 5) each stage of DPN offers different approaches to detecting nerve dysfunction, which may lead to different levels of prevalence depending on method of detection as shown in Figure 1.3.2 (page 7).

These different approaches can be broadly described as targeting either subclinical or clinical symptoms. The most common clinical methods rely on detecting reduced vibration through the 128Hz Rydel-Seiffer tuning fork or light touch with the 10g Semmes-Weinstein monofilament. As shown in Figure 1.3.1 (page 5), both vibration perception and light touch are limited to detecting neuropathy only in the later stages of diabetes, and are therefore unable to detect the subclinical nerve dysfunction that can precede the clinical symptoms by several years. In contrast to this, other tools and classifications attempt to incorporate in whole or in part, subclinical symptoms as part of their DPN diagnosis. These include nerve conduction, intraepidermal nerve fibre density (IENFD), sudomotor function, and the Michigan Neuropathy Scoring Instrument (MNSI), Toronto, Neuropathy Disability Score (NDS), and Neuropathy Symptom Score (NSS) scoring systems. These approaches attempt to quantify aspects of subclinical neuropathy, and in effect try to bring previously 'invisible' symptoms into the clinical realm. When studies on DPN prevalence, shown in Figure 1.3.2 (page 7), are analysed and pooled depending on whether diagnosis was based on purely clinical responses, or incorporated subclinical symptoms, the derived mean prevalence is shown in Figure 1.3.3 (page 9). This shows that studies that incorporate detection of subclinical symptoms tend to report a higher

DPN prevalence of 46.9% (Pop-Busui *et al.*, 2009; Kiani *et al.*, 2013; Xiong *et al.*, 2015; Szendroedi *et al.*, 2016), against 26.6% when compared to those that were limited to detecting clinical symptoms (Liu *et al.*, 2010; Li *et al.*, 2015; Ghandour *et al.*, 2018). This implies that a significant number of people with type 2 diabetes and early neuropathy would not be identified by methods that are unable to detect subclinical symptoms, such as those relying on the 10g monofilament. With time, diabetes neuropathy progresses from small to involve large nerve fibres, whereupon subclinical symptoms become manifest as sensory and motor neuropathies. The value of the early detection of subclinical symptoms therefore lies in presenting a therapeutic window during which, if glycaemic control is effected, progression to large fibre neuropathy can be prevented or at least delayed.

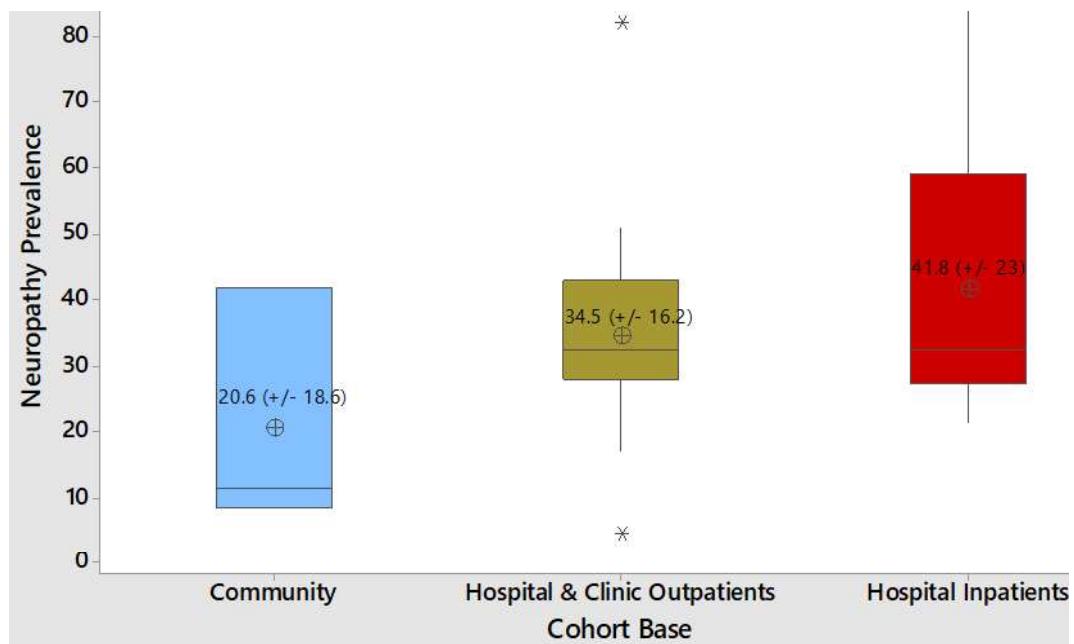
Figure 1.3.3: Neuropathy Prevalence Based on Clinical and Subclinical Symptoms



1.3.2 Prevalence based on target population

The disparity in DPN prevalence could also be partially attributed to different target populations as shown in Figure 1.3.4. These data show that from studies that involved community participants not seeking any treatment, the mean prevalence was 20.6%. They also show a mean prevalence of 34.5% was derived from studies in people attending primary care clinics and hospital outpatients, and the highest mean prevalence of 41.8% was from studies on hospitalised participants. This shows an overall tendency of increasing DPN prevalence with deteriorating health status, which in turn is linked to the duration of diabetes (Bansal *et al.*, 2014; Li *et al.*, 2015).

Figure 1.3.4: Neuropathy Prevalence Based on Population Profile



1.3.3 Prevalence based on assessment protocol and instruments

However, wide variations do exist from within homogenous populations, suggesting additional variation due to differences in assessment protocols. From the community based studies, DPN prevalence ranged from 8.4%-42%. Lu *et al.*, (2013) assessed 534 participants using the Neuropathy Symptom Score (NSS) and Neuropathy Deficit Score (NDS), and determined a prevalence of 8.4%. Both the NSS and NDS classification systems have subjective components (such as vibration or 10g monofilament assessment), which affect their validity and reliability when compared to an objective reference standard. This was demonstrated by Young *et al.*, (2008), who found the NDS had poor correlation against objective NCS (Spearman $\sigma = -0.29$, $p=0.003$). The semi-objective vibration perception threshold relies on subjective responses, and detected a prevalence of 11.5% from amongst 1,755 participants (Pradeepa *et al.*, 2014), but since vibration perception manifests later than other subclinical symptoms (such as nerve conduction and QST as in Figure 1.3.1 (page 5)) , this is likely an underestimate to the true DPN prevalence. Szendroedi *et al.*, (2016) found a prevalence of 42% based on the Toronto classification as defined by Bril and Perkins, (2002) from amongst 458 participants. However they used a battery of additional assessments, which varied their prevalence figures depending on which test combinations were used to form a diagnosis, with DPN prevalence ranging from 7% (confirmed DPN), through 23% (subclinical DPN), up to 42% (Toronto classification). This varied prevalence was also observed on hospital participants by Unmar, Zafar and Gao (2017), who relied on the Diabetes Neuropathy Symptoms and NCS to assess for neuropathy in 240 participants. They found a confirmed neuropathy prevalence of 33.8% (both NCS and neuropathy symptoms), suspected prevalence of 17.1% (either NCS or neuropathy symptoms but not both), and overall prevalence of 50.8% (either NCS and / or other signs and symptoms). These studies by Szendroedi *et al.*, (2016) and Unmar, Zafar and Gao (2017) highlight the varied prevalence within the same population depending on the assessment and diagnostic criteria, and the difficulty in comparing DPN prevalence across different studies, even from those that share similar population profiles.

The outpatients population formed the majority of studies derived for this review, with

prevalence ranging from 5.4% - 82%. Yan *et al.*, (2015) found the lowest prevalence of 5.5 % from amongst 12,772 participants across 6 hospitals, which was likely an underestimate since they relied on subjective responses to the 10g monofilament and 128Hz tuning fork for diagnosis. Liu *et al.*, (2010) found a prevalence of 17 % from amongst 1,193 participants across 12 hospitals, assessed with a 10g monofilament and 128Hz tuning fork, which was similar to 19% using the Toronto classification (Andersen *et al.*, 2018), and 20% using a biothesiometer (Khalil *et al.*, 2019).

These however stand in contrast to studies that assessed more parameters, by combining the 10g monofilament, 128Hz tuning fork, and biothesiometer for diagnosis, which found prevalence rates of 28% (Karvestedt *et al.*, 2011), 29% (Bansal *et al.*, 2014) and 38% (Ghandour *et al.*, 2018). Li *et al.*, (2015) found a prevalence of 33% using a 10g monofilament alone, whilst Ghandour *et al.*, (2018) determined neuropathy prevalence based on the 10g monofilament, 128Hz tuning fork, “losing slipper sign”, foot ulceration and previous amputation, and found DPN prevalence of 38.2%. However rather than being diagnostic; foot ulceration, deformity and amputation are consequences of, neuropathy. The above studies therefore likely underestimate given the subjective assessments (tuning fork and 10g monofilament), and differ in protocols with and thresholds, accounting for the variability in prevalence. No clear prevalence pattern emerges from these outpatient studies, and differences are likely due to the subjective diagnoses and non-standardised protocols across them. In addition, none report on the intra or inter-rater reliability of the investigators using these subjective methods, but Lanting *et al.*, (2020) demonstrated moderate but wide ranges in reliability for both the 128Hz tuning fork (Cohen’s κ = 0.54 – 0.68; 95%CI = 0.38 - 0.95, $p < 0.01$), and 10g monofilament (Cohen’s κ = 0.44 – 0.77; 95%CI = 0.09 - 0.99, $p < 0.01$).

Many of the outpatient studies relied on neuropathy scoring protocols such as the Michigan Neuropathy Scoring Instrument (MNSI), Neuropathy Deficit Score (NDS), Neuropathy Symptom Score (NSS), and the Toronto clinical neuropathy score. For the purposes of the following discussion, it is necessary to outline the Toronto and MNSI scoring systems. The Toronto system grades symptoms (numbness, pain, muscle

weakness, ataxia); sensory responses (pinprick, temperature, vibration, light touch, vibration, proprioception) and reflexes (knee, ankle) according to severity, to derive a maximum score of 19 points (Bril *et al.*, 2009). The Toronto then classifies overall severity according to the score, from no neuropathy (0–5), mild neuropathy (6–8), moderate neuropathy (9–11), and severe neuropathy (≥ 12). The MNSI has two constituent components: which depend on foot appearance (deformity, dry skin, callus, fissures) and evidence of neuropathy (ulceration, infection, loss of ankle reflex, loss of vibration perception). Any of the symptoms scores 1 point, and assessment is made bilaterally for a total of 16 points, and neuropathy diagnosis is usually made on the presence of 2 or more symptoms, set at MNSI ≥ 2 .

Using the Toronto classification, Andersen *et al.*, (2018) found a prevalence of 19% of confirmed neuropathy (confirmed by NCS with other signs and symptoms), which is similar to the 17.1% found by Szendroedi *et al.*, (2016) when they too relied on NCS alongside the Toronto classification on community participants. Charles *et al.*, (2011), based neuropathy on combined assessments in 1,161 participants using the 10g monofilament, 128 Hz tuning fork and MNSI, and found an overall prevalence of 32.5%, which is likely an underestimate given they used a higher neuropathy threshold (MNSI > 7 instead of MNSI > 2).

In a multinational study Pop-Busui *et al.*, (2009) based their neuropathy diagnosis amongst 2,314 participants of diverse ethnicities on the MNSI ≥ 2 , and found DPN prevalence of 51% in North America. Their findings are similar to those by Ismail-Beigi *et al.*, (2010), who based their neuropathy diagnosis on an MNSI > 2 , and examined 10,251 participants receiving intensive (n= 5095) and routine (n= 5106) glycaemic control intervention. At baseline, they found a prevalence of 43% (intensive control) and 42% (standard control), which increased to 45.4% (intensive control) and 47.9% (routine control) at the end of the trial.

Khawaja *et al.*, (2018), found a prevalence of 39.5% amongst 1,003 participants based on the MNSI ≥ 2 and physical history, which broadly mirrors the findings of Saber and Daoud, (2018) who assessed 250 participants, and found a prevalence of 31.2%.

The findings are also similar to Salvotelli *et al.*, (2015), who used the MNSI ≥ 2 and 10g monofilament on 3,591 participants and found a prevalence of 30.6%.

Using similar scoring instruments, the prevalence rates of 30.6% in Italy (Salvotelli *et al.*, 2015), 31.2% in Iran (Saber and Doud 2018), 32.5% in Denmark (Charles *et al.*, 2011), 35.1% in South Korea (Pan *et al.*, 2018), and 39.5% in Jordan (Khawaja *et al.*, 2008), all of which studied more homogeneous populations, stand in contrast to those of 43% in North America (Ismail-Beigi *et al.*, 2010) and 51% in North, Central and South America and Europe (Pop-Busui *et al.*, 2009) that studied heterogeneous populations.

The variation in the above studies suggests that ethnicity could play a role in determining DPN prevalence. Other studies have also reported ethnic differences in DPN prevalence, with speculation surrounding the role of skin microvasculature (Abbott *et al.*, 2010). Abbot *et al.*, (2010) relied on the NDS scores to diagnose DPN, and found a higher prevalence in both NDS and small nerve fibre dysfunction (20%; 43 % respectively) amongst Caucasian Europeans when compared to those of Indian ethnicity (15% NDS and 32% small nerve fibre dysfunction). Tahrani *et al.*, (2017) also found neuropathy prevalence based on 10g monofilament, more common in white Europeans (43.9%) when compared to participants of South Asian origin (23.8%), though this difference did not reach significance when adjusted for height.

The above studies however largely relied on subjective assessments, and in the absence of objective neuropathy assessments, they do not provide sufficient evidence on the effects of ethnicity on DPN prevalence. The MNSI, NSS, NDS and Toronto scores in themselves are made up of various subjective components of the neurological assessments (such as the 10g monofilament, 128Hz tuning fork, reflexes), that vary in application and protocol (Yang *et al.*, 2018). With the role of ethnicity unclear, this leaves the differences in protocols to largely account for the wide variation in prevalence reported using these instruments.

Objective measures include nerve conduction studies (NCS), intraepidermal nerve fibre density, confocal microscopy and sudomotor assessment methods. Hsu *et al.*, (2009) used NCS to diagnose sensory and motor dysfunction in 133 participants in Taiwan, and found an overall prevalence of 29.3%, which was made up of 9% with definite neuropathy (both motor and sensory conduction deficits), and 20.3% with suspected neuropathy (either motor or sensory deficit). Xiong *et al.*, (2015) used NCS in 131 participants, and found a

higher DPN prevalence of 43.5%.

In the German Diabetes Study Group, Szendroedi *et al.*, (2016) assessed 458 participants based on the Toronto neuropathy assessment criteria, in addition to electrophysiological tests, and found prevalence ranged from 7% (confirmed diabetes sensorimotor peripheral neuropathy), 20% (IENFD); 20% (CCM); 42% (Toronto), to 68% (sudomotor dysfunction); and overall prevalence depended on the criteria, definition, thresholds and the combinations of assessments used. From the outpatients population, Megalla *et al.*, (2019) reported the highest DPN prevalence of 82.2% based abnormal vibration perception, which is unsurprising given that all their participants had active foot ulcers, and were therefore of worse health status when compared to the other outpatient studies. They also reported a contrast in prevalence depending on assessment method, with prevalence ranging from 64.4% (10g monofilament), to 82.2% (biothesiometer), which affirmed earlier observations by Szendrioedi *et al.*, (2016) and Unmar *et al.*, (2017), in that prevalence of DPN depended on the assessment methods, tools and thresholds. Elrefai (2009), found the highest DPN prevalence of 84.2% in hospital participants in Jordan who had neurological deficits in either of quantitative sensory testing (QST), pain, ankle reflexes or the 10g monofilament. This is due to the use of tests for: small (QST), thinly myelinated (light touch) and large nerve fibres (pain; ankle reflexes); used in combination, on hospitalised participants. Unmar *et al.*, (2017), relied on the Diabetes Neuropathy Symptoms and NCS to assess for neuropathy in 240 hospital participants and found an overall prevalence of 50.8%, but the prevalence varied between 17.1%, 33.8% and 50.8% depending on which combination of tests and thresholds they used. Park *et al.*, (2018) examined 256 hospital participants in Korea based on a combination of tendon reflexes, the 10g monofilament and 128Hz tuning fork; and found a prevalence of 35.3%. Wang *et al.*, (2015) also found a 29.5% DPN prevalence in 1,275 hospital participants, based on NCS. Kizosi *et al.*, (2017), found a DPN prevalence of 29.4%, based on NSS and NDS scores amongst 248 hospital participants in Uganda. In contrast, Pai *et al.*, (2018) assessed DPN in 2,837 hospital participants in China using a combination NCS and the MNSI and found a prevalence of 21.3%.

From the hospital studies, no discernible pattern emerges with the overall prevalence ranging from 21.3% - 84.2%. It is possible that the specific participant profiles in each

study could account for some of these differences, but even from within the same study on the same participants DPN prevalence tends to have broad ranges. For example, Unmar *et al.*, (2017) found this ranged from 17.1% - 50.8%, and it can therefore be surmised that these wide ranges in prevalence on the same participants could be attributed to the different assessment methods, threshold criteria and tester variability. Other meta-analyses, including Iqbal *et al.*, (2018) also reported wide variations in DPN prevalence of between 7% - 59%, and Ziegler *et al.*, (2014) also pooled studies and estimated the prevalence of DPN to vary widely in people with type 2 diabetes with a median prevalence of 28%.

This review has found that the actual DPN prevalence in people with type 2 diabetes is masked behind divergent assessments criteria, thresholds, protocols, diagnostic instruments and definitions. The major determinants of prevalence are both practitioner dependant with the definition of neuropathy, type of instrument and the threshold criteria used for that instrument; and also participant dependant with respect to the relevant participant population. This further presses the need for a standardised objective assessment approach for DPN. Nerve conduction is one such approach, and it is suggested from Figure 1.3.1. (Chapter 1, page 5) that it detects nerve changes before the manifestation of other clinical symptoms (Brown *et al.*, 2017). From the above review, pooling the studies that relied on nerve conduction places the prevalence of DPN between 42%-50%, with a median of 46% amongst people with type 2 diabetes, and is in agreement with the 46% earlier suggested by Ziegler *et al.*, (2014).

1.3.4 Characteristics of sensory and motor neuropathy

Seminal investigations by Gilliatt and Willison (1962), Gilliatt (1966), Lamontagne and Buchthal (1970) and Behse, Buchthal and Carlsen, 1977) observed morphological features in the long nerves of people with diabetes, and reported segmental demyelination that was more severe at the peripheral end of the axons, which then advanced more proximally as the underlying diabetes progressed over time. Ever since, this has led to DPN being characterised as being a progressive “die-back” axonopathy which advances in

a distal to proximal pattern. DPN commonly presents with sensory symptoms earlier in the disease process before motor neuropathy (Zochodne, Ramji and Toth, 2008), with the evidence from the literature unclear as to why (Dobretsov, Romanovsky and Stimers, 2007; Andersen, 2012). However, the assertion that sensory neuropathy precedes motor has been challenged. Dyck *et al.*, (2011), Allen *et al.*, (2014) and Schamarek *et al.*, (2016) all observed concurrent conduction deficits in both motor and sensory nerves, suggesting that both motor and sensory neuropathy occur simultaneously, in contrast to clinical observations. Further challenges were put forward at a biochemical level that suggested the reverse, with motor preceding sensory neuropathy, with Zeileis, Hornik and Murrell, (2009) and Di Iorio *et al.*, (2006) observing an association between increased levels of the cytokine interleukine-6 (IL-6) and reduced peroneal nerve conduction velocity. These were corroborated by Schamarek *et al.*, (2016) who reported that increased levels of IL-6 were significantly associated with reduced peroneal nerve motor conduction velocity ($p=0.04$), but the same effect was not observed in the sural nerve, with no effect on sensory conduction velocity. IL-6 itself, as with most cytokines, has a complex and at times contradictory role. It is associated with features of motor nerve neuropathy, and yet has also been found to increase nerve regeneration and recovery after damage (Bauer, Kerr and Patterson, 2007; Deverman and Patterson, 2009), and even put forward as a therapy for neuropathy (Cox *et al.*, 2017). IL-6 therefore enjoys a complex role that perhaps depends on the metabolic context, such as the stage of diabetes that triggers its upregulation around nerve cells. It is therefore possible that IL-6 levels increase in the later stages of diabetes to then affect the motor nerves, but by this stage the sensory component has long been affected by other processes.

Despite these underlying biochemical processes selectively affecting the motor and sensory systems in different ways, it is likely that anatomical and structural features of the nervous system play a larger role in explaining the clinical observations. These clinical characteristics, where sensory neuropathy is detected before motor, could be explained by the anatomical and structural differences between the motor and sensory systems. This is shown in Figure 1.3.5, focusing on the respective anatomical locations of the cell bodies and axon lengths.

Figure 1.3.5: Showing Structural Features of the Central Nervous System and Motor and Sensory Neurons

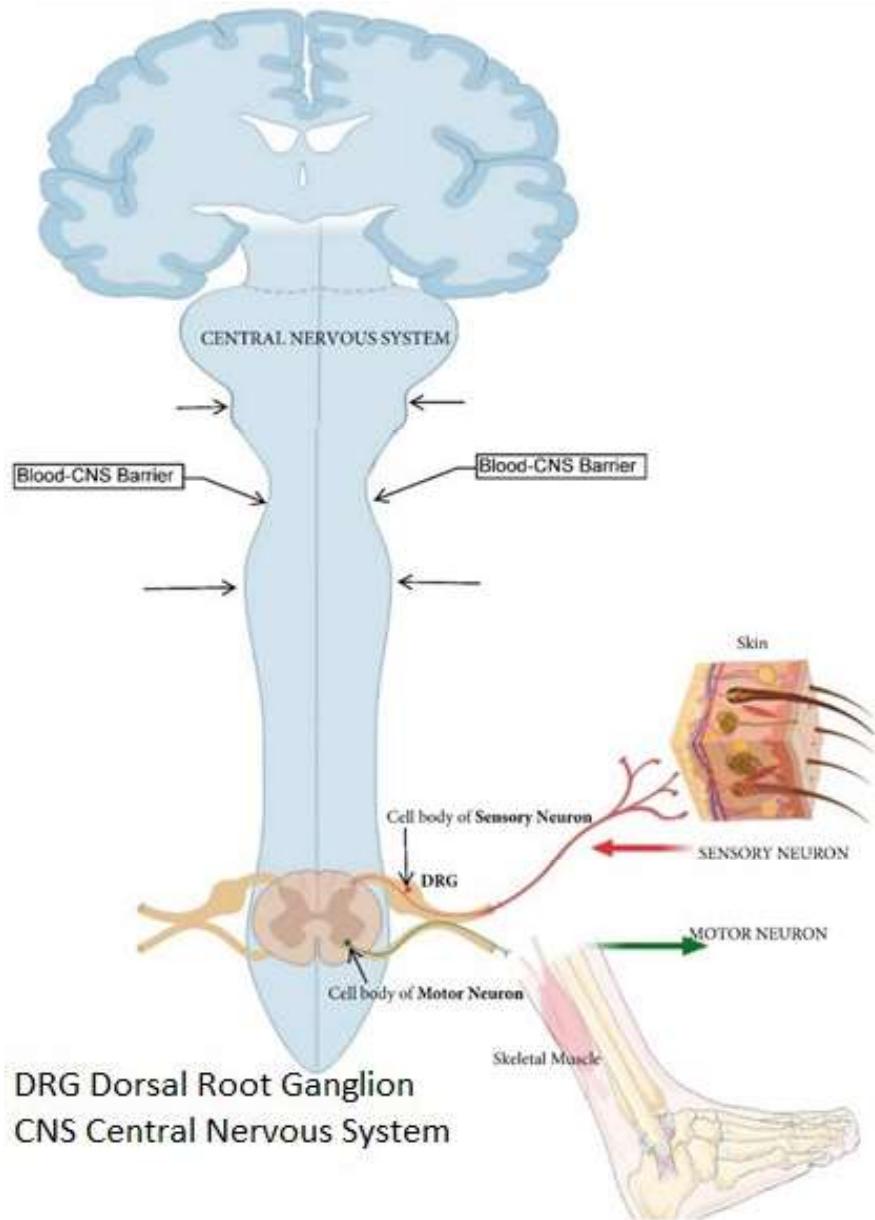


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Figure 1.3.5. shows the cell bodies of motor neurons having shorter axons and located within the central nervous system (CNS), whilst the sensory neurons have cell bodies outside the CNS and have longer axons. Motor cell bodies located within the CNS are

protected by the blood-CNS barrier (Ramji *et al.*, 2007), and have compensatory collateral reinnervation from other motor units, which means that functional motor deficits are difficult to detect in early diabetes (Kennedy, 2000; Kennedy and Zochodne, 2005). In contrast, cell bodies of sensory neurons are located in the dorsal root ganglia (DRG), outside the CNS, which leaves sensory neurons more susceptible to damage as they lie outside the protective blood-CNS barrier. Sensory neurons are more exposed to demyelination given their longer axons, and are less able to regenerate with the Schwann cells in the peripheral nervous system more challenged in providing nutritive and repair functions, leading to axonopathy (Landowski *et al.*, 2016; Prior *et al.*, 2017).

Various authors have suggested that differences could also be due to the nerves respective compositions, since the sensory fibres are made up of a combination of myelinated (Type A α and β) fibres, and the unmyelinated Type C, which have less protection against glycaemic damage, in contrast to the motor fibres which are composed of myelinated fibres (Types A α , β and γ), and are afforded protection by the myelin sheaths (Ebenezer and Polydefkis, 2014). Hence, DPN is characterised by sensory neuropathy whose axon loss precedes that of motor neurons. In addition, the clinical assessment of motor neuropathy is limited to reflex, balance and muscle power which are more difficult to quantify until the later stages of neuropathy, whereas the sensory system offers a much broader spectrum of modalities including touch, temperature, pressure, pain and vibration which can be assessed earlier on in the disease process.

Therefore, even though diabetes simultaneously affects both motor and sensory nerves, their respective structural and anatomical differences determine each system's manifestation of dysfunction and consequent clinical detection in response to glycaemic damage, and accounts for the sensory being detected before motor nerve changes. This early manifestation of sensory neuropathy has led to investigations on mechanisms responsible for DPN to therefore focus on the sensory nerves.

In a quest for possible therapeutic approaches, investigators have looked at which part of the sensory neuron, either the cell body or the axon, is first affected and the processes involved during neuropathy. There have been suggestions that the sensory cell body itself

is directly affected in early neuropathy, with axon loss as a secondary – rather than a primary feature of the syndrome (Zochodne, 2016). The anatomical location of the sensory cell body in the DRG, make it a prime target for the mechanisms responsible for developing DPN (Zochodne, 2014). Since the DRG lies outside the CNS, that leaves it more vulnerable to systemic metabolic changes that damage the sensory cell bodies, that in turn affect the sensory axons, leading to sensory neuropathy (Masaki Kobayashi and Zochodne, 2018). In addition, the composition of the sensory neurons leaves them more vulnerable to damage, with 79%-90% being small fibres (Malik *et al.*, 2005; Said, Baudoin and Toyooka, 2008) composed of thinly myelinated A δ or unmyelinated Type C fibres (Javed *et al.*, 2014). These fibres lack the advantages of myelinated conduction, and therefore consume more energy during signal propagation than the thicker myelinated fibres, resulting in them having higher metabolic demands (Feldman *et al.*, 2017). Due to this high demand, the DRG neurons are more vulnerable to small metabolic changes, and atrophy in the absence of adequate nutritional supplies. These metabolic insults upon the DRG are summarised in Figure 1.3.6., and include microvascular and glucose metabolising pathways, which are described in more detail later in section 1.3.5 of this chapter.

Figure 1.3.6 shows the location of the DRG, and an outline of the various mechanisms that could damage the cell body of the sensory neuron within the DRG, leading to sensory neuropathy. In support of this hypothesis, Zochodne, Ho and Allison (1994) had earlier reported reduced blood flow to the DRG in artificially induced sensory neuropathy in experimental rat models. Kamiya, Zhang and Sima (2006) then observed a 27% loss of sural nerve axons alongside a reduction in sural nerve conduction velocity of 22% over 10 months in Type 1 BioBreeding/Worcester rats. They however noted that despite cellular changes and axon loss, the cell bodies themselves were preserved.

The “die back” hypothesis therefore concurs with morphological findings by earlier researchers (Gilliatt and Willison, 1962; Lamontagne and Buchthal, 1970; Behse, Buchthal and Carlsen, 1977); other experimental models (Zochodne, Ho and Allison, 1994; Toth *et al.*, 2004; Kamiya, Zhang and Sima, 2006), and with the clinical features of sensory neuropathy, which has distal peripheral manifestations and advances more proximally.

Figure 1.3.6: Anatomical Representation of Sensory Dorsal Root Ganglion and Mechanisms of Diabetes Damage

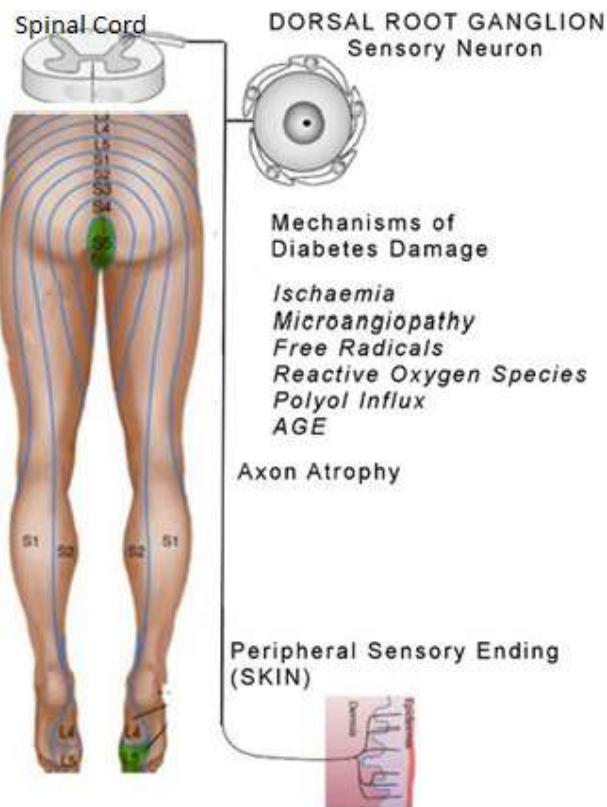


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1.3.5 Aetiology of DPN

The possible aetiologies of DPN are multifactorial, but broadly sit in microvascular and glucose metabolising pathways (Yagihashi, Mizukami and Sugimoto, 2011; Østergaard *et al.*, 2015; Yagihashi, 2016) as shown in Figure 1.2.1 (Chapter 1, page 4). When considering the vascular hypothesis, it is important to remember that the blood-CNS barrier, (see Figure 1.3.5 , Chapter 1, page 18), whilst it protects against circulating free radicals, metabolites and pathogens, it does not protect neurons against hypoxia or ischaemia (Palmer, 2010). DPN has long been considered to be primarily of microvascular

aetiology, with microvascular angiopathy of the vasa nervorum leading to axonopathy (Beggs *et al.*, 1992). In support of this hypothesis, Mohseni *et al.*, (2017) found reductions in endoneurial capillary density and lumen area in the sural nerves of type 2 diabetes participants over 10 a year period. This contrasts with the earlier findings of Theriault (1997) who, over 1 year, found no changes in the sural microvascular supply despite reductions in nerve fibre density. In addition, the microvascular hypothesis fails to fully account for the selective neuropathy that spares the motor whilst affecting the sensory fibres at an earlier stage of the disease; and the sparing of the central nervous system (CNS), despite CNS neurons being more prone to ischaemia (Zochodne, Ramji and Toth, 2008; Østergaard *et al.*, 2015; Yagihashi, 2016; Zochodne, 2016). With there being no changes in the vasa nervorum despite deteriorating nerve function during early stages of diabetes, these findings suggest that the vascular hypothesis is unlikely to be the trigger, but rather a co-factor in DPN as diabetes manifestations progress (Zochodne, Ramji and Toth, 2008; Zochodne, 2015; Masaki Kobayashi and Zochodne, 2018).

It has therefore been suggested that glucose metabolising pathways also play a role in the development of DPN as shown in Figure 1.2.1 (Chapter 1, page 4), although even these are not fully understood (Edwards *et al.*, 2008; Yagihashi, 2016; Zochodne, 2016). It is suggested that chronic hyperglycaemia overloads the glucose metabolising pathways and results in the excessive accumulation of sorbitol, advanced glycation end products (AGE), protein kinase C (PKC), hexosamine and reactive oxygen species (ROS) (Yagihashi, Mizukami and Sugimoto, 2011; Singh, Kishore and Kaur, 2014; Yagihashi, 2016). These by-products have complex involvements that impair neurovascular function and repair (sorbitol, PKC, ROS), downregulate neuron regeneration (AGE; hexosamine pathway), and increase hypoxia, vascular tissue damage and nerve demyelination (ROS) (Edwards *et al.*, 2008; Yagihashi, 2016). An additional factor in glucose metabolism is insulin, whose role in neuron signaling, regeneration and repair is gaining increased attention, however studies are confined to rat models. For instance, even low doses of insulin insufficient to reverse hyperglycaemia, were found to reverse neuropathy through increasing the conduction velocity and amount of myelinated fibres in the sciatic nerve (Singhal *et al.*, 1997), and increasing sural nerve conduction velocity in rats (Brussee, Cunningham and Zochodne, 2004). More recently, Rachana, Manu and Advirao (2018) found that insulin

increased Schwann cell activity, and improved rat sciatic nerve regeneration. These animal studies suggest that insulin plays a role in early DPN development, particularly in maintaining nerve function and perhaps even early recovery, but these observations are yet to be confirmed in human models.

Thus it is evident that DPN manifests due to a combination of defective insulin signalling, glucose metabolising and microvascular pathways that lead to nerve degeneration, a reduction in the quantity of nerve fibres, and an impaired ability in sensory nerve repair. To summarise, DPN is a complex feature that is not fully understood, and has several aetiologies and manifestations, which has led to different diagnostics approaches and divergent reports on its prevalence. There is however broad agreement that it manifests prior to macrovascular dysfunction, as discussed in section 1.4 (page 33), and that it is interlinked with both macro and microvascular dysfunction, which is further discussed in section 1.5.2 on pages 50-51.

1.3.6 Neurological Assessments

Following from the earlier conclusions from section 1.3.4 of this chapter (page 19), the diabetic foot neuropathy assessments focus on the sensory component mainly due to the broader detection modalities it offers, and sensory neuropathy has been identified as the strongest predictor of foot ulceration (Roden and Roden, 2007; Paisey *et al.*, 2016). NICE Guidelines NG19 (2015) recommend assessment sensory neuropathy with either the 10g monofilament (Semmes-Weinstein) or 128 Hz tuning fork (Rydel-Seiffer), and consequently these have become the two most common methods. This is despite both having variability in methods of application, for instance in how much pressure is applied during testing, are vulnerable to temperature conditions and have further subjective components in test response and interpretation (Dros *et al.*, 2009; Haloua, Sierevelt and Theuvenet, 2011; Lavery *et al.*, 2012; Lai *et al.*, 2014; Won and Park, 2016; Chauhan *et al.*, 2018). In addition, findings from the Glycaemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study showed that they only detect sensory neuropathy in 38% of suspected 'early' cases and in 61% of patients with

advanced neuropathy, and neither is reliable in detecting early symptoms (Herman and Kennedy, 2005). Given that in about 50% of patients, diabetic neuropathy is subclinical (Amin and Doupis, 2016; Won and Park, 2016), the subjective nature of the clinical assessments inhibits early detection, and therefore they likely underestimate diabetic sensory neuropathy. With the limitations facing the recommended tests, such as wide variability, lack of standardised protocols and an inability to detect early neuropathy, other objective neuropathy reference standards have been proposed. These lie in two broad camps: those relying on detecting nerve density and/or function in smaller type C fibres (IENFD, CCM, sudomotor function); and those assessment electrophysiological function (nerve conduction studies).

1.3.7 Objective Diabetes Sensory Neuropathy Assessments

IENFD requires a biopsy and microscopy to count the quantity of nerve fibres in a given patch of skin (Ebenezer *et al.*, 2007; Loseth *et al.*, 2008; Divisova *et al.*, 2016; Timar *et al.*, 2016). This involves puncturing the calf skin to collect specimens for examination, and is thus highly invasive and presents ulceration and infection risks in already vulnerable patients. Along with CCM, which assess the quantity of nerves in a given corneal area (Ziegler *et al.*, 2014; Azmi *et al.*, 2015; Ishibashi *et al.*, 2016; Maddaloni and Sabatino, 2016), it requires extended specialist analysis and neither is practical for assessment neuropathy in a routine clinic setting. Further to this, Ziegler *et al.*, (2014) found that despite CCM showing early neuropathic changes; this could not be correlated to IENFD findings which showed no changes to skin nerve fibre density. This highlights one of the difficulties in establishing a universally objective neuropathy reference standard in early stage diabetes, which derives from the assumption that diabetes affects different parts and organs of the body to the same extent, an assumption that is challenged by the poor correlation between CCM and IENFD findings. It also shows that the diabetic changes observed in the later stages of diabetes such as corneal and visual degeneration and depletion of skin nerve endings, are not necessarily correlated in its earlier stages. Therefore only IENFD is relevant to the feet, and Ziegler *et al.* (2014)'s findings suggest that, in the early stages of diabetes, detecting CCM neuropathic changes in the eye,

cannot be used to infer or act as a reference standard for occurrences in the feet. Moreover, both IENFD and CCM are affected by age (Divisova *et al.* 2016), and other variables such as ethnic differences which makes it difficult to have normative values, and leaves them poorly reproducible (Voortman *et al.*, 2017). The above uncertainties limit IENFD and CCM applicability, and it is not yet possible to rely on them as reference standards for early neuropathy. Therefore the diagnostic reference standard for early detection of neuropathy needs to be site specific, and in this case focussed on the lower leg, since the temporal sequence in which diabetes affects different organs and parts of the body has not been established (Ziegler *et al.* 2014).

Sudomotor methodologies include the Neuropad® (Trigocare International, Wiehl, Drabenderhöhe, Germany) and the Sudoscan® (Impeto Medical, Paris, France) (Bordier *et al.*, 2016), which both detect dysfunction affecting the autonomic fibres. The Neuropad® detects foot sweating through colour change (Tentolouris *et al.*, 2008), and was suggested by NICE for the earlier detection of diabetic neuropathy (National Institute for Health and Care Excellence, Medical Technology Guidance, 2017). However, this did not determine practicality of application in a podiatry clinic, as accounting for patient acclimatisation and setup it takes up to 20 minutes to complete, and requires even longer application times to increase specificity (Tsapas *et al.*, 2014), with cost implications. Neuropad® function relies on moisture detection over 10 minutes, which is longer than portable nerve conduction, and leaves it vulnerable to external environmental factors such as temperature and humidity, and the interpretation of its colour change carries a subjective component.

The Neuropad® has low specificity, with positive and negative likelihood ratios (LR) of $LR+ = 2.44$; and $LR- = 0.22$ respectively (Tsapas *et al.*, 2014), therefore it would require further referral for confirmatory diagnosis with additional testing, such as nerve conduction tests. Similarly, the Sudoscan® relies on sweating to measure skin conductance (Sanz-Corbalan *et al.*, 2018). Compared to the 10g monofilament, Sanz-Corbalan *et al.*, (2018) found the Sudoscan® demonstrated good sensitivity (100%) and accuracy ($AUC = 0.82$; 95% CI = 0.76-0.87), but poor specificity (33%) at predicting ulceration over 3 ½ years in 263 type 2 diabetes patients. It can be argued that their cohort had late rather than early stage neuropathy, would have high false positives due to the low specificity, and given that

comparisons were against the 10g monofilament and participants developed ulceration within 3 ½ years; the Sudoscan® had excellent predictive value in an already more susceptible cohort.

In addition, both the Sudoscan® and Neuropad® results also depend on the weather, the participant's emotional state, medications, and ethnicity (Freedman *et al.*, 2014; Mao *et al.*, 2017). For instance, the drug metformin affects neurotransmitter activity and hence sweating function, independent of neuropathy status (Muntzel, Abe and Petersen, 1997; Manzella *et al.*, 2004; Markowicz-Piasecka *et al.*, 2017; Patel *et al.*, 2017). This therefore introduces uncertainty in the interpretation of results, and limits the usefulness of sudomotor tests and leaves scope for objective nerve conduction tests.

1.3.8 Nerve Conduction Mode of Operation

All sensory nerve conduction devices assess nerve functionality based on two main parameters, namely on how quickly an electric charge covers a fixed distance, giving its velocity (metres per second); and the amount of charge that is left over and detected at the receiving end, shown by the amplitude (volts). In physiological terms, the velocity reflects the extent of myelination, with demyelination shown as slowing of conduction velocity, whilst the amplitude is a direct reflection of the quantity of nerve fibres (Perkins, Ngo and Bril, 2002). Several investigations, as described in the following section 1.3.9 (page 28), have shown amplitude to reduce, followed by the velocity, with progression of neuropathy (Gilliatt and Willison, 1962; Gilliatt, 1966; Lamontagne and Buchthal, 1970; Behse, Buchthal and Carlsen, 1977; Perkins, Ngo and Bril, 2002). When a charge is initiated anywhere along a nerve, the charge travels along the axon in both directions simultaneously (Mortimer and Bhadra, 2004). Whether the detection is done in the same direction as, or against the usual nerve signal propagation determines whether a device operates in an orthodromic or antidromic manner, and is one of the differences between fixed sensory nerve conduction and the portable devices. Fixed sensory nerve conduction devices detect the electric charge that travels in the opposite direction to that of usual nerve signals. With reference to the sural nerve, fixed nerve conduction charge is initiated proximally and is detected distally, in antidromic fashion, as shown in Figure 1.3.7.

Figure 1.3.7: Showing Antidromic Stimulation by Fixed Nerve Conduction

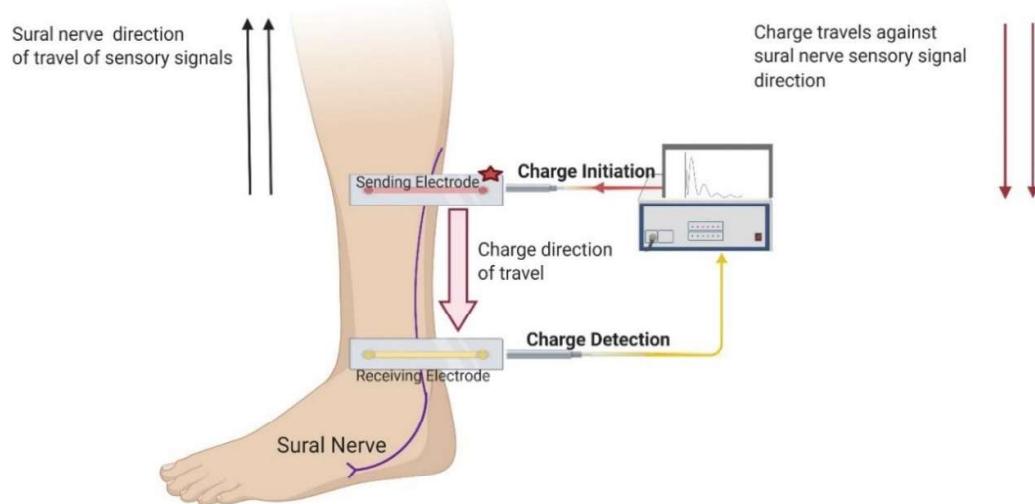


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By contrast, in orthodromic stimulation of portable nerve conduction (DPNCheck®), the charge is detected proximally, and in the same direction as the sensory nerve signals, as shown in Figure 1.3.8.

Figure 1.3.8: Orthodromic Stimulation by portable nerve conduction (DPNCheck®)

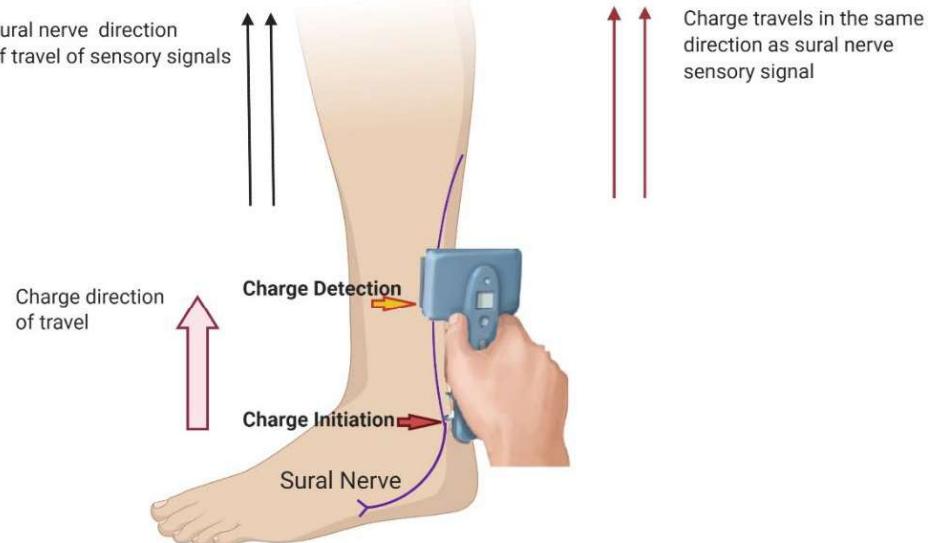


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1.3.9 **Neurological Assessments: Evolution of Nerve Conduction**

The use of conduction to assess nerve health spans several decades. Dawson and Scott (1949), experimented with obtaining reliable sensory nerve velocities and amplitudes through the skin. Their early work was advanced by Gilliatt and Sears (1958), who established normative values for the upper sensory (median and ulnar) nerves. During the 1960s, Gilliatt and Willison observed the slowing of nerve conduction velocity in peripheral nerves of people with diabetes, and attributed this to segmental demyelination (Gilliatt and Willison, 1962; Gilliatt, 1966). Slowing of nerve conduction velocity in diabetes neuropathy was further confirmed by Lamontagne and Buchthal (1970), before Behse and Buchthal (1977) quantified and correlated sural nerve biopsy morphological findings to conduction deficits. They observed velocity slowing of up to 30% in otherwise intact nerves but with segmental demyelination, but if velocity deficits exceeded 30% they found loss of entire axons. They therefore described diabetes sensory neuropathy as characterised by early demyelination, before axonopathy that was more severe at the distal end of a nerve, which then advanced more proximally with diabetes progression. During the initial stages of diabetes, axon loss was observed alongside reduced conduction amplitude, whilst the velocity was largely intact and maintained by the remaining myelinated axons. As the number of live axons decreased with diabetes progression, conduction velocity then slowed and stopped altogether when the last remaining axons in that portion of the nerve were lost. Despite recruiting only 12 volunteers with diabetes, the longitudinal nature of the study where 7 participants were followed up for up to 8 years, allowed sural nerve electro-morphological features to be tracked alongside diabetes progression.

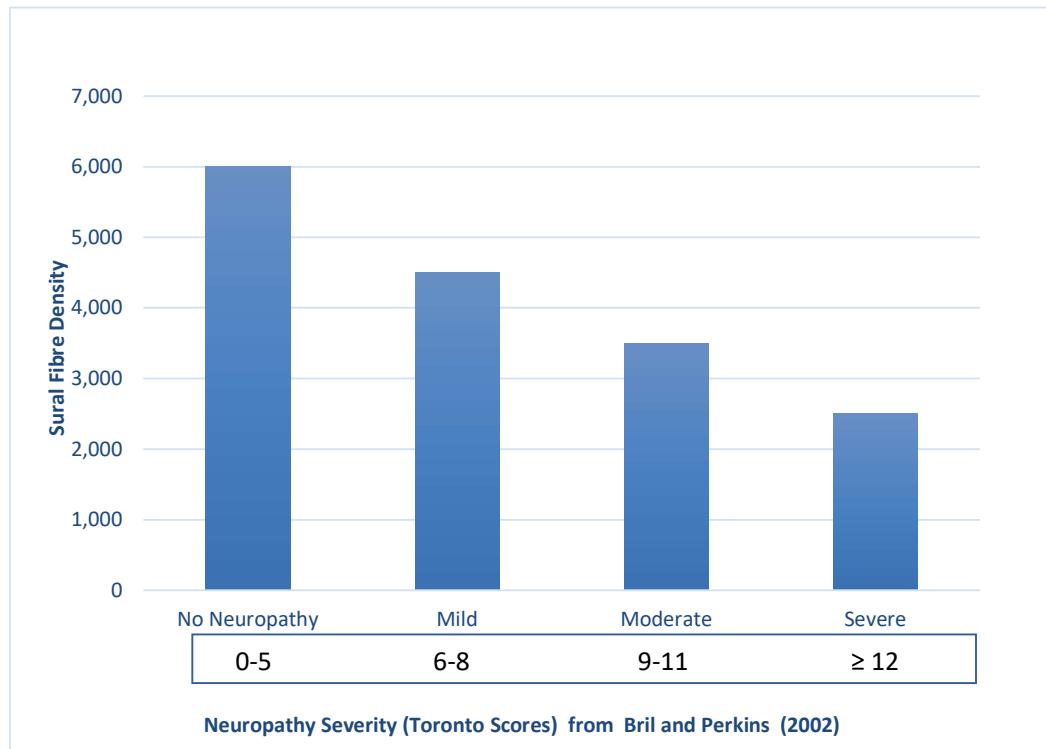
Partanen *et al.*, (1995) observed the natural history of diabetes neuropathy, and its effects on nerve conduction in the upper and lower body extremities, when they compared 142 healthy, age and sex matched, against 132 diabetes participants in a case control study over 10 years. They showed that loss of sural nerve function was greater in the type 2 diabetes participants, with velocity reducing from 48.3 m/s to 44.4 m/s ($p = 0.001$); and amplitude reduction from 9.2 to 5.5 μ V ($p = 0.001$). In contrast, for healthy participants sural nerve function remained mostly unaffected, with small reductions in

velocity from 51 – 50.5 m/s ($p=0.2$), and amplitude from $10.1\mu\text{V} – 9.7\mu\text{V}$ ($p = 0.3$) which were minimal, and not significant. This therefore implied that in people with diabetes there was significant deterioration in sural nerve function and progression to neuropathy, when compared to healthy participants who showed little changes. When comparing the upper and lower extremity nerves, the sural nerve showed the largest reduction in conduction velocity (- 3.9 m/s) and amplitude (- 3.7 μV), and hence was the most sensitive to glycaemic changes. This study placed the sural nerve as the most sensitive to, and prime target for, assessment the effects of diabetes neuropathy.

Albers *et al.*, (1996) investigated nerve conduction parameters in people with subclinical neuropathy from The Early Diabetes Intervention Trail. They found the frequency of conduction abnormalities most common in the sural nerve (68% right and 67% left foot), followed by the median sensory (60%), peroneal (46%) and median motor (36%) nerves. The sural nerve in diabetes participants showed greater changes in response to hyperglycaemia when compared to other nerves, as well as showing minimal differences bilaterally, therefore making it an ideal target for detecting neuropathic changes. These results are similar to the earlier work by Partanen *et al.*, (1995). They also reported that in diabetes participants with mild neuropathy, sensory amplitudes were 10-15 μV lower, and conduction velocities 4-14 m/s slower when compared to healthy participants. These also agree with earlier findings from the diabetes control and complications trial (DCCT), which found sural nerve velocities to reduce by 2.8 m/s over 5 years, albeit in type 1 diabetes participants, (DCCT Research Group, 1995).

Bril and Perkins, (2002) compared neuropathy status based on the Toronto classification, to sural fibre density and conduction amplitude, and found with each progressive neuropathy stratification the sural fibre density decreased, as shown in Figure 1.3.9.

Figure 1.3.9: Showing Decreasing Sural Nerve Fibre Density with Increasing Toronto Neuropathy Score Severity



Their observations led to the assumption of a temporal sequence characterised by reduction in sural nerve amplitude as the earliest and more sensitive sign of nerve damage, before loss of sural nerve conduction velocity. This assumption was carried to a later study that sought to establish validity for a portable nerve conduction device, the DPNCheck® (NC-stat® DPNCheck®; Neurometrix, Inc., Waltham, MA, USA) against a reference fixed nerve conduction counterpoint device (Medtronic, Mississauga, Canada) in 72 participants. They reported high Pearson correlation of $r = 0.95$ ($p < 0.001$) but a systematic bias where the portable DPNCheck® underestimated the sural nerve amplitude by $1.2\mu\text{V}$ when compared to the reference device. With a threshold of $6 \mu\text{V}$, they determined 92% sensitivity, 82% specificity and overall accuracy of 89% for the DPNCheck® in the diagnosis of sensory neuropathy. This study only considered nerve amplitude and not conduction velocity, which is an important parameter particularly in cases of mild neuropathy that are characterised by high amplitudes but slower velocities (Charles *et al.*, 2010). Whilst the devices have high correlation (Pearson $r = 0.95$) in

measuring the number of fibres (amplitude), the extent of agreement in how they measure velocity is not determined, which would have strengthened the validity findings. Nevertheless, the value of this study lies in establishing criterion validity for a portable nerve conduction device based on amplitude, against legacy fixed nerve conduction equipment which was cumbersome, required specialised setup and interpretation, and not suitable for routine clinical use.

A review of these studies show that the sural nerve is most sensitive to electrophysiological changes, has morphological features that correlate directly with neuropathy severity, and taken together support the use of the sural nerve in the diagnosis of sensory neuropathy in people with type 2 diabetes. The sural nerve also demonstrated almost uniform bilateral manifestations (Albers *et al.*, 1996; Perkins, Ngo and Bril, 2002), which suggests that unilateral sural nerve assessments can be conducted. Nerve conduction has since been proposed as a reference standard, with the foot, and functional evaluation of the long sural nerve in particular, as the prime target for neuropathy diagnosis (Albers *et al.*, 2007; Yang *et al.*, 2014; Z. Yang *et al.*, 2017).

1.3.10 Challenges in the clinical adoption of nerve conduction in the diagnosis of sensory neuropathy

Previous work has established the role of sural nerve conduction evaluation when diagnosing sensory neuropathy (Partanen *et al.*, 1995; Albers *et al.*, 1996; Perkins, Ngo and Bril, 2002; Bril *et al.*, 2009). Despite this, nerve conduction remains mostly confined to research laboratories and specialised neurology units, and faces barriers in becoming a mainstream clinical assessment method as previous devices were time consuming, bulky and complex, often requiring technical expertise to operate (Banach, 2015; de Souza, de Souza and Nagvekar, 2015; Won and Park, 2016). In addition, despite recommendations supporting nerve conduction in the diagnosis of sensory neuropathy, no formal consensus exists in the clinical context for the foot in particular (Lee *et al.*, 2014; Fateh *et al.*, 2015; Poulose *et al.*, 2015; Chatzikosma *et al.*, 2016; Hamasaki and Hamasaki, 2017). Finally, the diagnosis of neuropathy is based on two parameters, velocity and amplitude, which adds

complexity to the interpretation, rather than if a single measure were available. Hence there is continued reliance on the 10g monofilament (Semmes-Weinstein) and 128 Hz tuning fork (Rydel-Seiffer) as the main standard neuropathy assessment and diagnostic methods, despite their shortcomings (Dros *et al.*, 2009; Haloua, Sierevelt and Thevenet, 2011; Lavery *et al.*, 2012; Lai *et al.*, 2014; Won and Park, 2016), leaving nerve conduction poorly used as a pragmatic tool in clinical practice.

Recent advances on nerve conduction devices now offer simpler, quicker and more portable versions such as the earlier described DPNCheck® (Kong *et al.*, 2008; Poulose *et al.*, 2015; Chatzikosma *et al.*, 2016; Won and Park 2016). This device has potential to be an objective clinical 'reference standard' whilst addressing some of the barriers towards wider clinical use. As with other nerve conduction devices however, despite being used in research, it remains to be evaluated pragmatically in a routine clinical setting where other quicker and more convenient, but less reliable, physical examination tests are used in the assessment of neuropathy in people with type 2 diabetes. There is therefore the need, for the purposes of earlier identification of those with neuropathy, to evaluate the pragmatic use of DPNCheck® in the clinical assessment of neuropathy in people who have type 2 diabetes, and compare it against current guidelines.

1.4. Diabetes Ischaemia

Diabetes ischaemia can be defined as the macro and microarterial occlusion induced by chronic hyperglycaemia to the different components of the arterial system. A further aspect of the diabetic foot assessment therefore is a determination of the arterial supply, which is a strong predictor of healing potential (Alavi *et al.*, 2014a, 2014b). However, in people who have diabetes, current methods of assessment the arterial supply can give a less clear picture due to the masking effects of neuropathy (Boulton, 2013). It has been suggested that the microarterial, rather than the macroarterial component of the peripheral arteries, could potentially be a stronger predictor of healing potential in people with type 2 diabetes (Yang *et al.*, 2013; Lalithambika *et al.*, 2014; Pardo *et al.*, 2015; Rajagopalan *et al.*, 2017). This section therefore aims to provide the justification to

detect microischaemia as part of the diabetic foot assessment, alongside the assessment of neuropathy.

1.4.1 Aetiology of Diabetes Ischaemia

Anatomically, the microarterial supply is physiologically defined as the arterial vessels whose lumen diameter is less than 200 μ m, whilst the macroarterial supply are the arteries whose lumen size exceeds this. Both macro and microarterial vessels share an endothelial cell layer, and it is the dysfunction of this layer through various mechanisms, that acts as the primary physiological trigger to ischaemia (Kota *et al.*, 2012; Sharma, Schaper and Rayman, 2019; Vella and Petrie, 2019), as shown in Figure 1.4.1.

Figure 1.4.1: Showing Mechanisms for ischaemia in Type 2 Diabetes.

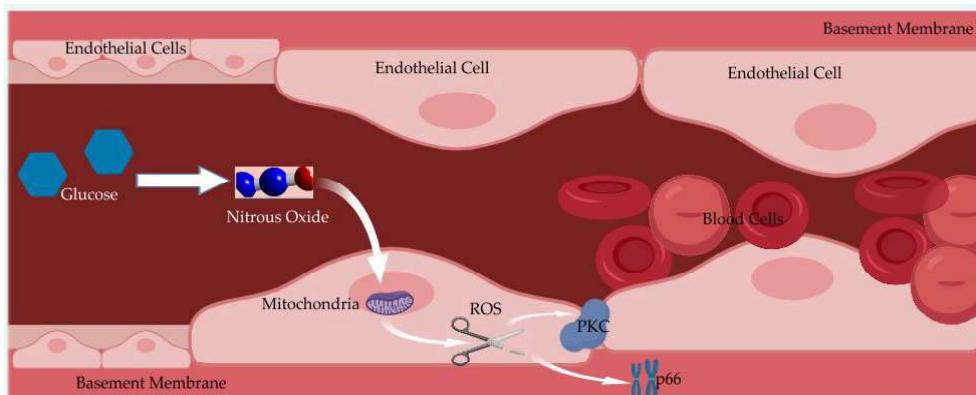


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Some of these mechanisms are as shown in Figure 1.4.1. For example hyperglycaemia reduces bioavailability of nitrous oxide, which has many important functions including limiting the accumulation of reactive oxygen species (ROS) (Ngo *et al.*, 2005; Camici *et al.*, 2007; S.-L. L. Yang *et al.*, 2017). With reduced nitrous oxide, there is increased ROS bioavailability from the mitochondria, which has several downstream effects. These include increased p66 gene expression (Pagnin *et al.*, 2005; Camici *et al.*, 2007), protein kinase C (PKC) activation (Archvadze *et al.*, 2018; Shen *et al.*, 2018), and advanced glycation end products (AGE) (Hosseini and Abdollahi, 2013; Yagihashi, 2016). The p66 gene impairs endothelial cell function, and people with type 2 diabetes have been found

to have increased levels of p66 gene expression (Pagnin *et al.*, 2005) and its absence in p66 deficient mice resulted in a protective effect with reduced ROS and reduced endothelial impairment (Camichi *et al.*, 2019). PKC is from a family of “master proteins” that sit at a crossroads of several controlling physiological pathways. PKC therefore has several exertions on other proteins, with its increased activation leading to further functional and structural implications for the endothelial wall, including altering its growth, permeability, apoptosis, repair and how it responds to physiological changes (Geraldes and King, 2010). PKC also leads to genetic mutations in the p66 gene, in addition to combining with other ROS to trigger atherosclerotic vascular inflammation, basement membrane thickening and the formation of foam cells that set the stage for macro and micro vascular occlusion, as shown in Figure 1.4.1. (Geraldes and King, 2010; Shen *et al.*, 2018).

To summarise, both large and small vessels share common mechanisms of damage due to the effects of hyperglycaemia on the endothelial cells. Chronic hyperglycaemia leads to a combination of reduced nitrous oxide, increased ROS, PKC, AGE and p66 gene overexpression, that precipitate other events including micro and macroarterial dysfunction.

1.4.2 Diabetes Macroischaemia

The primary process in diabetes macroischaemia is atherosclerosis, secondary to chronic inflammation and injury to the arterial intima. This leads to an increase in fatty deposition in the arterial walls, with the resulting lumen narrowing and arterial stiffening (Fowler, 2008), as shown in Figure 1.4.2.

Figure 1.4.2. Showing progressive vessel occlusion following endothelial cell dysfunction

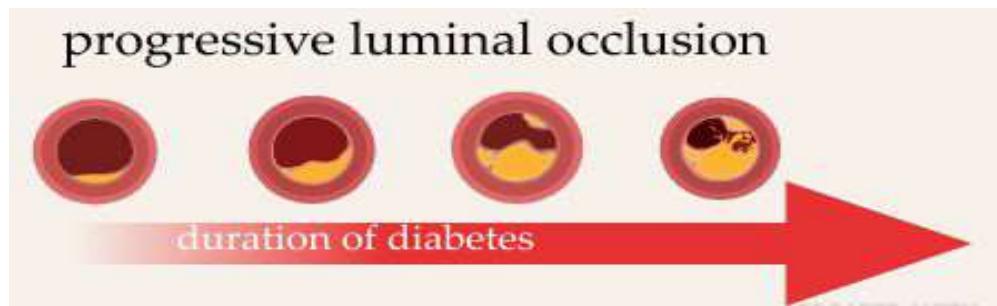


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In the feet, this peripheral ischaemia is termed peripheral vascular disease (PWD), and is clinically detected by reduced or absent pulses on doppler ultrasound in the event of arterial blockage, or via incompressible arteries in the presence of arterial calcification (Aerden *et al.*, 2011). Many clinical assessments are focused on identifying macroischaemia, with the recommended clinical standard being the ankle brachial pressure index below 0.9 (ABI < 0.9), which has been used for several decades (Ikem *et al.*, 2010; Bruno, Reesink and Ghiadoni, 2017; Karam and Stephenson, 2017). Based on the physiological definition in section 1.4.1 (page 33), the digital arteries in the toes are at the terminal ends, but still part of, the macrocirculation. From the digital arteries is derived a modification of the ABI, called the toe brachial index (TBI) which has been found to be more reliable in people with diabetes (de Meijer *et al.*, 2008; Löndahl *et al.*, 2011; Pardo *et al.*, 2015; Rosfors, Kanni and Nyström, 2016).

1.4.3 Prevalence of Diabetes Macroischaemia

The prevalence of peripheral ischaemia amongst people with Type 2 diabetes depends upon several factors, including the population base (hospital or community), thresholds, gender, age and ethnicity (Figure 1.4.3). Prevalence of peripheral ischaemia amongst people with type 2 diabetes was estimated following a literature search of major databases (PubMed, Science Direct and SCOPUS) on studies conducted between 2009 – 2019, that measured peripheral vascular disease in type 2 diabetes participants, and published their findings in English, for which full text was available.

Figure 1.4.3: Showing Studies on Prevalence of Diabetes Macroischaemia

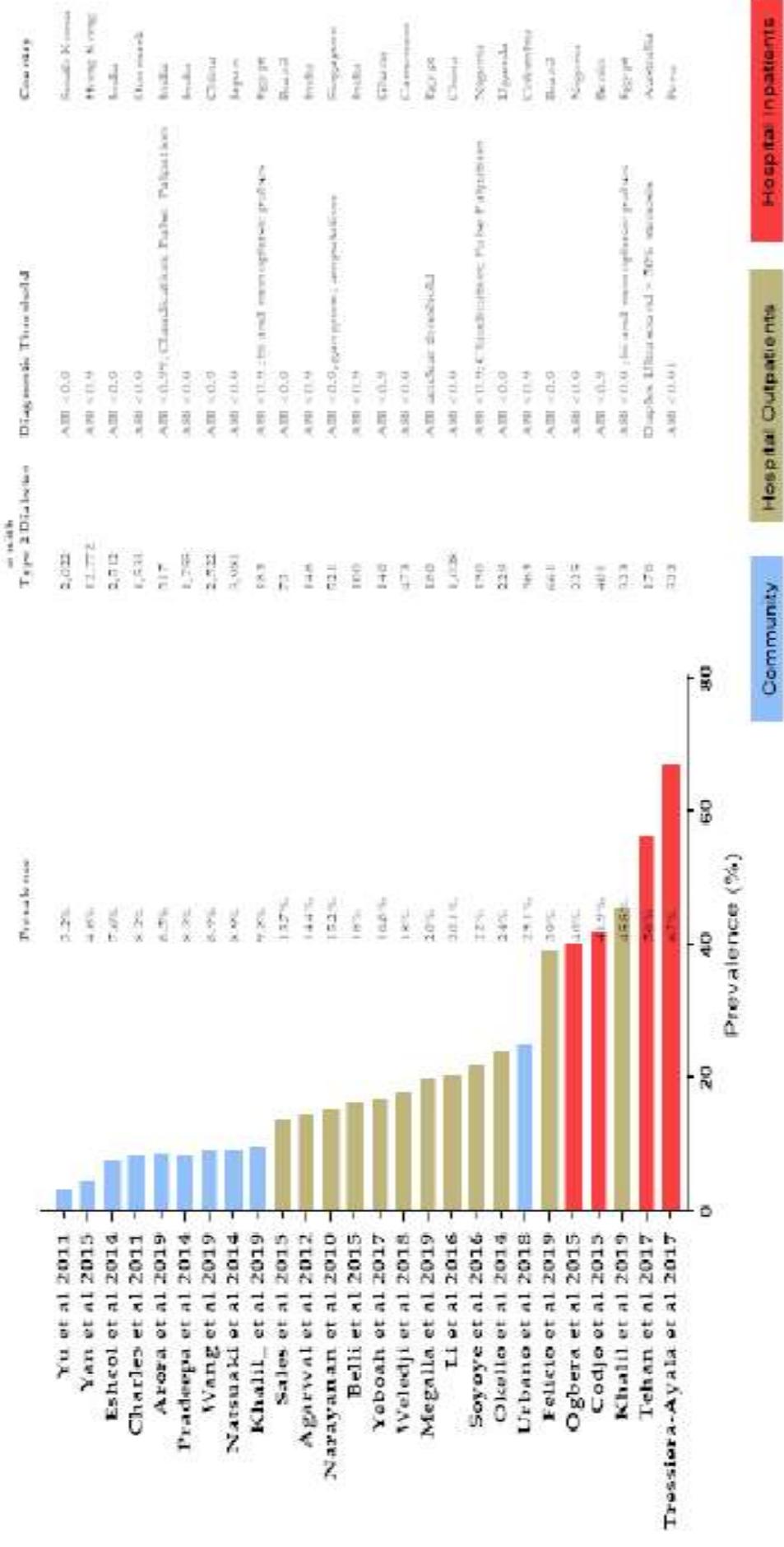


Figure 1.4.3 shows the studies identified following the literature search, and show a global prevalence of peripheral ischaemia in people with type 2 diabetes ranging between 3.2% - 67.1%, and was higher in hospital than in community based populations. The majority of the studies identified were mainly hospital outpatient based. Even from within the participants of the respective studies, there were wide variations in prevalence depending on the underlying health status of the studied population and study characteristics, as shown in Figure 1.4.4.

Figure 1.4.4: Showing Pooled Prevalence of Peripheral Ischaemia in Participants with Type 2 Diabetes based on Participant Population.

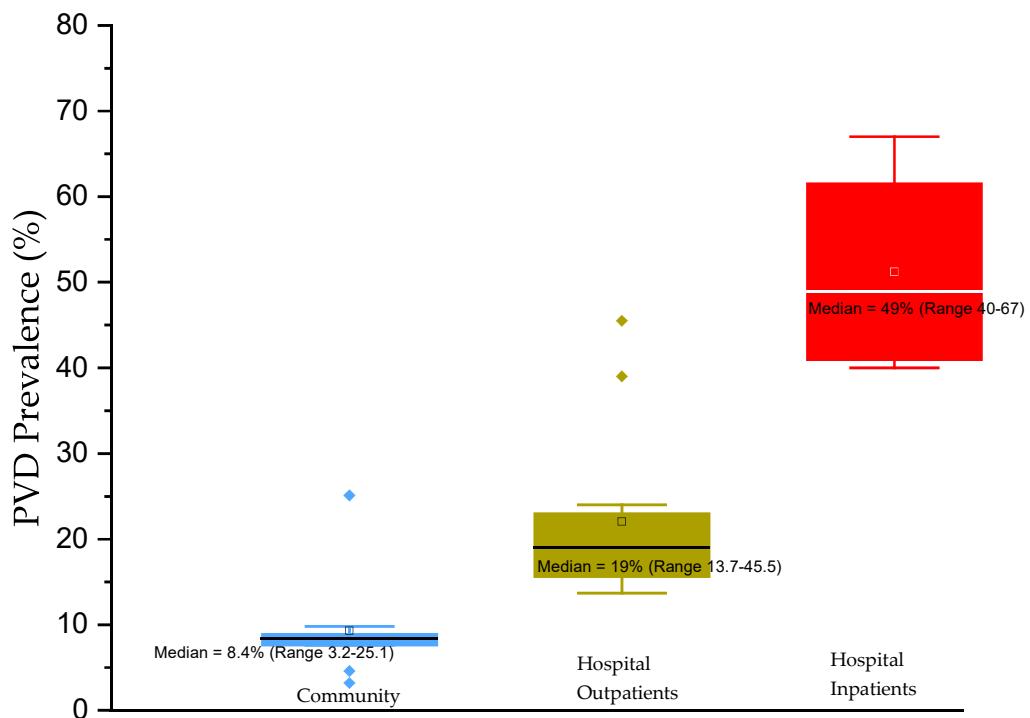


Figure 1.4.4 shows that community based studies had the lowest peripheral ischaemia prevalence of 8.4%, whilst hospital outpatients had a prevalence of 19%, with the highest prevalence of 49% amongst hospital inpatients.

Amongst community based populations, Yu *et al.*, (2011) reported the lowest prevalence of 3.2% amongst 2,002 participants in South Korea, although their recruitment strategy is

unclear. Yan *et al.*, (2015) reported a prevalence of 4.6% for confirmed ischaemia for ABI < 0.9 , and 9.6% for borderline ischaemia if the ABI was between $0.9 - 0.99$. They attracted 12,772 participants via an online portal, most of whom (10,952) had no abnormalities on assessment, had been diagnosed with diabetes for a relatively shorter duration (7 years) and were not actively seeking treatment, which could explain the lower 4.6% prevalence. Eschol *et al.*, (2014) reported a prevalence of 7.6% from amongst 2,512 outpatients from a private clinic in India; which was similar to an 8.9% prevalence from outpatients in Japan (Natsuaki *et al.*, 2014). Charles *et al.*, (2011), based on an ABI threshold < 0.9 , on 1533 participants with type 2 diabetes in Denmark and found a prevalence of 8.2%. This is similar to reported prevalences of 8.2% (Pradeepa *et al.*, 2014); 8.5% (Arora *et al.*, 2019); 9.2% (Khalil *et al.*, 2019) and 8.9% (Wang *et al.*, 2019). From the community studies, Urbano *et al.*, (2018) reported the highest prevalence of 25.1%, from a sample of 363 participants as part of wider study. Even though they state to have recruited 10,000 community participants overall, the health status of the 363 responders with diabetes is unclear, nor did they record the type of diabetes. It is therefore possible that the diabetes responders could have had it for longer, and as a result of poorer health status were receiving care as hospital outpatients, thus accounting for the higher peripheral ischaemia prevalence in contrast to other community studies. Despite this, based on the ABI < 0.9 , this review found the median prevalence of peripheral ischaemia in the community based studies to be 8.4%.

From the hospital outpatient populations, most of the studies found ischaemia prevalence ranging from between 13.7% - 24%, with some outliers declaring 39% (Felicio *et al.*, 2019) and 45.5% (Khalil *et al.*, 2019). Sales *et al.*, (2015) reported a 13.7% prevalence from amongst 73 outpatients in Brazil, which was similar to a 14.4% prevalence from amongst 146 participants in India (Agarwal *et al.*, 2012); 15.2% from amongst 521 participants in Singapore (Narayanan *et al.*, 2010); and 16% from 100 outpatients in India (Belli *et al.*, 2015). Studies based in African countries reported similar prevalences of 16.8% across Ghana (Yeboah *et al.*, 2017), 18% in Cameroon (Weledji *et al.*, 2018), 20% in Egypt (Megalla *et al.*, 2019), 22% in Nigeria (Soyoye *et al.*, 2016), and 22% in Uganda (Okello *et al.*, 2014). In contrast, Felicio *et al.*, (2019) found a higher

prevalence of 39% in Brazil, from a mixed population whose participants were either newly diagnosed or had existing co-morbidities including gangrene and ulcers and from which about 50% were actively smoking. This could therefore account for the increased prevalence when compared to other studies. Similarly, Khalil *et al.*, (2019) found a higher prevalence of 45.5% from amongst outpatients with diabetes in Egypt. This could again be explained by the higher rates of kidney disease (46%) and retinopathy (48%), which indicate that the participants had worse health status than other outpatient populations, and therefore had higher prevalence of peripheral ischaemia.

The hospital inpatient studies showed highest prevalence rates for peripheral ischaemia, ranging from 40%-67% depending on the severity of symptoms and diagnostic methods. Ogbera *et al.*, (2015) found a prevalence of 40% from amongst 225 hospitalised patients in Nigeria, which was similar to 41.1% found by Codjo *et al.*, (2016) from amongst 401 participants in Benin with a similar patient profile. Tehan *et al.*, (2017) found a higher prevalence of 56% in Australia using arterial duplex for diagnosis which is unsurprising given it is a reference standard and more specific and sensitive to arterial stenosis. Tresierra-Ayala and García Rojas, (2017) found the highest prevalence of 67% from amongst 322 inpatients in Peru, although they included participants who already had complications such as foot ulcers, necrosis and gangrene which would have increased the study's ischaemia prevalence.

The median prevalence of diabetes macroschaemia therefore varies depending on the participants' health profile, from 8.4% in community, 19% in outpatients, up to 49% amongst hospital inpatients. Unlike neuropathy, the assessment of ischaemia appears more standardised and coherent around a common standard: the ABI.

1.4.4. The ABI in the assessment of diabetes macroischaemia

With the exception of Tehan *et al.*, (2017) who relied on arterial duplex, the studies used standardised doppler ABI < 0.9 as the diagnostic threshold, and were therefore more readily comparable. The major limitations from the reviewed ischaemia investigations are a reliance on the macrosupply and the exclusion of calcified arteries in defining

macroischaemia. Arterial calcifications, when the ABI > 1.2 , give a falsely elevated ABI, even in the presence of ischaemia, and therefore exclusive reliance on the lower ABI threshold underestimates true peripheral ischaemia prevalence which can occur in the presence of arterial calcification. This is, in turn, due to the limitations of the ABI itself, which has been shown to be unreliable in determining ischaemia in diabetes participants. In addition, the ABI is a macroarterial assessment method, but since the macroarteries do not directly deliver blood supply to tissues, the ABI is therefore unable to fully predict healing capacity, nor is it able to detect changes in the microarterial supply that occur in the earlier stages of diabetes (Shapiro and Nouvong, 2011; Gazzarusso *et al.*, 2013; Lalithambika *et al.*, 2014). Indeed, it requires microarterial considerations to explain some paradoxical macroarterial observations, such as an increase in peripheral arterial blood flow in patients with type 2 diabetes (Corbin *et al.*, 1987), and despite an intact macroarterial supply, with good ABI, and detecting no defects, there is localised tissue ischaemia because of micro blockages (Jorneskog, 2012).

More recently Chuter *et al.*, (2020) found the ABI had low sensitivity (0.6, 95% CI = 0.48-0.71; $p = 0.097$), good specificity (0.87, 95% CI = 0.78-0.92; $p < 0.001$) and a diagnostic odds ratio of 9.8 (95%CI= 5.2 – 18.2; $p < 0.0001$), against colour duplex ultrasound, in the assessment of ischaemia in people with diabetes. The lower sensitivity implies that in people with diabetes, the ABI carries a moderate likelihood of giving false negatives, where people with ischaemia are incorrectly classified as non-ischaemic. These limitations mean that the ABI is less valid and reliable in the assessment of ischaemia in people with diabetes, which has been suggested previously (Ozdemir *et al.*, 2013; Trevethan, 2018; Vriens *et al.*, 2018a) and lends support towards alternatives such as the TBI that could be more effective at assessment (Hoyer, Sandermann and Petersen, 2013; Barshes *et al.*, 2016).

1.4.5 The TBI in the assessment of diabetes macroischaemia

Because of the relative sparing of the digital vessels in calcification, the TBI using the hallux has been found to be more reliable than the ABI (Widmer *et al.*, 2012). However the TBI also has limitations in patients with toe amputations, and is a poor predictor of

tissue survival and chronic foot ulceration (Kalani *et al.*, 1999), and there is poor diagnostic data for identifying thresholds for ischaemia (Yamada *et al.*, 2008). There is even less evidence supporting the diagnostic thresholds for the TBI, although most studies set the ischaemia threshold at ≤ 0.7 despite little evidence to support this. Some researchers have used even lower thresholds, for example Park *et al.*, (2012) compared TBI against angiography in 15 people with diabetes (30 limbs), gangrene or claudication. They found a diagnostic threshold of ≤ 0.6 gave an automated TBI system a sensitivity of 100% and specificity of 100%, and all patients with $TBI > 0.6$ showed no evidence of ischaemia on angiography. By contrast, three other investigations set a threshold of $TBI \leq 0.7$, including Weinberg *et al.*, (2013), who compared TBI to digital subtraction angiography (DSA) in 92 patients attending a vascular laboratory. They found that against DSA Trans-Atlantic Inter-Society Consensus II definition for ischaemia, a TBI threshold of ≤ 0.7 had 92% sensitivity, although specificity was not described. Bunte *et al.*, (2015) also compared the TBI to angiography in 31 patients with critical limb ischaemia, and with a TBI threshold ≤ 0.7 , found it had sensitivity of 92% but poor specificity of 17%. Finally, Tehan *et al.*, (2015) assessed 119 patients (73 with diabetes) and compared the TBI against colour doppler ultrasound, and found that a $TBI \leq 0.7$ had sensitivity of 64% and specificity of 82%. The studies largely focused on hospital populations with existing macro-ischaemic complications, but despite similar populations from the above studies it is difficult to determine TBI performance with very broad variations in sensitivity (64% - 100%), specificity (17% - 100%) and different TBI thresholds (0.6; 0.7). This has been raised previously, for example by Hoyer, Sandermann and Petersen (2013), who identified studies with TBI 'normal' lower limits as low as 0.49 (Brooks *et al.*, 2001). More recently, NICE CG147 (National Institute for Health and Care Excellence, 2018) also identified a lack of quality clinical evidence to support the commonly used values (≤ 0.6 , ≤ 0.7 , ≤ 0.75), with the resultant absence of a universally accepted TBI threshold. For the purposes of the ischaemia assessments in Chapter 7, a threshold of $TBI \leq 0.7$ was selected for the sake of comparison with other studies as the most commonly used standard, but bearing the above limitations in mind.

Therefore, the two main macrocirculatory assessment methods themselves face limitations, namely; the ABI being less reliable due to the calcification effects of diabetes

on arterial vessels; the TBI having little evidence to justify the commonly used thresholds, and jointly neither the ABI nor TBI having the ability to detect microcirculatory function and arterial supply quality which plays a role in ulcer healing (Clairotte *et al.*, 2009; Aerden *et al.*, 2011; Eleftheriadou *et al.*, 2019a). Ignoring the role of the microcirculation can give rise to paradoxical observations, as highlighted by Forsythe, Brownrigg and Hinchliffe (2015) and Forsythe and Hinchliffe (2016). They describe studies involving patients who have diabetic foot ulcers and severe macroischaemia managing to heal without vascular intervention (Elgzyri *et al.*, 2013); and others whose ischaemic patients undergo successful re-vascularisation with improvements in ABI/TBI, yet 40% experienced recurrent ulceration within 12 months (Pound *et al.*, 2005). This highlights the complex vascular picture diabetes presents and suggests that apart from the gross quantity of arterial flow volume alone, other factors involving the microcirculation and arterial quality, play a role in wound healing (Forsythe, Brownrigg and Hinchliffe, 2015; Forsythe and Hinchliffe, 2016).

With such limitations surrounding macroischaemia assessments, it has been suggested that rather than primarily assessment the macrocirculation, the local tissue micro-perfusion is also relevant in people who have diabetes, and may be more effective in ischaemia assessment (Alexandrescu *et al.* 2012).

1.4.6 Diabetes Microischaemia

For the purposes of this discussion, the microarterial supply is defined physiologically, as the arterial vessels with a lumen diameter of less than 200 μ m. Previous work established that diabetes blunts the microarterial response to physiological changes (Fromy *et al.*, 2002; Stehouwer, 2018). However, the prevalence of diabetes microischaemia is difficult to establish because of the wide variety of definitions used to describe it. For instance, some classifications include neuropathy, despite evidence to suggest that other mechanisms act as a trigger and neuropathy occurs in parallel with – rather than as a consequence of, microvascular dysfunction (Zochodne, 2014; Cashman and Höke, 2015; Pham *et al.*, 2015; Bussmann and Storkebaum, 2017; Prior *et al.*, 2017). The exact

processes that account for diabetes microcirculatory responses are themselves not fully understood, with the two prominent theories proposing either a haemodynamic or capillary steal hypothesis (Chao and Cheing, 2009; Kabbani *et al.*, 2013).

With respect to the skin, from Figure 1.4.1 (Chapter 1, Section 1.4.1, page 33), the haemodynamic hypothesis suggests that due to chronic hyperglycaemia, the blood is more dense, and the microvascular structures such as the basement membrane thicken in response. This makes it more difficult for nutrients and messaging cytokines to diffuse through, and the microvasculature becomes less responsive to local tissue changes. The thickened basement membrane narrows the flow channel, and along with increased blood viscosity, leads to microarterial blockages (Figure 1.4.2 in Chapter 1, Section 1.4.2, page 35) with resulting localised tissue ischaemia (Chao and Cheing, 2009).

As an alternative, the capillary steal hypothesis was proposed to account for the paradoxical increase in peripheral circulation in people with diabetic neuropathic ulcers (Østergaard *et al.*, 2015). In order to understand capillary steal, it is necessary to outline the skin and its microvasculature, as shown in Figure 1.4.5.

Figure 1.4.5: Showing Skin Microvasculature

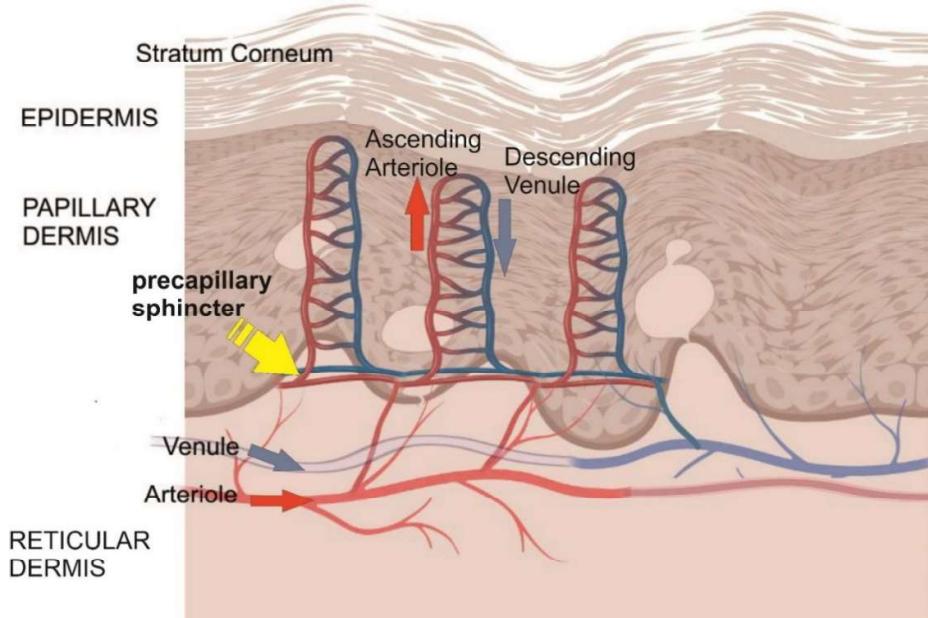


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The capillary steal hypothesis proposes that autonomic denervation results in loss of vasoconstriction, with dysfunction of the arterio-venous shunts and precapillary sphincter, as shown in Figure 1.4.5 (Chao and Cheing, 2009). This leads to blood being diverted away from the ascending arterioles and away from the papillary dermis which, despite increasing the macrocirculatory pool in the reticular dermis, results in net localised tissue ischaemia (Krishnan *et al.*, 2004; Krishnan G., 2006; Lanting, Barwick, *et al.*, 2017; Lanting, Twigg, *et al.*, 2017). These observations have been reported in tissues of diabetes patients post-injury (Jorneskog, Brismar and Fagrell, 1995; Lanting, Barwick, *et al.*, 2017).

Both the haemodynamic and capillary steal theories therefore have their proponents, and it is likely that both pathways overlap in microischaemia but dominate at different stages of diabetes; with the haemodynamic process being more dominant prior to microvascular injury, and later the capillary steal process making it more difficult to recover the capillary circulation as earlier suggested by Jorneskog, Brismar and Fagrell (1995).

Early damage from hyperglycaemia has been found to affect capillary flow in the feet of people who have diabetes and in turn affecting nutrient delivery and clearance, which makes the feet more vulnerable to ulceration and reducing their healing capacity (Kabbani *et al.*, 2013). According to Flynn and Tooke (1992), the dermal microvasculature is made up of two main components; namely, a nutritive capillary flow (10-20% of total skin blood flow) and a thermoregulatory arteriovenous shunt flow (80-90%), controlled by both sympathetic vasoconstrictor and vasodilator nerves depending on anatomical location (dorsal or plantar) (Chao, Zheng and Cheing, 2012). In glabrous skin, which lines the plantar aspect of the foot, the skin layers are thicker and the microcirculation is composed of highly innervated arteriovenous anastomoses under the control of sympathetic vasoconstrictor nerves. In contrast, within the non-glabrous hairy skin on the dorsum of the foot, the arteriovenous anastomoses are sparse, but innervated by both sympathetic vasodilator and vasoconstrictor nerves (Machado-Moreira and Taylor, 2012). Under normal temperature conditions, the arterioles are kept under vasoconstriction, but this changes in response to a challenge such as infection, trauma or heat, whereupon vasodilation occurs and oxygen delivery to surrounding tissues increases. This mechanism becomes impaired with the loss of autonomic control (Type C denervation) as

occurs in diabetes. Further to this, the other diabetic microvascular effects such as basement membrane thickening and alteration of mediated responses to trauma or heat, mean capillary oxygenation is reduced when compared to that detected in the feet of individuals who do not have diabetes (de Meijer *et al.*, 2008). It is therefore possible to detect this reduction in transcutaneous capillary oxygenation, and impaired tissue oxygenation has been found to be an independent risk factor for diabetic foot ulceration (Ladurner *et al.*, 2010).

1.4.7 Assessment of microcirculation: Transcutaneous Oxygen in Detecting Microischaemia

The direct assessment of the microcirculation has proven difficult, with the capillary refill assessment being poorly reliable (Boyko *et al.*, 1997; Chang *et al.*, 2013), and more direct methods such as skin puncture being invasive, further risking ulcerating the patient (Shapiro and Nouvong, 2011). Quicker indirect ways of determining local tissue perfusion involve measuring transcutaneous oxygen tension ($TcPO_2$).

The skin is suited for the monitoring of ischaemia as it is readily accessible and skin physiology gives direct indications of underlying local parameters such as metabolic activity and blood and oxygen supply (Löndahl *et al.*, 2011; Houben, Martens and Stehouwer, 2017; Marcoccia *et al.*, 2020). $TcPO_2$ detection was developed in neonatology, where the chest skin was used to determine oxygen levels in new born infants (Eberhard *et al.*, 1975). Tremper and Huxtable (1978) showed that applying heat to the skin resulted in vasodilation with increased capillary blood flow, and loosened the lipid structures within the stratum corneum, which improved diffusion and increased dermal oxygen levels. When the arterial supply is compromised however, these responses are impaired, and $TcPO_2$ can therefore be used to distinguish between ischaemic and non-ischaemic states. Dowd, Linge and Bentley (1983) examined $TcPO_2$ in 62 participants with three different levels of ischaemia, and compared these to 161 healthy participants with a 45mmHg diagnostic threshold, and found lower $TcPO_2$ levels with increasing severity of ischaemia. They found 24% had ≤ 45 mmHg if they had intermittent claudication but no other skin signs (15 participants) ; 93% were below 45mmHg if they had claudication and

skin changes but no gangrene (14 participants) ; and 100% had less than 45mmHg if gangrene was present (all 33 participants). A fourth group elected to undergo amputation (24 participants), and it was observed that those whose $TcPO_2$ was ≥ 40 mmHg healed (14 participants), whilst all participants with ≤ 40 mmHg (10 participants) failed to heal. Despite the subjective classification of ischaemia used in this study, Dowd, Linge and Bentley (1983) proved that $TcPO_2$ could be used to distinguish between different levels of ischaemia and predict healing potential. Pecoraro *et al.*, (1991) went further and investigated whether $TcPO_2$ status in 46 participants with diabetes had an impact on ulcer healing time. They found that 38 participants had $TcPO_2$ levels of 56.3 mmHg, and their foot ulcers healed within 4 weeks, whilst for the remaining 8 participants, with a mean $TcPO_2$ of 26.9 mmHg, their foot ulcers failed to heal within the same period. The difference between the healing and non-healing groups was significant ($p = 0.003$), and the early healing group had significantly higher rates of epithelialisation ($p = 0.04$). They also determined the risk ratio, and calculated that in participants with $TcPO_2 \leq 20$ mmHg , there was a 39 fold risk of early healing failure (RR = 39; 95% CI: 2.8 – 1211; $p = 0.001$). Whilst these results were promising, the small sample and the very wide confidence interval weaken the study's external validity and it is difficult to determine the extent to which $TcPO_2$ alone had on predicting risk and healing potential. More recently, Pawlaczyk-Gabriel *et al.*, (2014) sought to characterise microcirculatory changes 216 people with different grades of ischaemia based on the Rutherford scale, against 27 controls. Control participants had the highest values ($TcPO_2$ of 64.3 mmHg); in contrast to both Rutherford class 0-1 (79 participants; $TcPO_2 = 47.5$ mmHg), and Rutherford class 3-4 (137 participants; $TcPO_2 = 19.8$ mmHg) with all $TcPO_2$ group differences significant at $p < 0.001$. There were 60 people with diabetes unevenly spread across the 3 groups, and it is unclear what type of diabetes, or impact this had on the results, which limits this study's applicability in people with diabetes.

Taken together however, the three studies show that $TcPO_2$ can be used to distinguish between different severities of ischaemia and it could potentially estimate healing time and healing capacity.

1.4.8 Transcutaneous Oxygen Sensor Mode of Action – Clark Type probe

The most common mechanism by which transcutaneous oxygen is measured is based on the Clark type probe, as shown in Figure 1.4.6. At normal skin temperatures, capillary oxygen diffusion rate is too slow to give reliable readings, but Tremper and Huxtable (1978), and Hutchison, Rocca and Honeybourne (1981) showed that raising this to over 42°C results in hyperaemia, increasing oxygen delivery and raising diffusion to detectable levels. The oxygen left over from local metabolic activity as it passes through the dermal layers, diffuses to the skin surface and it has been found to reach equilibrium after about 15-20 minutes (W Deng *et al.*, 2014). At the skin surface, a probe detects the amount of oxygen, which, after about 10-15 minutes, stabilises and directly correlates to the arterial supply at these temperatures, which was found by Hutchison, Rocca and Honeybourne (1981) to have strong correlation ($r = 0.9$; $p < 0.001$).

Figure 1.4.6: Showing oxygen detection by Clark type $TcPO_2$ probe on the skin

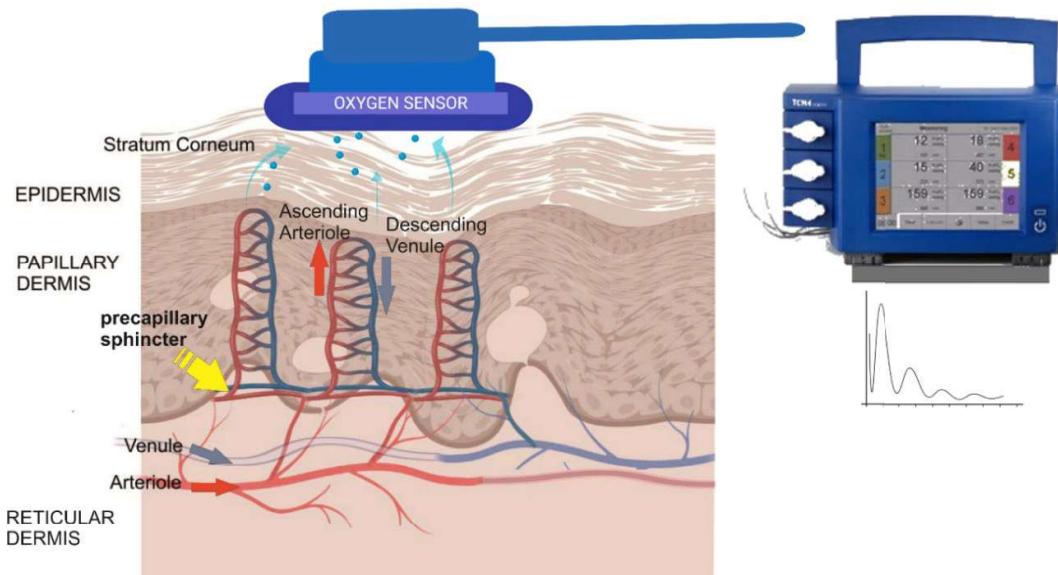


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Skin structure is different depending on its location and the functional requirements of the aspect of the body. On the foot, skin at the plantar aspect bears body weight and is therefore thicker, with capillaries lying deeper, and oxygen consumption in the dermal

layers is higher (Shapiro and Nouvong 2011a). This means less of the deeper underlying parameters, such as blood arterial supply and oxygen levels, permeate through to the skin surface to be detected, leaving plantar foot skin oximetry readings being less representative of underlying microarterial oxygen. This was demonstrated by Smith *et al.*, (1995), who compared TcPO₂ readings from the dorsal and plantar aspects of feet in 656 participants with diabetes when the foot was warmed to 44°C, and found, with arterial dilation, increased arterial delivery and oxygen levels, the dorsum toe and metatarsal head TcPO₂ levels increased by a mean of +35.6 mmHg (95% CI: 34.2-37). In contrast plantar toe and plantar metatarsal TcPO₂ levels simultaneously and unexpectedly dropped by - 8.8 mmHg (95% CI: 7.7 – 9.9), showing that plantar skin readings may be less representative of the underlying true physiological state than dorsal readings.

The most common method of TcPO₂ detection uses a modified electrochemical, so called 'Clark type' - electrode sensor with an integrated skin heater. However, these Clark type sensors are affected by lengthy setups of up to 10 minutes, with additional time for calibration, suffer from falsely elevated readings due to 'measurement drift' (Urban *et al.*, 2015), and are less reliable in areas surrounded by inflammation and infection (Williams, Price and Harding, 2006). They also require costly peripherals such as membranes, complex calibration and specialised software to interpret the waveforms. The Clark type sensors are very sensitive to movement, moisture and temperature fluctuations therefore they risk becoming less practical in a clinical examination room, which are rarely as controlled as in a laboratory setting (Oriani *et al.*, 1996; Kalani *et al.*, 1999; W Deng *et al.*, 2014). In addition, probe calibration and changing membranes are time consuming and prone to inducing errors and probe damage. The validity of a photochemical sensor – Medicap (Medicap Précise 8001; Medicap Homecare GmbH, Ulrichstein, Germany; Moor instruments), against the reference electrochemical, Clark type sensor (TCM400 Radiometer®), is outlined in Chapter 5. The potential advantages of the photochemical technique are that the system comes readily calibrated, and sensor cleaning is easy without the requirement for membrane change. According to the manufacturer the Medicap is also designed to be more portable, and quicker to set up and run.

This section highlights two aspects; broadly for the need to establish TcPO₂ as a potential microischaemic assessment alongside the recommended macroischaemic standards in

people with type 2 diabetes; and secondly for the need to investigate the performance of a novel type of photochemical sensor which may offer advantages over the established Clark type.

1.5 Diabetes Foot Ulceration.

1.5.1 The diabetes foot ulcer.

A diabetic foot ulcer is a chronic wound, commonly on pressure points such as the plantar foot aspect or apex of the toes, that precipitates in patients with diabetes as a result of multiple factors, and often presents as neuropathic or neuroischaemic in nature (Lepantalo *et al.*, 2011). Boulton (2006) describes the Rothman model, which outlines the pathway to ulceration as a combination of ischaemia, neuropathy and trauma as risk factors; with later authors recognising foot deformity and infection as additional factors that combine to precipitate chronic ulceration (Lepantalo *et al.* 2011). Summarising the preceding sections of this introductory chapter it is possible to outline the cascade of events that lead to diabetes foot ulceration. From Section 1.3, the biggest risk factor in diabetic foot injury is the manifestation of sensory neuropathy, which predisposes the foot to trauma (Vinik *et al.*, 2008; Monteiro-Soares *et al.*, 2012; Alavi *et al.*, 2014a). As detailed in sections 1.4.1 and 1.4.2, ischaemia affects both the micro and macro circulation with the arterial supply being the biggest determinant of healing capacity, and the microcirculation playing a key role particularly in local nutrient delivery to facilitate healing (Alavi *et al.*, 2014a; Sharma, Schaper and Rayman, 2019). Once injured, arteriosclerosis, alongside endothelial cell dysfunction, basement membrane thickening, and microcirculatory impairment, results in a defective arterial supply (Alavi *et al.* 2014a). This impairs healing of the injury and promotes wound chronicity as it affects the delivery of repair nutrients to the damaged tissue, slowing the immune response, and allows persistent infection (Alavi *et al.*, 2014a; Spichler *et al.*, 2015). The state of chronicity, with or without resultant infection, increases arterial demand that exceeds the capacity of the compromised circulation, which exacerbates ischaemic ulceration and the risk of amputation (Prompers *et al.*, 2007; Alavi *et al.*, 2014a). Therefore the diabetic

foot ulcer is a consequence of multiple precipitating factors, primarily neuropathy which predisposes the foot to injury, and ischaemia which impairs healing.

Neuropathy and ischaemia have been identified as key risk factors responsible for ulcerations, amputations and deaths in people with diabetes (Alavi *et al.*, 2014b; Armstrong *et al.*, 2020).

1.5.2 Potential association between neuropathy and ischaemia in diabetes foot ulceration

Previous work has also established associations between large nerve fibre function and arterial flow, where McCormick *et al.*, (2015) found that loss of vibration perception was significantly associated with an increase in arterial flux ratio (β coefficient -0.074 ; 95% CI -0.13 , -0.02], $p=0.01$). Other investigations had provided descriptions of vasa nervorum physiological abnormalities being associated with nerve changes. Williams *et al.*, (1980), found endothelial hyperplasia affecting microcirculatory flow to sural nerve fibres on 11 patients, which was later confirmed by Timperley *et al.*, (1985) on 10 patients with type 2 diabetes. Giannini and Dyck, (1995) found that in these participants, the basement membrane had thickened. The effect of nutritional supply on nerve morphology was further suggested by Malik *et al.*, (2005) who observed segmental demyelination of the sural nerve axons alongside basement membrane thickening on 11 participants. These early studies are challenged by modest samples (≤ 11 participants), some of which were not age or gender matched, and add to the assumption that neuropathy is of microangiopathic aetiology, earlier discussed in section 1.3.5 (pages 21-22). Although this assumption is not conclusive, with other evidence suggesting parallel processes that damage nerve fibres (Zochodne, Ramji and Toth, 2008; Zochodne, 2015; Masaki Kobayashi and Zochodne, 2018); the studies are consistent in finding that changes to the sural nerve vasa nervorum occur alongside changes in nerve morphology in people with type 2 diabetes. It is then possible to envisage how these processes would effectively “starve” the sural nerve fibres of growth factors and nutrients necessary for growth, repair and maintenance of the myelin sheaths and hinder recycling of by-products – which are the hallmarks of subclinical neuropathy (Dyck *et al.*, 1986; Weisman *et al.*,

2013; Perkins and Bril, 2014; Kobayashi and Zochodne, 2018), resulting in changes that can potentially be detected by nerve conduction.

Not only does it suggest a link between micro-ischaemic changes to subclinical nerve function, but also the reverse; with nerve conduction (DPNCheck®) potentially acting as a proxy for microcirculation, echoing earlier suggestions by Flynn and Tooke (1995).

Subsequent investigations by Cusick *et al.*, (2005) on 3,711 participants found that increased severity of neuropathy, and micro and macrovascular disease, were associated with greater risk of death at 5 years, with 18.9% (95% CI (17.2–20.6)) all cause mortality amongst those with type 2 diabetes. More recently Chammas, Hill and Edmonds, (2016) investigated the causes of death amongst 364 participants (243 with diabetes foot ulcer – matched with 121 diabetes non-ulcerated controls) over 11 years. Ischaemic heart disease was the major cause of death, and those with foot ulcers died 5 years earlier (68.2 ± 8.7 years) compared to controls (73.1 ± 8 years, $p = 0.02$). They determined that those with diabetes foot ulcers faced a more than doubled risk of mortality compared to the control group, and death due to ischaemic heart disease was significantly linked to neuropathic foot ulcers (OR 3.1, 95% CI 1–9.4, $p = 0.05$). Neuropathy could therefore play a more prominent role in vascular disease and death than previously envisaged.

With nerve function having strong associations with both metabolic (BMI, HbA1c) and vascular (basement membrane thickening; cardiovascular mortality) parameters, it is therefore important to pick up subclinical neuropathy at a stage where the therapeutic window is broad enough for interventions to be effective. Detecting subclinical neuropathy would allow for earlier and more aggressive interventions targeting control of these risk factors (HbA1c, blood pressure, BMI) that could arrest neuropathy progression and prevent subsequent ulcerations, amputations and deaths. Rather than wait to treat the later complications, the aims of this doctoral thesis are driven by the need for a clinical focus on the earlier identification of neuroischaemia, to give time to implement measures that could prevent these complications in the first instance.

1.6 Diabetes Foot Neuroischaemia Assessments

1.6.1 Diabetes foot screening and diabetes foot assessment

Often in the literature, the terms assessment, screening and diagnosis are used interchangeably. Screening can be defined as an application of tests that take a snapshot and estimate the state of health on an otherwise healthy population (Goodie and Wilfong, 2019) . This is done for the purposes of classifying those who are either likely or unlikely to have a particular condition, with those suspected being further referred for confirmatory tests for a diagnosis. Assessment can be defined as a process of gathering information over time in order to quantify the nature of a health condition, determine a diagnosis, and developing or justifying the relevant treatment to address the diagnosed condition. More detailed investigations can be carried out, and therefore several snapshots of a person's health are taken over the assessment phase in order to build a more comprehensive picture to help with accurate diagnosis and the administration of the appropriate treatment. This can be summarised as shown in Figure 1.6.1.

Figure 1.6.1. Showing the differences between screening, assessment and diagnosis.

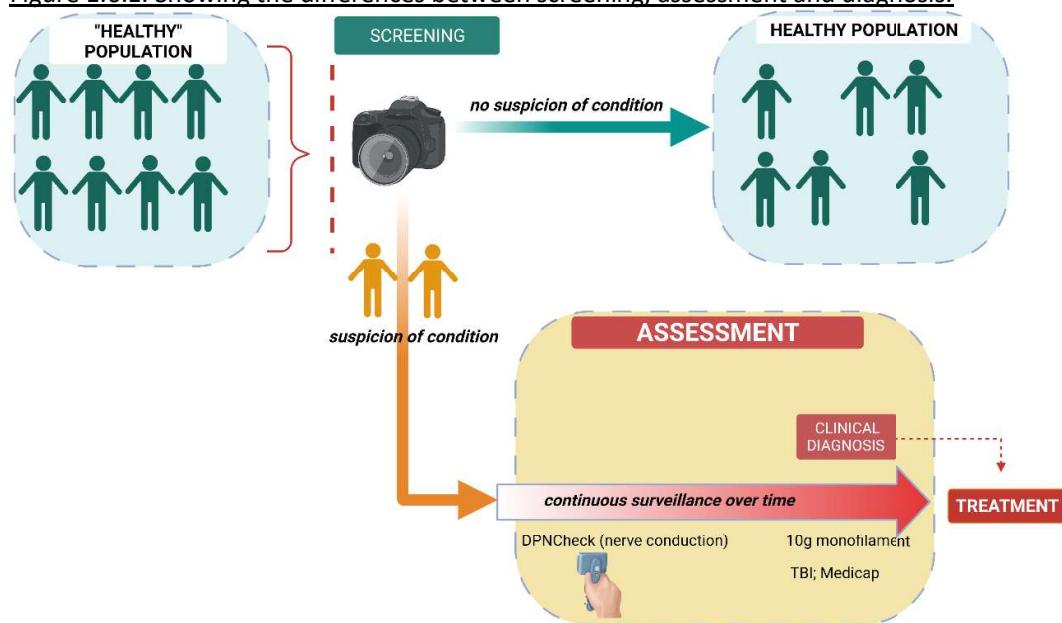


Image: Author's own. Created with Biorender.com

With regards to neuropathy in general, people who have been diagnosed with type 2 diabetes are screened for retinopathy, but with regards to foot ulceration risk specifically, it can be argued that people forgo the screening phase and enter into a phase of constant surveillance where they are periodically assessed for neuropathic (usually with the 10g monofilament) and ischaemic (ABI/TBI) changes. Once these become manifest, this elevates the person's risk status and more aggressive and intensive management is justified. However it is often too late for these to be effective in preventing deterioration, with consequent progression towards ulceration, amputation and death. This thesis targets people who have already been diagnosed with type 2 diabetes, and investigates the effectiveness of the devices (DPNCheck and Medicap), during the surveillance phase. Therefore for the purposes of classification, these can be described as assessment – rather than screening devices.

1.6.2 Diabetes foot assessments: NICE NG19 Guidelines

From section 1.5.1, current guidelines by the NICE NG19 (2015) on the management of the diabetic foot are therefore constructed around determining the risk of ulceration (neuropathy) and estimating healing potential (ischaemia). These in turn are utilised during the diabetes foot assessment following NICE NG19 recommendations; for neuropathy determined by either a 10g monofilament (Semmes-Weinstein) or 128 Hz tuning fork (Rydel-Seiffer); and determining limb ischaemia by palpation, hand held doppler or the ankle brachial pressure index (ABI). Taken together, these neuroischaemic assessments become the key determinants on a patient's risk of developing an active diabetes related foot problem, which can be stratified according to Table 1.6.1.

Table 1.6.1: Showing risk stratification according to NICE Guidelines NG19 (2015).

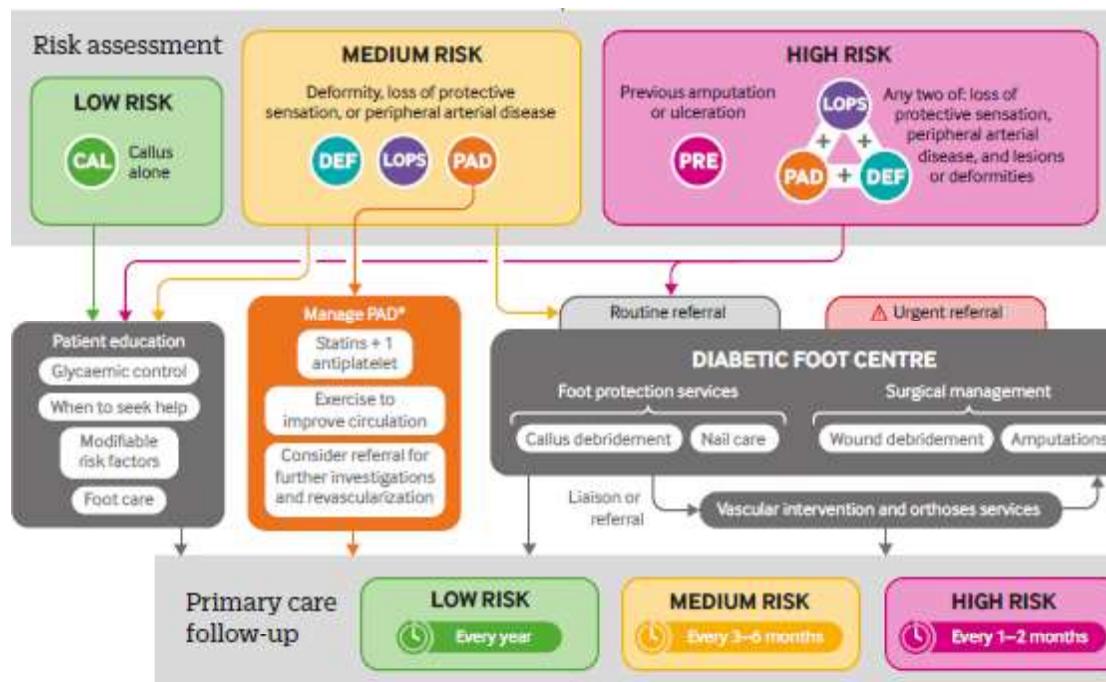
	Neurological Function	Vascular Function	Other Factors
LOW RISK	No sensory deficit	Pedal pulses present	Callus may be present
MEDIUM or INCREASED RISK	Either neurological or mild vascular deficit (mild limb ischaemia)		Foot deformity; Callus
HIGH RISK	Neurological and Vascular deficit Neurological or Vascular deficit in combination with other factors		Previous ulceration Previous amputation Chronic kidney disease Foot deformity.
ULCERATED	(Active Diabetic Foot Problem)		

The NICE NG19 (2015) recommendations are designed to be practical, simple to conduct and quickly and accurately determine a patient's risk of developing a diabetic foot problem, which then affects the management approach towards their care. An important aspect of this is that the early identification of a patient's risk status would allow for earlier intervention, such as tighter glycaemic control, modification of other vascular risk factors and enhanced patient engagement, to help delay or prevent the advancement to active foot ulceration, amputation and death. Each component of the neuroischaemic assessment however presents challenges. For instance the sensory neurological assessments are poorly standardised, rely on subjective responses, remain vulnerable to operator variability and are poorly sensitive at identifying early neuropathy (Won and Park, 2016). The assessment of ischaemia is heavily focused on the macrosupply, despite the ABI being less reliable in diabetes patients and the TBI having varying reference values with little supporting evidence (Shapiro and Nouvong, 2011; Eiken *et al.*, 2019; Chuter *et al.*, 2020). Therefore it is emerging that the NICE NG19 (2015) recommended assessments may not be effective enough to use for the early assessment of neuroischaemia (Williams, Harding and Price, 2005; Potier *et al.*, 2009; Arad *et al.*, 2011; Tehan *et al.*, 2015; Brown *et al.*, 2017, Trevetahn, 2018) which has consequential effects on early intervention strategies.

1.7 The Importance of Early and Accurate Assessment of Neuroischaemia in People with Type 2 Diabetes.

The importance of early and accurate risk stratification is underlined by the fact that a person's risk status guides the extent of clinician contact, input, and foot health management (Figure 1.7.1), which are key factors in determining individual mortality (Simmons and Zgibor, 2017).

Figure 1.7.1: Showing Risk Stratification and Management of Type 2 Diabetes Patients



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There is evidence supporting early intervention regarding lifestyle changes (Bailey *et al.*, 2005; Tuomilehto and Schwarz, 2016), exercise (Gerhard-Herman *et al.*, 2017), early metformin use (Aroda *et al.*, 2017), and other forms of improving glycaemic control in people with type 2 diabetes (Chatterjee, Khunti and Davies, 2017), that prevent or delay ulceration, amputation and mortality (Cefalu *et al.*, 2016; Barry *et al.*, 2017; Dy, Bennett and Sharma, 2017). Due to the respective subjective components and variability in application, the current assessment approaches for neuroischaemia could have impaired ability to detect dysfunction (Williams, Harding and Price, 2005; Potier *et al.*, 2009; Arad *et al.*, 2011; Tehan *et al.*, 2015; Brown *et al.*, 2017; Trevethan, 2018). These approaches therefore likely underestimate risk; and poorly risk stratify individuals during the early stages of diabetes neuroischaemia, leading to delays and effectively narrowing or shutting the early “intervention window”. This leaves those who are in fact at a higher risk status being misclassified and treated as lower risk, with limited access to more intensive management provided to known higher risk individuals. The current health service guidelines – built around the NICE ‘Footcare for people with diabetes’ pathway – suggest a wait for a change in the risk status, either from when neuroischaemic changes become evident in the later stages of diabetes - or until the person develops an ulcer; to justify more intensive intervention (NICE 2020). To detect this change, annual assessments are undertaken in community by GP surgeries, and mostly funded under the Quality Outcomes Framework (QOF) outlined in section 1.1.

By the time change in risk status is detected it may be too late to implement effective preventative strategies. The objective nerve conduction and TcPO₂ devices have the potential to accurately determine an individual's' risk status in the early stages of diabetes, potentially ahead of the current NICE NG19 recommended methods, thus ‘buying time’ for preventative clinical management.

1.8 Problem Statement

Individuals who have diabetes require earlier identification of neuropathy and ischaemia, with objective methods that can both identify dysfunction and monitor progression

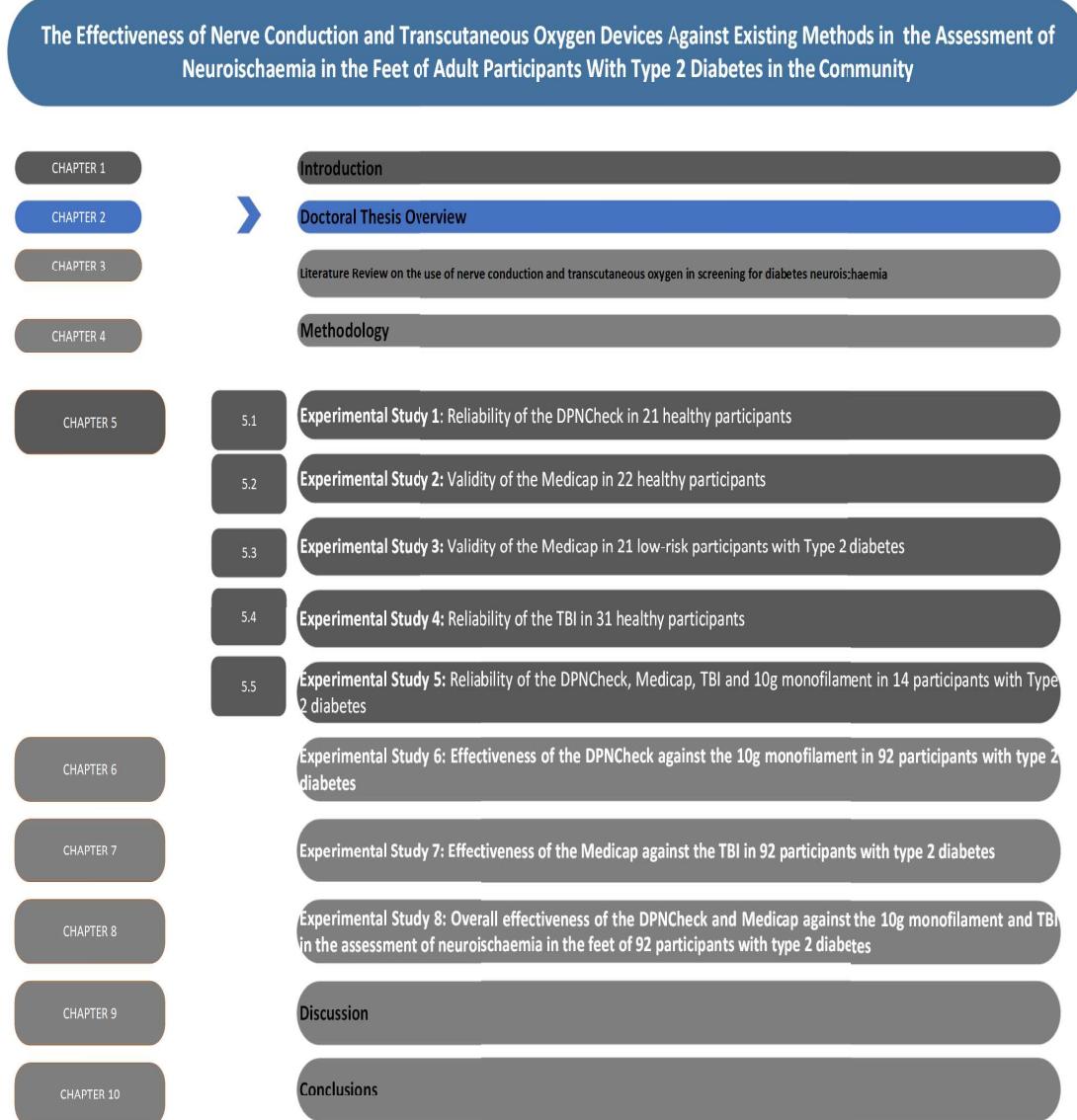
better and at an earlier stage of diabetes than existing methods. It is the purpose of this doctoral thesis to investigate the extent to which nerve conduction (NCstat® DPNCheck®; Neurometrix, Inc., Waltham, MA, USA) and TcPO₂ (Medicap Homecare GmbH, Ulrichstein, Germany; Moor instruments) can detect neuropathy and ischaemia, respectively, in individuals who have type 2 diabetes when compared against NICE NG19 (2015) recommended approaches. The nerve conduction and TcPO₂ devices have the potential to provide earlier detection of neuropathy and ischaemia, and help in the earlier identification and accurate risk stratification, and therefore earlier intervention, of patients at risk of ulceration. In addition, the standardised approach to these devices could reduce subjective application and interpretation, and reduce regional variations in assessment approaches that disproportionately penalise those from ethnic minorities (Davis, 2008) and in areas of social deprivation, with consequent variation in ulcerations, healing times, amputations and deaths. Overall, these proposed new assessment devices could improve the effectiveness of measures such as patient empowerment towards making informed choices, and influence decision making and service planning and overall improve clinical management. It is hypothesised that these devices are more effective in the assessment of neuroischaemia than current methods. Therefore the overall aim of this doctoral thesis is to determine the effectiveness of nerve conduction and TcPO₂, as methods that can be used in the assessment of neuroischaemia and identification of ulceration risk in people with type 2 diabetes when compared to existing NICE NG19 (2015) approaches.

Chapter 2 DOCTORAL THESIS OVERVIEW

This doctoral thesis explores the effectiveness of objective assessment tools for neuropathy and ischaemia, against those advocated by NICE NG19 (2015). Chapter 1 broadly outlined the development of the objective assessment tools to be investigated in this doctoral thesis, namely; nerve conduction for neuropathy and TcPO₂ for ischaemia; and their potential advantages over current approaches. Chapter 1 also highlighted the scale of the problem caused by diabetes foot ulceration, alongside the potential limitations of current assessment methods, and the contributions by diabetes neuropathy and ischaemia to ulceration risk and stratification. This chapter provides a summary of the doctoral journey and an overview of the doctoral thesis, before a structured review of current literature on nerve conduction and TcPO₂ in the assessment of neuropathy and ischaemia respectively in Chapter 3. The methodological approach to the proposed overall investigation is described in Chapter 4, which includes investigations into reliability and validity of the devices (Chapter 5) before the individual neuropathy (Chapter 6) and ischaemia (Chapter 7) experimental investigations. Chapter 8 provides overall results of the nerve conduction (DPNCheck®) and TcPO₂ (Medicap) devices both jointly and against their respective counterparts. These precede discussions on the findings, clinical implications, the study's limitations and future research proposals all outlined in Chapter 9, and the conclusions in Chapter 10.

An overview of this chapter within the context of the doctoral thesis, is shown in Figure 2.1.

Figure 2.1. Representation of an overview of the doctoral thesis



2.1 Aim

The overall aim of this doctoral thesis is to determine the effectiveness of the DPNCheck® and Medicap devices in the assessment of neuroischaemia in people with type 2 diabetes, when compared to existing NICE NG19 (2015) clinical methods.

2.2 Primary Research Questions

2.2.1 Is the DPNCheck® more effective in the assessment of sensory neuropathy in a podiatry clinic when compared to the 10g monofilament?

2.2.2. Is the Medicap more effective in the assessment of ischaemia in a podiatry clinic when compared to the TBI?

2.3 Primary Research Objectives

The objectives of the study are to assess the clinical effectiveness of using the DPNCheck® (nerve conduction device) in the assessment of sensory neuropathy; and the Medicap (TcPO₂ device) in the assessment of ischaemia, in a podiatry clinic setting in people with type 2 diabetes, when compared to the recommended methods according to NICE NG19 (2015).

If demonstrated to be effective, the evidence can be used to suggest recommendations that could improve the early assessment of diabetic foot neuroischaemia. More effective assessment can be used to better determine foot ulceration risk status and can advance diabetic foot health service delivery models across the United Kingdom. The following primary research questions will enable this doctoral thesis to meet the above objectives.

2.3.1. To identify the knowledge gaps on the use of nerve conduction and TcPO₂ as neurological (DPNCheck®) and ischaemia (Medicap) assessment methods in people with type 2 diabetes.

2.3.2. To assess in the feet of patients with type 2 diabetes, whether the DPNCheck® is more effective in the assessment of sensory neuropathy compared to the 10g monofilament.

2.3.3. To assess in the feet of patients with type 2 diabetes, whether TcPO₂ is more effective in the assessment of ischaemia when compared to the TBI.

2.4 Primary Outcome Measures

The primary outcome measure is the numbers of people suspected of having:

- 2.4.1 **neuropathy** (DPNCheck® vs 10g monofilament); and/or
- 2.4.2 **ischaemia** (Medicap vs TBI);

based on the respective assessments. The additional investigations and the corresponding aims and objectives are therefore as follows:

2.5 Secondary Research Questions

- 2.5.1 Overall, what is the effectiveness of the DPNCheck® and Medicap, in determining the risk status of people with type 2 diabetes in the community, when compared to current guidelines (NICE CG19) 2015.

2.6 Secondary Research Objectives

- 2.6.1 To determine whether the combined use of (nerve conduction + TcPO₂) is more effective at identifying people with neuropathy and/or ischaemia than the combined NICE NG19 recommended methods (10g monofilament + TBI)

- 2.6.2 To determine whether the detection of neuropathy using nerve conduction alone is more effective at identifying people 'at risk' (with neuropathy and/or ischaemia) than the combined recommended methods (10g monofilament + TBI)

- 2.6.3 To determine whether the detection of ischaemia using TcPO₂ alone is more effective at identifying people 'at risk' (with neuropathy and/or ischaemia) than the combined recommended methods (10g monofilament + TBI).

- 2.6.4 To determine whether people with ischaemia, have nerve conduction impairment.

- 2.6.5 To determine whether people with nerve conduction impairment, have ischaemia

- 2.6.6 To determine the effect of ankle circumference on nerve conduction values.

2.7 Secondary Outcome Measures

2.7.1 The numbers of people identified as having neuropathy and/or ischaemia based on combined nerve conduction and TcPO₂, compared to those identified as having neuropathy and/or ischaemia based on the 10g monofilament and TBI.

2.7.2 The numbers of people identified as having neuropathy by nerve conduction alone; compared to the number of people identified with neuropathy and/or ischaemia based on the combined recommended methods (10g monofilament and TBI).

2.7.3 The number of people identified as having ischaemia by TcPO₂ alone; compared to the number of people identified with neuropathy and/or ischaemia based on the combined recommended methods (10g monofilament and TBI)

2.7.4 The nerve conduction values of the people identified with ischaemia.

2.7.5 The TcPO₂ and TBI values of those identified with nerve conduction impairment.

2.7.6 Correlate the ankle circumferences to nerve conduction values.

2.8 Doctoral Thesis Overview

2.8.1 Literature Review (Chapter 3)

The literature review in Chapter 3 (page 65) provides a theoretical justification and identifies gaps in knowledge, on the use of nerve conduction and TcPO₂ devices in the assessment of diabetes neuroischaemia. Any identified knowledge gaps in the use of these devices, will then be incorporated into the study design outlined in Chapter 4 (page 82), in addition to how the combined use of TcPO₂ and nerve conduction introduces a novel aspect to the project.

2.8.2 Reliability and Validity Experimental Studies (Chapter 5)

From the literature review in Chapter 3 (page 65), it was identified that the DPNCheck® had undergone previous investigations to establish its validity and reliability, whilst the Medicap was a more novel device. This therefore determined the reliability and validity investigations outlined in Chapter 5 (page 107), in the following series of experimental studies:

Chapter 5.1: Experimental Study 1: (page 111) investigates the reliability of the DPNCheck® in healthy participants, and compares it against published data

Chapter 5.2: Experimental Study 2: (page 118) investigates the validity of the Medicap in healthy participants.

Chapter 5.3: Experimental Study 3: (page 134) builds on experimental study 2, and investigates the validity of the Medicap in participants with type 2 diabetes classified as low risk of ulceration according to NICE guidelines (NG19).

Chapter 5.4: Experimental Study 4: (page 145) to determine the reliability of the TBI in healthy participants.

Chapter 5.5: Experimental Study 5: (page 153) to determine the reliability of the DPNCheck®, Medicap, 10g monofilament and TBI in 14 participants with Type 2 diabetes.

Building on from these reliability and validity experimental studies, the following experimental studies aimed to answer the primary doctoral research questions:

2.8.3 Experimental studies to answer the primary research questions

Chapter 6: Experimental Study 6: (page 164) to determine the effectiveness of the DPNCheck® in the assessment of sensory neuropathy against the 10g monofilament in participants with type 2 diabetes.

Chapter 7: Experimental Study 7: (page 173) to determine the effectiveness of the Medicap in the assessment of ischaemia against the TBI in participants with type 2 diabetes.

2.8.4 The overall results are summarised in **Chapter 8** (page 184)

2.8.5 **Chapter 9** (page 223) provides a discussion on the findings from the experimental studies, along with the clinical implications, limitations, and proposals for future research.

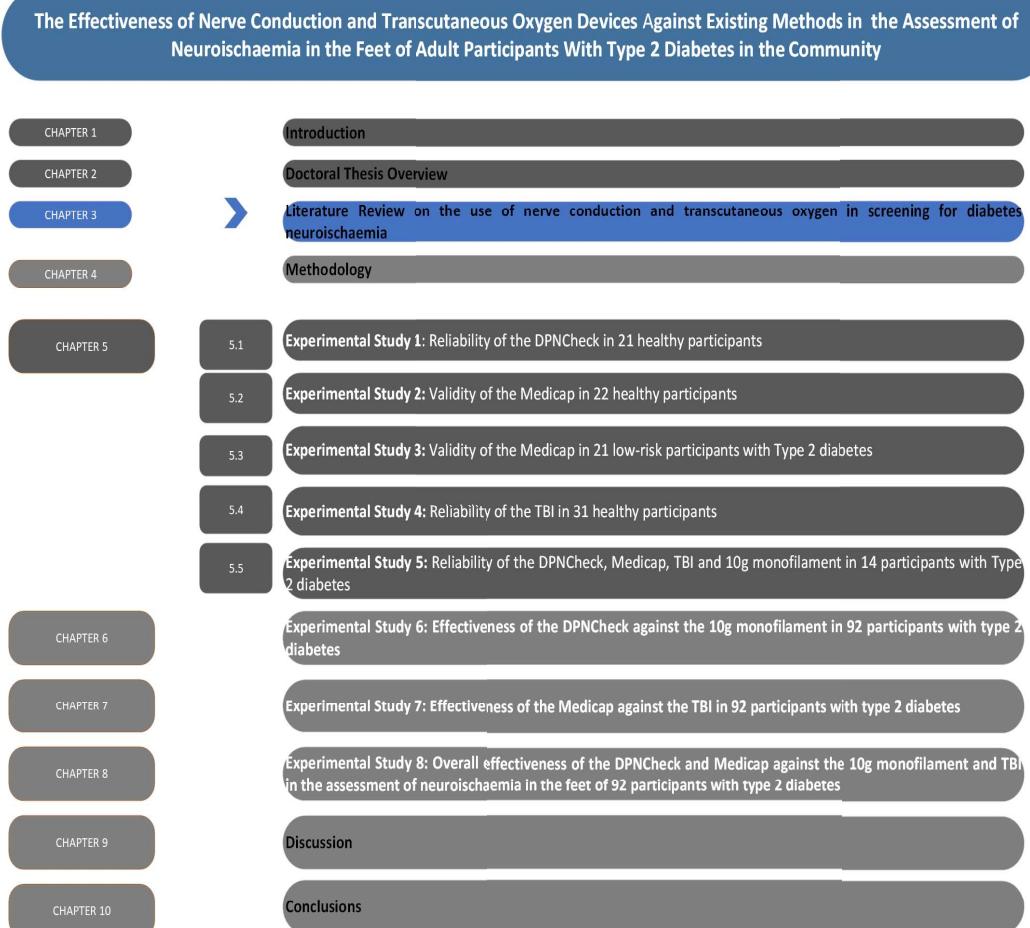
2.8.6 **Chapter 10** (page 238) summarises the conclusions from the overall thesis following the experimental investigations.

Chapter 3 LITERATURE REVIEW ON NERVE CONDUCTION AND TRANSCUTANEOUS OXYGEN IN THE ASSESSMENT OF DIABETES NEUROISCHAEMIA

3.1 Introduction

Through Chapter 1, the problem statement pertaining to the importance of earlier and accurate assessment of neuropathy and ischaemia in people with type 2 diabetes was introduced (section 1.8, page 56). Chapter 2 outlined the primary and secondary research questions and objectives, and gives an overview of this doctoral thesis, which leads to a structured review of the literature, as shown Figure 3.1.

Figure 3.1: Showing Chapter 3 within the thesis context.



This chapter goes on to provide a structured critical review of the academic literature on the use of nerve conduction and TcPO₂ in the diagnosis of neuroischaemia in people with type 2 diabetes.

The first section focuses on the use of portable nerve conduction in the assessment of diabetes sensory neuropathy (section 3.3), followed by the use of TcPO₂ in the assessment of diabetes ischaemia (section 3.4). The findings from the systematic review are used to identify gaps in knowledge and to inform the design phase of the doctoral investigations. Consideration is given to the respective validity and reliability of portable nerve conduction and TcPO₂; and their applicability as novel objective devices in the assessment of diabetes neuroischaemia. The current challenges regarding clinical assessment of neuropathy using nerve conduction, and uncertainty surrounding assessment of ischaemia using a new TcPO₂ method, is presented (section 3.5) along with the need for future research in this area in particular.

3.2 Search strategy.

Two search strategies were used, one each for neuropathy and ischaemia

3.2.1 Nerve conduction in diagnosing diabetes neuropathy.

Searches were conducted on Pubmed, Sciencedirect and Scopus on diabetes nerve conduction assessments for the years 2010 – 2019, using the following ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND "neurological" OR "neuropathy" AND "nerve conduction"[All Fields] AND ("Assessment"[Journal] OR "assessment"[All Fields] OR "assessment"[All Fields]).

3.2.2 Transcutaneous Oxygen in diagnosing diabetes ischaemia.

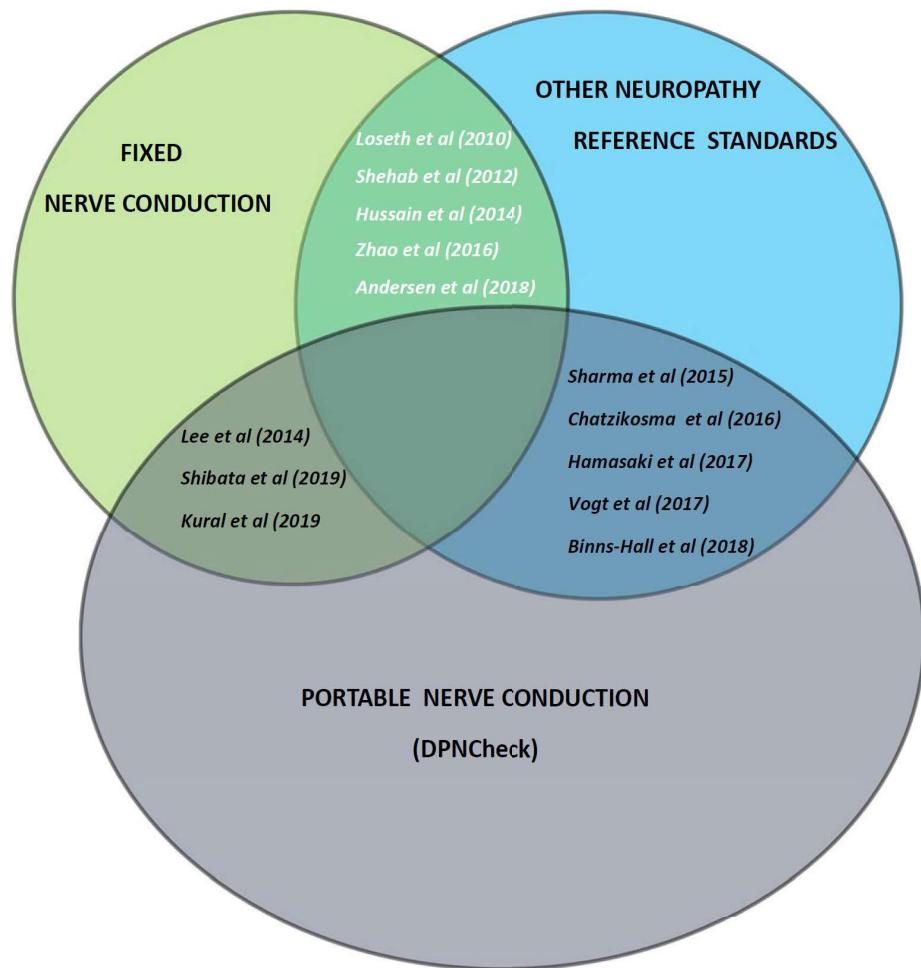
Searches were conducted on Pubmed, Sciencedirect and Scopus on TcPO₂ assessments from the years 2008 - 2019 using the following ("diabetes mellitus"[MeSH Terms] OR

("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] AND "TcPO₂"[All Fields] OR "transcutaneous"[All Fields] AND "ischaemia" OR "vascular" AND ("Assessment"[Journal] OR "assessment"[All Fields] OR "assessment"[All Fields]). With the Medicap a more novel device, the search years were extended to cover from 2008 – 2019.

3.3 Use of the DPNCheck® portable nerve conduction device in the assessment of diabetes peripheral neuropathy.

This section outlines advances that established the validity of portable nerve conduction in the diagnosis of diabetes sensory neuropathy over the last 10 years, and builds on earlier work by Behse and Buchthal (1977), Perkins *et al* (2006) and others as outlined in Chapter 1.3.8. The search described in 3.2.1 yielded 13 studies on the utility of nerve conduction in the assessment of sensory neuropathy. Those that did not include portable nerve conduction (5), were excluded, leaving 8 for the review as shown in Fig 3.3.1:

Figure 3.3.1: Literature search on the use of nerve conduction in diagnosing diabetes peripheral neuropathy



DPNCheck® validity was established based on investigations against fixed nerve conduction and other neuropathy reference standards.

3.3.1 DPNCheck® validity against fixed nerve conduction

The DPNCheck® was compared against fixed nerve conduction (Sierra Wave, Cadwell Laboratories) on 44 participants, 28 of whom had type 2 diabetes by *Lee et al.*, (2014), where it demonstrated excellent sensitivity (71%) and specificity (95%). The DPNCheck® also showed excellent intra-rater (0.97 (median 5, IQR 2-9); and inter-rater (0.86 (median 3, IQR 2-8) based on ICC (2,1) correlations. Bias analysis showed the DPNCheck® had

minimal amplitude bias of $-0.1 \pm 3.6 \mu\text{V}$ and excellent accuracy when compared to the reference device; but there was consistent overestimation of velocity of $+8.4 \pm 6.4 \text{ m/s}$. Some of these differences could be attributed to the operational differences between the devices, for instance the DPNCheck® stimulates the sural nerve antidromically, and measures velocity based on pulse completion leading to a shorter time lag, and hence an overestimation for velocity. The ROC curves for each diagnostic parameter, taken separately (velocity and amplitude) had thresholds of 48m/s for velocity (88% sensitivity and 94% specificity) and 6 μV for amplitude (82% sensitivity and 94% specificity). When combined, abnormality in either velocity ($\leq 48\text{m/s}$) or amplitude ($\leq 6\mu\text{V}$) gives the DPNCheck® 95% sensitivity and 71% specificity for diagnosing sensory neuropathy. It is unclear if a sample size calculation was performed to determine DPNCheck® validity, and therefore the bias in velocity, with a relatively wide standard deviation, could be reduced by a larger more representative sample. A sample of 28 participants with type 2 diabetes could be underpowered to show the true measurement bias, if any, between the DPNCheck® and fixed nerve conduction, which would need to be accounted and corrected for when determining diagnostic thresholds. This study showed that portable nerve conduction (DPNCheck®), whilst its' operational features differ from, had excellent reliability and validity when compared to, reference nerve conduction.

With a larger sample of 56 participants with type 2 diabetes, Shibata *et al.*, (2019) sought to determine the validity and reliability of the DPNCheck® against the fixed nerve conduction (Neuropack X1). They found the DPNCheck® velocity had excellent correlation of Pearson $r = 0.8$ (95% CI 0.79 – 0.8-0.9), and the amplitude had good correlation of $r = 0.6$ (95% CI 0.5-0.7). They also found excellent intra-rater reliability for both velocity (ICC = 0.9 (95% CI 0.8 – 0.9)); and amplitude (ICC = 0.8 (95% CI 0.8 – 0.9)). Inter-rater stability also showed substantial to almost perfect agreement, with velocity = 0.8 (95% CI 0.6-0.9) and amplitude = 0.8 (95% CI 0.7 – 0.9). The DPNCheck® showed small but consistent bias, with Bland-Altman analysis showing small overestimations for velocity (+3 m/s), and amplitude (+2.4 μV). For velocity; the AUC was 0.6 for both devices, and thresholds for maximum accuracy were 44 m/s for the fixed device (71% sensitivity; 54% specificity), but for the DPNCheck® this could not be determined given the lack of prominent convexity. For amplitude; the AUC was 0.7 for both devices, and the thresholds for maximum

accuracy were $\leq 6\mu\text{V}$ (87% sensitivity; 44% specificity) for the DPNCheck®; and $3\mu\text{V}$ (96% sensitivity; 41% specificity) for fixed nerve conduction. They observed less overestimation in velocity compared to Lee *et al.*, (2014), but this cannot be determined as definitive as their sample was still relatively small, the form of ICC was not described, and the analysis had no AUC for velocity.

The small samples were addressed by Kural *et al.*, (2019) , who advanced on the earlier studies by comparing the validity and reliability of the DPNCheck® against fixed nerve conduction (Dantec Keypoint.Net) on 200 participants, of which 168 with type 2 diabetes completed assessment. Taking mean leg measurements, they found an excellent linear correlation on amplitude ($r = 0.76$); and moderate correlation for velocity ($r = 0.55$); both significant at $p < 0.001$. They also found the DPNCheck® had good sensitivity and specificity for amplitude with $\text{AUC} > 0.8$, and fair sensitivity and specificity for velocity with AUCs between 0.7 and 0.8. For DPNCheck® amplitude they found a diagnostic threshold of $6\mu\text{V}$ gave 96% sensitivity, 71% specificity, 54% PPV, and 98% NPV; whilst a $4\mu\text{V}$ threshold gave it 78% sensitivity, 89% specificity, 71% PPV, 92%NPV. Bias analysis revealed the DPNCheck® underestimated both velocity (-2.8 m/s) and amplitude ($-1\mu\text{V}$) when compared to fixed nerve conduction, which could be due to the devices being used at different sites, participants being assessed at different times, and operational variation between the fixed and portable devices. DPNCheck® underestimation also contrasts against earlier overestimations (Lee *et al.*, 2014; Shibata *et al.*, 2019), which could be attributed to diurnal variation and in study sites with a larger sample. The bias does mean that for borderline cases, the DPNCheck® risks giving false positives, thereby potentially overestimating neuropathy prevalence. However this bias is minimal, and is preferable within a clinical context where borderline cases can be considered to have neuropathy as a precautionary measure.

It is however difficult to directly compare these studies as they used different fixed reference devices (Sierra Wave; Neuropack; Dantec), each with different operating parameters and thresholds. These studies also suggest that operational differences between fixed and portable DPNCheck® nerve conduction, discussed earlier (Chapter 1.3.8, page 26-27) could account for the bias observations and imperfect correlations. For instance fixed nerve conduction uses near nerve adjustable and narrow electrodes which

operate antidromically at a fixed 32°C, in contrast to the DPNCheck® that has broad sensors that operate orthodromically and across a wider (23°C - 33°C) temperature range. There are further differences between the fixed devices and the DPNCheck®, in signal latency and processing that could account for differences in velocity and amplitude. The DPNCheck® has a higher stimulating amplitude charge (70mA) compared to fixed devices (20mA), which means more of this amplitude is “left over” for the DPNCheck® to detect. As identified by Lee *et al.*, (2014), the DPNCheck® has a shorter latency due to measuring time from stimulus completion, whereas the fixed devices measure time from stimulus initiation giving them longer latency and hence slower estimation of velocity. The true extent of measurement bias in the DPNCheck®, compared to fixed nerve conduction is therefore challenged by these differences in reference devices and operating parameters. Despite this, the DPNCheck® had comparable diagnostic accuracy based on AUCs and ROC curves, and against each fixed device demonstrated excellent sensitivity, specificity, and velocity and amplitude correlations.

The results therefore support the view that the DPNCheck® has criterion validity in diagnosing diabetes sensory neuropathy against fixed nerve conduction.

3.3.2 DPNCheck® Validity against other neuropathy diagnostic standards.

The DPNCheck® has also been compared to other neuropathy diagnostic standards. Sharma, Vas and Rayman (2015) compared the DPNCheck® and the LDIFlare against the NDS as a reference standard on 162 type 2 diabetes participants. Participants were divided into those without neuropathy, and those with varying degrees of neuropathy according to the NDS scores. They demonstrated very strong positive and significant correlations ($p < 0.001$) between LDIFlare and DPNCheck® sural nerve velocities in healthy (Pearson $r < 0.90$) and in all neuropathy groups (Pearson $r = 0.8$); and between LDIFlare and sural nerve amplitudes across the healthy (Pearson $r = 0.88$) and all neuropathy groups (Pearson $r = 0.73$). From amongst those with neuropathy, there were significant associations between LDIFlare and conduction parameters within each category, from mild neuropathy (velocity $r = 0.6$ $p = 0.03$; amplitude $r = 0.7$; $p = 0.002$); moderate neuropathy (velocity $r = 0.8$ $p = 0.001$; amplitude $r = 0.7$ $p = 0.02$) and severe

neuropathy (velocity $r = 0.8$ $p = 0.004$; amplitude $r = 0.8$ $p = 0.008$). ROC curves within each category of neuropathy showed that the DPNCheck® had high sensitivity in the diagnosis of neuropathy, with AUC for each category ranging from 0.8 to 0.9. Nerve velocity decreased progressively with increasing severity of neuropathy, from healthy controls (50.2 ± 5.7 m/s) ; diabetes with no neuropathy (49 ± 12.7 m/s) , mild neuropathy (40.1 ± 8.4 m/s); moderate neuropathy (32.2 ± 7.7 m/s) and severe neuropathy (26.5 ± 8.1 m/s) all significant at $p < 0.0001$. The same trend was observed for nerve amplitude, from healthy controls (18.5 ± 4.1 μ V), diabetes with no neuropathy (16.1 ± 8.5 μ V), mild neuropathy (11.3 ± 5.1 μ V); moderate neuropathy (6.5 ± 3.8 μ V) and severe neuropathy (2.9 ± 1.9 μ V), with all differences significant at $p < 0.0001$. The NDS assesses components of both small and large fibre neuropathy, and was used in this study to categorise severity, whilst the LDIFlare assesses small fibre neuropathy (Krishnan and Rayman, 2004; Illigens *et al.*, 2013). The study shows that nerve conduction has strong correlations with early manifestations of small fibre neuropathy, as detected by the LDIFlare. In terms of the DPNCheck® velocity diagnostic thresholds, the study found this to be 40.1 m/s for mild neuropathy; which is comparable to 40m/s found by Kural *et al.*, (2019). The amplitude threshold was higher, with mild neuropathy at 11.3 ± 5 μ V instead of about 6μ V, and suggests that the small fibre components of the NDS play a larger role in determining mild neuropathy, than the large fibre components. This study demonstrated that the DPNCheck® has strong associations with LDIFlare small fibre neuropathy, but it would have been strengthened by determining respective LDIFlare and DPNCheck® sensitivity and specificity against the NDS.

The diagnostic performance of the DPNCheck® was compared to the NDS by Chatzikosma *et al.*,(2016), on 46 healthy controls and 114 participants with type 2 diabetes. The NDS diagnosed 42 diabetes participants as having neuropathy, and the DPNCheck® performance gave 91% sensitivity and 86% specificity, with a PPV of 79 % and an NPV of 94%. They further reported LR+ of 6.5, and LR- of 0.1. From the healthy cohort the NDS found no participants with neuropathy, yet the DPNCheck® diagnosed 4% as neuropathic. This highlights some of the limitations of the NDS, as it is burdened by its subjective components which could lead to it giving false negatives. This study shows that the DPNCheck® could itself have been the reference standard, and be more effective at

assessing diabetes neuropathy than the NDS.

DPNCheck® performance was also compared to that of the ankle reflex by Hamasaki and Hamasaki (2017), on 680 participants. They reported that the ankle reflex identified 208 cases of neuropathy, and ruled out 382 participants. From these 382, it was reported that the DPNCheck® diagnosed neuropathy in a further 90 cases (24%). Despite reporting this, a closer look at their figures suggested a miscalculation which was communicated to the authors and editor, and revealed instead that in fact this should be 472 as having no neuropathy. From these 472 participants, the DPNCheck® diagnosed an additional 90 neuropathy cases (which would be 19%). Based on these figures, the authors stood by their reported sensitivity (81%) and specificity (46%), and LR+ of 1.5 for the DPNCheck®, but this is affected by the false negatives (19%) from the ankle reflex. This study therefore suggests that the DPNCheck® has more sensitivity and specificity in the diagnosis of sensory neuropathy than the ankle reflex.

The DPNCheck® was used as the reference standard against the 10g monofilament, the Sibbald 60 second tool, and self reporting by Vogt *et al.*, (2017) in 90 participants with type 2 diabetes. They found the 10g monofilament had 86% sensitivity and 59% specificity with $\kappa = 0.4$ but also a false positive rate of 23%; the Sibbald tool had 98% sensitivity and 47% specificity with $\kappa = 0.2$; and self-reporting had 74% sensitivity and 49% specificity with $\kappa = 0.2$. The study population spent extended periods of time barefoot, with consequent thickened plantar callus, which would affect neuropathy assessment based on the Sibbald 60 second tool and the 10g monofilament, which are both based on subjective reporting. The DPNCheck® itself was however unable to find the sural nerve in 9% of participants, which could possibly be attributed to ethnic variations in sural nerve anatomy (Fong *et al.*, 2016; Owolabi *et al.*, 2016; Shivji *et al.*, 2019). Despite this, the study highlights the limitations of other assessment tools that rely on subjective responses, and further demonstrates the value of the DPNCheck® even in low resource settings.

The assessment abilities of the DPNCheck®, 10g monofilament, and the Sudoscan® were compared against the Toronto scoring system as a reference standard by Binns-Hall *et al.*, (2018) on 231 participants with type 2 diabetes. The Toronto scoring system itself found neuropathy prevalence of 31%, with the 10g monofilament finding 14%, the Sudoscan®

38%, and the DPNCheck® 52%. Against the Toronto scoring system, the Sudoscan® had 93% sensitivity and 53% specificity whilst the DPNCheck® had 84% sensitivity and 68% specificity. The Sudoscan® had a correlation of spearman $r = -0.43$ ($P < 0.001$), and both the DPNCheck® velocity and amplitude had $r = -0.7$ $p < 0.001$ against the Toronto scoring system. These results show that DPNCheck® had the strongest correlation to the Toronto scoring system when compared to the Sudoscan® or the 10g monofilament. It must be borne in mind that the Toronto scoring system itself has subjective components as outlined in Chapter 1.3.3 (page 11), that leave it vulnerable to false negatives, and likely to underestimate neuropathy prevalence. The DPNCheck® was the most objective of the tests and had the highest rate of suspecting neuropathy. The study therefore adds support to the use of the DPNCheck® in the assessment of sensory neuropathy.

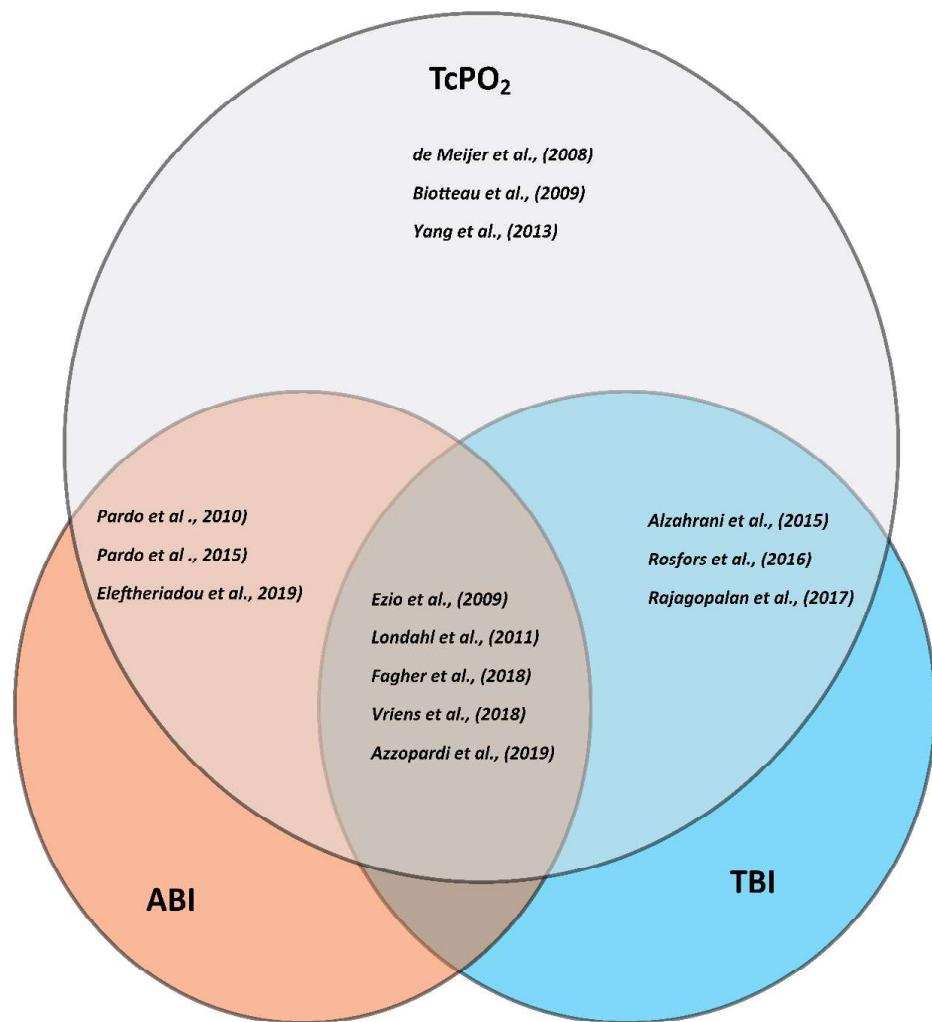
These studies also show that the DPNCheck® has associations with small fibre neuropathy, and is more effective at the assessment of neuropathy than other clinical reference standards such as the NDS and Toronto scoring system, all of which can give false negatives and underestimate neuropathy prevalence. The main limitation of these neuropathy standards and other neuropathy assessment tools such as the 10g monofilament is their reliance on subjective responses, which introduces wide variations in validity and reliability. Therefore, a summary of DPNCheck® validity against both fixed nerve conduction and other neuropathy clinical tools show that it has criterion validity, showed excellent reliability and is effective at assessing diabetes neuropathy.

Only 1 study compared DPNCheck® to 10g monofilament performance, which was done on a population that spends extended periods of time barefoot, which in turn makes it difficult interpret 10g monofilament performance. The established criterion validity and assessment ability in research settings, alongside the study by Vogt *et al.*, (2017) in a low resource environment, leave potential to investigate the effectiveness of the DPNCheck® as a routine clinical tool to screen for neuropathy in type 2 diabetes participants against the 10g monofilament, as recommended by NICE (NG19) guidelines.

3.4 Use of transcutaneous oxygen in the assessment of diabetes peripheral ischaemia

The literature search conducted as outlined in 3.2.2, identified 14 studies. These are shown in Fig 3.4.1, with all the studies extracted for review having used Clark-type probes to detect $TcPO_2$.

Figure 3.4.1: Literature search on the use of $TcPO_2$ in diagnosing diabetes ischaemia



Since ischaemia is a change in the arterial supply, the utility of $TcPO_2$ to detect this rests on establishing reference values, its ability to detect arterial changes and how it compares to other established measures such as the ABI and TBI.

de Meijer et al., (2008) sought to establish $TcPO_2$ reference values with a TCM400, from

amongst 35 Type 2 and 25 Type 1 diabetes participants, compared to 60 healthy participants. Healthy participants had a mean $TcPO_2$ of 56 (+/- 8.8) mmHg, compared to people with type 2 diabetes (48.6 +/- 8.9 mmHg), and the difference measured from the dorsum of the foot of 7.4 mmHg was significant (95% CI, 3.7–11.2; $p < 0.01$). $TcPO_2$ was also lower amongst type 2 compared to type 1 diabetes participants, with the difference of 3.4 mmHg (95% CI, -1.28 - 7.99; $p = 0.15$) not reaching statistical significance, and $TcPO_2$ could not distinguish between the diabetes groups. However, $TcPO_2$ could distinguish between healthy and participants with type 2 diabetes in people without neuroischaemic complications. In a later study, Eleftheriadou *et al.*, (2019b) investigated the effect of diabetic peripheral neuropathy on $TcPO_2$ in 63 healthy and 100 participants with Type 2 diabetes found that participants with diabetes neuropathy had lower $TcPO_2$ values (48 mmHg) than the healthy cohort (55.4 mmHg) and with a significant difference of 7.4 mmHg ($p < 0.001$). This suggests that whilst, $TcPO_2$ can distinguish between participants with and without diabetes neuropathy, the studies do not provide diagnostic threshold values for ischaemia.

Yang *et al.*, (2013) determined $TcPO_2$ threshold values, with a TCM400, in 61 participants with diabetic foot ulcers, who were grouped into 3 groups depending on ulcer outcome at 9 months. This resulted in 36 healed ; 8 improved ulcers (if >/ 50% reduction) ; and 17 with no improvement after 9 months. They found that the mean $TcPO_2$ for each group was 32mmHg (intact healed); 30mmHg (improved ulcer) and 15 mmHg (no improvement), and no healing occurred in any group if $TcPO_2$ was below 10 mmHg, whilst all participants with $TcPO_2$ above 40mmHg healed. It was also determined that 25mmHg was the most accurate threshold for predicting healing ability, giving an $AUC = 0.8$ (95% CI 0.7 – 0.98), sensitivity of 88.6%, and specificity of 82.4% . Whilst there were differences in age between the groups, with those who showed no improvement being older (72 years) than those who healed (66 years), the authors did not find this significant ($P = 0.78$). This study therefore shows that $TcPO_2$ can predict healing potential in people with diabetes foot ulceration.

Biotteau *et al.*, (2009) set out to establish $TcPO_2$ values at the chest and feet, in 120 participants with critical limb ischaemia, divided into 60 people with diabetes and 60 without diabetes. At the chest, they found those with diabetes had lower $TcPO_2$ (median

= 53, range 43-57 mmHg) compared to those without diabetes (median = 60; range 49-65 mmHg) and the difference of 7 mmHg was significant ($p < 0.01$). At the foot level, they found $TcPO_2$ to be 3 mmHg lower in the feet of people with diabetes (median = 12, range 3-34 mmHg) compared to those without diabetes (median = 15; range 3-36 mmHg), but this did not reach statistical significance. Therefore, in contrast to the chest $TcPO_2$ values, those derived from the foot could not distinguish between diabetes and non-diabetes participants in people with critical limb ischaemia. This can be due to the increased severity of peripheral ischaemia in this group of participants, which, when compared to de Meijer *et al.*, (2008) and Yang *et al.*, (2013), had advanced to a stage where $TcPO_2$ failed to distinguish between those with and without diabetes. This study therefore suggests a window during which foot $TcPO_2$ values can be valuable in distinguishing between those with and without diabetes, and in predicting DFU healing potential, but this window is confined to before the manifestation of advanced peripheral ischaemia. It further suggests the value of $TcPO_2$ rests in detecting and tracking changes in perfusion, as investigated by Pardo *et al.*, (2010); who compared $TcPO_2$ against the ABI in tracking vascular changes in 151 diabetes participants undergoing transluminal angioplasty. They found the ABI showed an increase from 0.67 to 0.8 after angioplasty ($p < 0.001$), and $TcPO_2$ increased from 27mmHg to 40mmHg ($p < 0.001$). There was poor correlation between $TcPO_2$ and ABI ($r = 0.2$; $P = 0.2$). This introduced a disparity between macro and microischaemic assessments, as also found by Eleftheriadou *et al.*, (2019b), who found poor correlation between $TcPO_2$ and the ABI from 100 participants with diabetes ($r = 0.2$ ($p = 0.002$)), which remained significant after regression analysis. In addition the ABI was unable to be obtained in 25% of cases before, and 18% after revascularisation. Their study shows that both $TcPO_2$ and ABI can detect ischaemic changes, but since $TcPO_2$ was obtained in all cases, it also suggests the potential of $TcPO_2$ as a better measure than ABI in ischaemic assessments. Pardo *et al.*, (2010) had also highlighted a potential value of $TcPO_2$ in tracking metabolic changes, particularly changes in oxygen delivery. This was investigated by Löndahl *et al.*, (2011), who used hyperbaric oxygen to stimulate ulcer healing, and tracked ischaemic changes using $TcPO_2$, TBI and the ABI in 75 DFU participants. They could obtain the ABI and TBI on 68 participants, from which they found moderate-good correlation between the ABI and TBI ($r = 0.65$; $r^2 = 0.42$; $p = 0.0003$).

Following Pardo *et al.*, (2010), it was also not possible to determine macroischaemia in all cases (unable to obtain TBI/ABI in 9%); whereas the TcPO₂ was taken in all (100%). There was no significant correlation between TcPO₂ and the TBI or the ABI (figures not provided). Healing rates were higher the greater the oxygen delivery, with healing rates ranging from 100% (for TcPO₂ \geq 75 mmHg) ; 73 % (TcPO₂ between 51-74mmHg) , 50 % (for TcPO₂ between 26-50mmHg), to 0% with no healed ulcers if TcPO₂ was below 25mmHg. TcPO₂ was therefore significantly correlated to the healing rate (all $p < 0.05$). In contrast, there were no correlations between ulcer healing and ABI or the TBI. This study shows TcPO₂ as a better predictor of ulcer healing, and as a better metabolic assessment method when compared to the ABI or TBI.

Advancing on this and on their earlier study from 2010, Pardo *et al.*, (2015) compared the pre and post operational performance of TcPO₂ against ABI over 8 weeks, in 40 diabetes participants undergoing transluminal angioplasty. As a mirror to their earlier study, they obtained TcPO₂ measurements in all (100%) of cases; whilst it was not possible to obtain the ABI in 15% of participants even post-revascularisation, adding support to the utility of TcPO₂ as a better measure for tracking ischaemia in this group of participants. The TcPO₂ significantly increased from 28.1mmHg to 48 mmHg after 8 weeks ($p < 0.001$), whilst the ABI also significantly increased from 0.48 to 0.77 at 1 week and was still 0.77 at 8 weeks ($p = \text{significant}$). TcPO₂ was more sensitive to ischaemic improvements post surgery, as it continued to gradually increase for the duration of the 8 weeks, whilst the ABI remained static after 1 week. The two measures showed further disparities in tracking ischaemia; in 12.5% (5 participants) the ABI remained low, yet the TcPO₂ increased; which could be attributed to an improvement in the collateral circulation as detected by TcPO₂, which the ABI cannot assess. In another 17.5% (7 participants) the ABI increased whilst the TcPO₂ did not, which the authors attributed to microplaques dislodged during revascularisation that proceeded to block the microarteries, whilst sparing the larger arteries. Because of these disparities, and with the two assessments measuring different parameters, there was again minimal correlation ($r = 0.19$; $p < 0.2$) between TcPO₂ and ABI.

Similarly, Rosfors, Kanni and Nyström (2016) compared TcPO₂ to TBI in 498 participants with CLI divided into 210 with Type 2, 90 with Type 1, and 198 with no diabetes. They

found that the TBI underestimated ischaemia in between 17%-18% of people with and without diabetes, and the TBI could not be obtained in 16 participants. Comparing the two methods diagnostic ability showed fair agreement, with weighted kappa = 0.35 (95% CI = 0.3-0.4), showing differences between macro and microischaemic assessments. Following this, Azzopardi *et al.*, (2019) compared the agreement between pulse palpation, waveform, ABI, TBI and TcPO₂ in 50 participants with type 2 diabetes. They found significant differences (all p < 0.0005) in the ischaemia prevalence ranging from 93% (pulse waveform), 57% (ABI), 30% (TcPO₂), 28% (TBI), to 23% (palpation), and moderate association between the tests (Cramer's V = 0.5). However there are wide disparities between ischaemia prevalence based on macrocirculation, such as between the ABI (57%) and TBI (28%), with the suggestion that the prevalence from the TBI (28%) itself is closer to that obtained by manual palpation (23%). So despite there being poor agreement between the assessment tests for ischaemia as established by other studies (Pardo *et al.*, 2015; Rosfors, Kanni and Nyström, 2016; Eleftheriadou *et al.*, 2019b) , the absence of an objective reference standard in the study by Azzopardi *et al.*, (2019) leaves their observations open to subjective interpretation, and the prevalence itself would vary depending on the diagnostic threshold chosen for each test. This had earlier been investigated by Vriens *et al.*, (2018b), who compared the diagnostic performance of the pole test, TcPO₂, TBI and ABI against reference arterial duplex, amongst 60 new ulcerations in diabetes participants. The participants had complex comorbidities such as pulmonary, kidney and heart complications and 25% were hospital inpatients. Overall, 33% had PAD, and they found the best diagnostic performance was from the pole test, with 97% specificity, 28% specificity, and PPV = 0.83 and NPV = 0.73. TcPO₂ had 28 % sensitivity, 66% specificity; and the TBI had 89% sensitivity and 45% specificity; and the ABI had 68% sensitivity and 59% specificity. All tests had poor negative likelihood ratios, and the assessment tests were unsuitable to be used in this group of participants given their existing comorbidities. The duplex ultrasound is itself a reference standard for macroischaemia, and it was therefore unsurprising that the TcPO₂ poorly compared to the macrovascular assessments, whilst the pole test was the only one to introduce a vascular challenge against gravity which gave it the best diagnostic performance.

Earlier, Ezio *et al.*, (2010) had compared the diagnostic ability of TcPO₂ against toe and

ankle pressures in 261 diabetes participants. They were unable to obtain ankle pressures in 109 participants (42%), and further unable to obtain toe pressures in 72% of participants. In contrast TcPO₂ was measured in all 261 participants. There were further differences in the interpretation of diagnostic thresholds, with ankle pressures indicated as normal in 50 participants, yet TcPO₂ diagnosed ischaemia. In a further 10 participants the ankle pressure was above 89mmHg (no vascular deficit), yet the TcPO₂ indicated severe ischaemia (12mm Hg). These discrepancies could be attributed to both the differences in the macrocirculation as measured by ankle and toe pressures, and microcirculation as measured by TcPO₂; and effects of diabetes on these different macro and micro arterial components.

The ability of TcPO₂ in predicting outcomes against the TBI was also investigated by Alzahrani, Alzahrani and Hussain (2015) across 3 participant groups, namely; healthy (30), with type 2 diabetes and no ulceration (51) and those with DFU (40). The TBI diagnostic threshold for ischaemia was < 0.7. They found no significant baseline differences in TcPO₂ between the 3 groups, and no significant differences in the TBI between healthy and participants with no ulceration. They found significant TBI differences between both healthy vs DFU participants, and between type 2 diabetes participants with and without ulcers (all $p < 0.001$). For outcomes, from amongst the DFU group, 15 healed, 10 remained ulcerated, and 10 died, and there were no significant differences in baseline TcPO₂ between those who healed (40.4 mmHg), those who remained ulcerated (39.6 mmHg) and those who died (40.9 mmHg). TcPO₂ could not therefore predict outcomes in those with DFU, perhaps because of coexisting macrovascular comorbidities. In contrast, the TBI could distinguish between those DFU that healed (0.67) and those with DFU who died (0.36) ($p < 0.005$), but no significant TBI differences were found between unhealed DFU participants and those who died. The relatively high death rate (> 28%) suggests underlying comorbidities, and those who died had relatively increased TcPO₂ levels (40.9 mmHg) which has been previously established as high enough to achieve healing (Londahl *et al.*, 2011); but low TBIs (0.36) indicative of compromised macrovascular status. These results could be largely explained by the TcPO₂ methodology employed, where the TcPO₂ probe was placed, against established protocol, at the tip of the toe, instead of at the non-glabrous dorsum of the foot or directly by the peri-wound area. The systemic TcPO₂

measures would have been affected by the thicker glabrous skin, and therefore unlikely to have been a valid representation of the underlying microischaemic status. It is therefore unsurprising that the study does not find significant group $TcPO_2$ differences, which, unlike the TBI, determines healing potential at a very localised, rather than systemic level. The $TcPO_2$ parameters were therefore similar across all three groups, but these groups had significantly different underlying macrovascular complications, as detected by the TBI.

In a similar study, but placing the $TcPO_2$ probe at the dorsum of the foot, Fagher, Katzman and Londahl (2018) evaluated the threshold values of $TcPO_2$, APBI and toe blood pressure in predicting 1 year all-cause mortality amongst 236 DFU participants. They found that for $TcPO_2$ values $< 25\text{mmHg}$, the healing rate was 8.8% and amputation rate was 36%. $TcPO_2 > 25\text{mmHg}$ had 26% healing rate and 13% amputation rate. The ABI between 0.9 and 1.3 had a 33% healing rate, and values outside those limits had a 16% healing rate. 15% (35 participants) died, and accounting for confounders, they found $TcPO_2 < 25\text{mmHg}$ as independently predicting 1-year mortality (Hazard Ratio = 2.8 (95% CI 1.34–5.91, $p = 0.006$)), whilst ABI and toe blood pressure had no significant effect. Their probe placement would have given them more valid $TcPO_2$ values, and these challenged the earlier findings of Alzahrani, Alzahrani and Hussain (2015), who did not find $TcPO_2$ as a predictor mortality in people with DFU.

Rather than predicting mortality, Rajagopalan *et al.*, (2017) compared ABI and $TcPO_2$ in predicting healing and amputation from amongst 564 DFU participants. For wound healing, they found an $ABI < 0.9$ had $OR = 23$, with $PPV = 75\%$ and $NPV = 88.5\%$; whilst $TcPO_2 < 40\text{mmHg}$ had $OR = 4.2$, $PPV = 35.3\%$ and $NPV = 88\%$. On predicting amputation, $ABI < 0.6$ was found to have 68% sensitivity and 99% specificity; whilst $TcPO_2 < 22.5\text{mmHg}$ had 75% sensitivity and 100% specificity. Multivariate logistic regression showed; for wound healing $ABI < 0.9$ had $OR = 3.5$ (95% CI 2.2–5.7); whilst $TcPO_2 < 40\text{ mmHg}$ had $OR = 0.7$ (95% CI 0.6–0.8); and for amputation $ABI < 0.9$ had $OR = 0.5$ (95% CI 0.1–0.2); with $TcPO_2 < 40\text{mmHg}$ had $OR = 3.0$ (95% CI 2.1–4.3). These results suggest that both approaches could be complementary, with the ABI a better predictor of wound healing, whilst the $TcPO_2$ a better predictor of amputation. However, there is variability in thresholds, as for instance lowering the ABI to < 0.4 gives 100% sensitivity and 80

specificity for wound healing. Similarly, TcPO₂ could be adjusted to improve its ability to predict both healing potential and amputation.

A synthesis of these studies suggests that TcPO₂ has established reference values to estimate mortality, (Fagher, Katzman and Londahl, 2018) and ulcer healing (Rajagopalan *et al.*, 2017), but it compares poorly against macrocirculatory assessments (Azzopardi *et al.*, 2019) including the macro index tests such as arterial duplex (Eleftheriadou *et al.*, 2019b). As a microcirculatory measure it however offers potential advantages over other assessments, particularly as it can be measured in most, if not all participants even when it is not possible to carry out ABI/TBI (de Meijer *et al.*, 2008; Löndahl *et al.*, 2011; Pardo *et al.*, 2015; Rosfors, Kanni and Nyström, 2016). Whilst it is affected by the macrocirculation (Eleftheriadou *et al.*, 2019b), it is a very localised measure of perfusion, and accounts for collateral circulation and is therefore more sensitive to ischaemic changes which can be used to monitor perfusion status at specific sites (Pardo *et al.*, 2015) and track metabolic oxygen changes (Löndahl *et al.*, 2011).

An additional aspect to the reviewed studies is that they were carried out with Clark type electrochemical probes, and none used the Medicap which employs photochemical probe technology. When considered alongside the wide disparities in patient population and methodologies used, this leaves open the potential to investigate TcPO₂ with a photochemical probe directly against the TBI to screen for ischaemia in a type 2 diabetes clinical population.

3.5 Summary on the use of nerve conduction and transcutaneous oxygen in the assessment of neuroischaemia in people with type 2 diabetes.

A review of the literature reveals that the criterion validity of the DPNCheck® in diagnosing neuropathy has been established, but it also showed limited use of the DPNCheck® as a routine clinical device. This is not helped by the several assessment tests that already exist, so any potential advantages offered by the DPNCheck® are buried underneath the burdens imposed on clinicians by divergent devices and protocols and it is seen as just yet another device to add the existing multitude in the assessment of neuropathy.

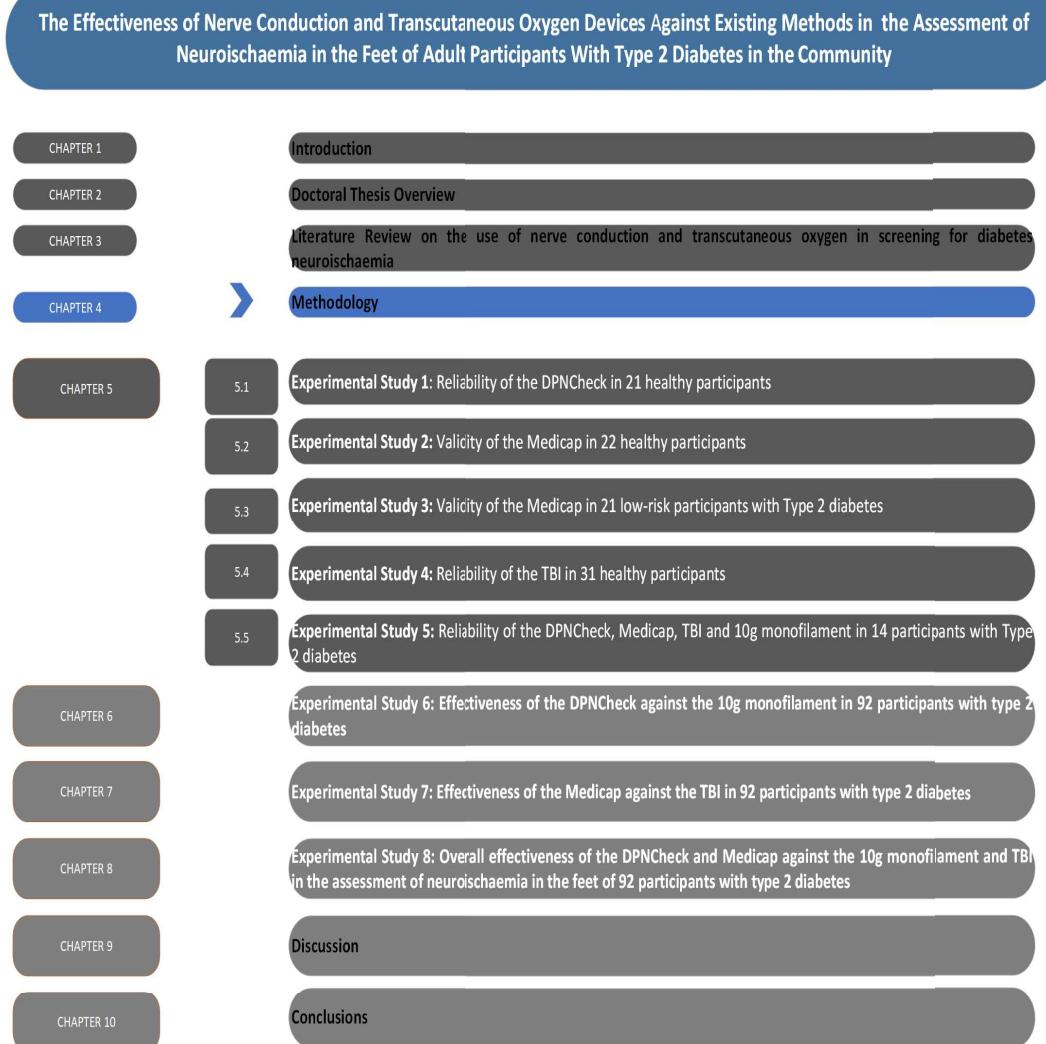
The review also showed the potential offered by TcPO₂ particularly in tracking ischaemic changes and being able to be used in all participants, in contrast to established macrocirculatory assessments such as the ABI and TBI. There were also no identified studies that used photochemical probes, which are an advancement on Clark type electrochemical probes, showing that the Medicap is a more novel device.

No studies combined the use of portable nerve conduction and TcPO₂ in assessment neuroischaemia and in risk stratification in people with type 2 diabetes. This therefore leaves potential to investigate the effectiveness of the DPNCheck® (portable nerve conduction) and Medicap (photochemical TcPO₂) in the assessment of pedal neuroischaemia. They have the potential to provide more effective assessment and risk stratification than current approaches, through giving a more accurate picture of neuroischaemic health in the feet of individuals who have type 2 diabetes. Such knowledge would help identify, at an earlier stage, those patients who are more likely to deteriorate to DFU and hence are more likely to benefit from early intervention.

Chapter 4 METHODOLOGY

The results of the structured literature review outlined in Chapter 3 demonstrated the gap in evidence on the clinical use of portable nerve conduction and transcutaneous oxygen in the assessment of neuroischaemia in people with type 2 diabetes in the community. Therefore, the main aim of this investigation is to explore the effectiveness of the DPNCheck® and Medicap in the assessment of neuroischaemia in the feet of people with type 2 diabetes, when compared to existing clinical methods. An overview of the methodology, within the context of the thesis, is shown in Figure 4.1.

Figure 4.1: Showing an overview of the methodology chapter within the thesis context.



4.1 Philosophical approach

Epistemologically, this research is seen through a positivist lens, in believing that there is an objective “true state” of neuroischaemia in people with type 2 diabetes. The NICE NG19 (2015) recommended clinical assessments only give a vague view of this state, and therefore the picture is not clear enough to show early nerve and arterial changes to help prevent complications. It is important to obtain a clear picture of this true state in order to make clinical management decisions which are effective when they are based on a more accurate state of health, rather than on a vague one. The hypothesis deduced from this is that the new devices (DPNCheck® and Medicap) can give a picture that is clearer and closer to that truth of underlying neuroischaemia, than existing methods (10g monofilament and TBI).

4.2 Study Design

In order to achieve these philosophical aims, a series of cross-sectional observational studies were undertaken to establish the reliability, validity and effectiveness of the DPNCheck® against the 10g monofilament in the assessment of sensory neuropathy, and the Medicap against the TBI in the assessment of ischaemia, in adults with type 2 diabetes.

4.2.1 Reliability and validity studies (Chapter 5)

Experimental Study 1: (page 111) to determine the reliability of the DPNCheck® in healthy participants, and compared it against published data

Experimental Study 2: (page 118) to determine the validity of the Medicap in healthy participants.

Experimental Study 3: (page 134) to determine the validity of the Medicap in participants with type 2 diabetes classified as being at low risk of ulceration according to NICE guidelines (NG19)

Experimental Study 4: (page 145) to determine the reliability of the TBI in healthy participants.

Experimental Study 5: (page 153) to determine the reliability of the DPNCheck®,

Medicap, 10g monofilament and TBI in 14 participants with Type 2 diabetes.

4.2.2 Experimental Studies to answer the primary research question:

Building on from the validity and reliability experimental studies, the following studies are aimed at answering the primary doctoral research questions:

Experimental Study 6: Chapter 6: (page 164) to determine the effectiveness of the DPNCheck® in the assessment of sensory neuropathy against the 10g monofilament in participants with type 2 diabetes.

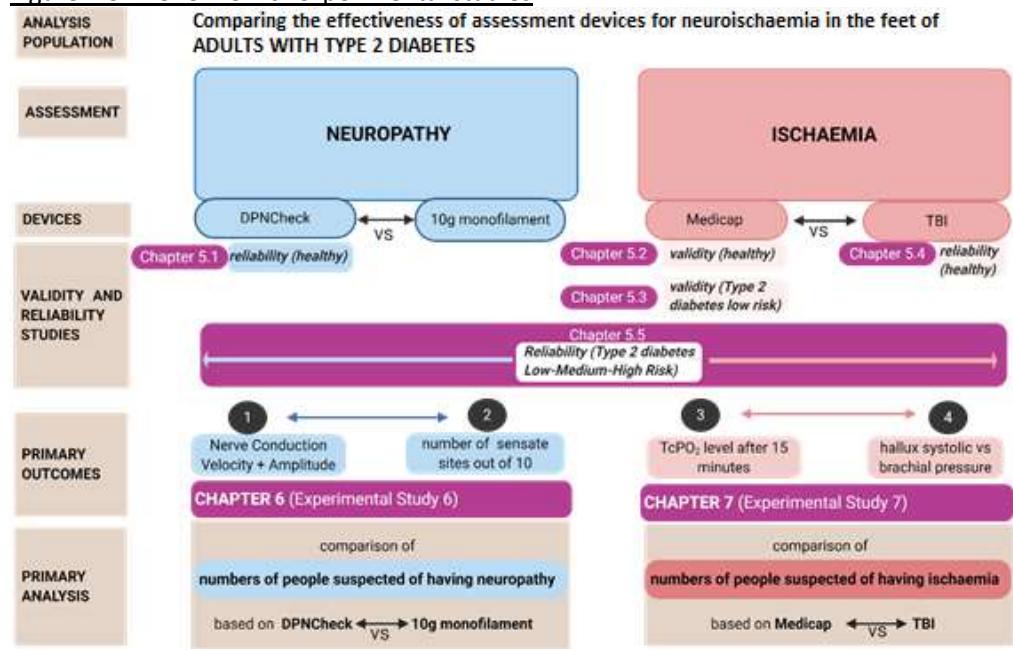
Experimental Study 7: Chapter 7: (page 173) to determine the effectiveness of the Medicap in the assessment of ischaemia against the TBI in participants with type 2 diabetes.

Experimental Study 8: Chapter 8: (page 184) brings together the neuropathy and ischaemia investigations, to determine the overall effectiveness of the DPNCheck® and Medicap in the assessment of neuroischaemia when compared to the 10g monofilament and TBI. These are summarised in Figure 4.3.1.

4.3 Study specific aims and objectives

An overview of the experimental studies is shown in Figure 4.3.1.

Figure 4.3.1: Overview of experimental studies



4.3.1 Experimental Study 1: (Chapter 5.1, page 111)

The aim of experimental study 1 was to establish the test-retest (intra-rater) reliability of the DPNCheck® in healthy participants, and compare it against published data. This was achieved according to the following objectives:

- To determine the test-retest reliability of the DPNCheck® in assessing sural nerve function in the feet from a convenience sample of 22 healthy participants.

4.3.2 Experimental Study 2: (Chapter 5.2, page 117)

The aim of experimental study 2 was to determine the validity of the Medicap in healthy participants. The following objectives were set:

- to compare the Medicap TcPO₂ readings to that of a reference device (TCM400) in the feet of healthy participants
- to determine if the probe location on the foot, had an effect on TcPO₂ readings

4.3.3 Experimental Study 3: (Chapter 5.3, page 134)

Building on experimental study 2, the aim of experimental study 3 was to determine the validity of the Medicap in participants with type 2 diabetes classified as at low risk of ulceration according to NICE guidelines (NG19). This was done according to the following objectives:

- a) to compare the Medicap TcPO₂ readings to that of a reference device (TCM400) in the feet of low risk participants with type 2 diabetes.
- b) as a validity investigation it was important to examine and determine the extent of measurement bias, which was done through Bland-Altman analysis (Bland and Altman 1986).
- c) Depending on the shape and distribution of data, either the Spearman σ (non-parametric) or the Pearson r (parametric) correlation was used to determine the strength of linear correlation between the Medicap and TCM400. The Kappa statistic was used to assess the level of agreement between devices.

4.3.4 Experimental Study 4: (Chapter 5.4, page 145)

Experimental study 4 aimed at determining the reliability of the TBI in healthy participants, based on the following objectives:

- a) to determine the reliability of the TBI in healthy participants.

4.3.5 Experimental Study 5: (Chapter 5.5, page 153)

The aim of experimental study 5, was to determine the reliability of the DPNCheck®, Medicap, 10g monofilament and TBI, in the first 30 participants with Type 2 diabetes, recruited to the main study. This was based on the following objectives:

- a) to determine the intra-rater reliability of the DPNCheck®
- b) to determine the intra-rater reliability of the Medicap
- c) to determine the intra-rater reliability of the 10g monofilament
- d) to determine the intra-rater reliability of the TBI

4.3.6 Experimental Study 6: (Chapter 6, page 164)

The aim of experimental study 6, was to determine the effectiveness of the DPNCheck® in identifying sensory neuropathy against the 10g monofilament in participants with type 2 diabetes, according to the following objectives:

- a) to assess in the feet of patients with type 2 diabetes, whether nerve conduction using the DPNCheck®, is more effective at detecting sensory neuropathy compared to the 10g monofilament.

4.3.7 Experimental Study 7: (Chapter 7, page 173)

The aim of experimental study 7 was to determine the effectiveness of using the Medicap in identifying ischaemia against the TBI in participants with type 2 diabetes, based on the following objective:

- a) to assess in the feet of patients with type 2 diabetes, whether TcPO₂ using the Medicap, is more effective at detecting ischaemia when compared to the TBI.

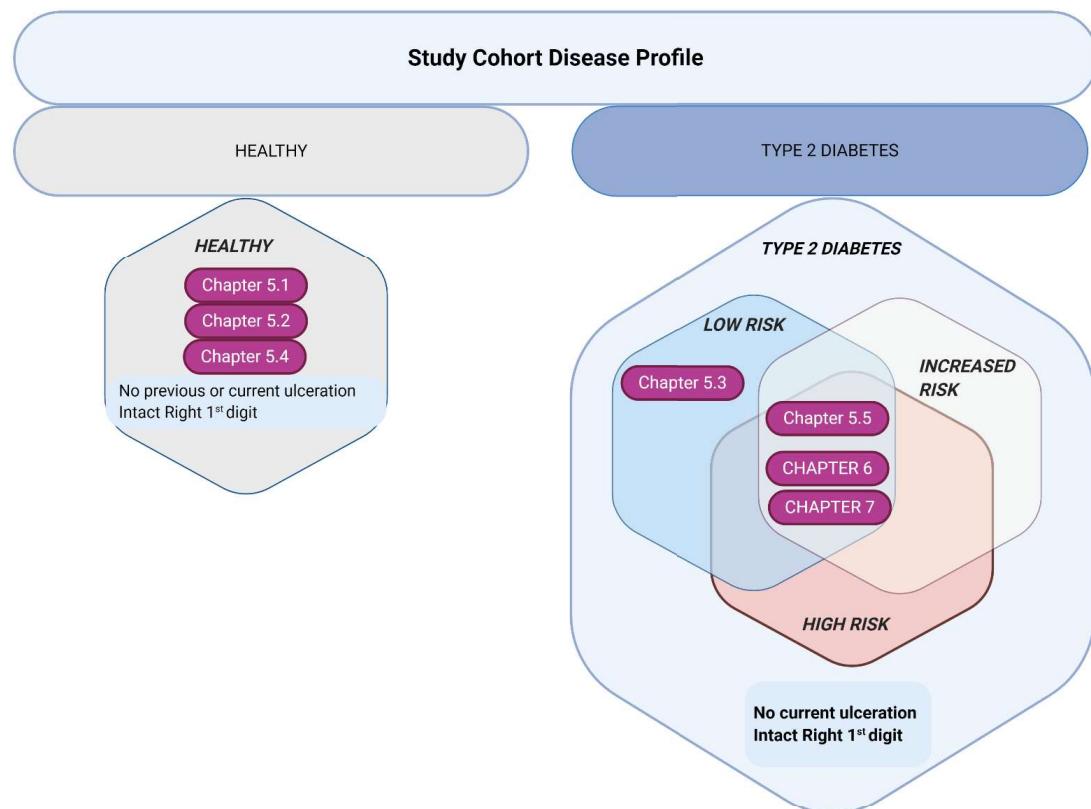
4.4 Analysis Populations

Primary analysis will be based on completion of the primary outcome data (nerve conduction, 10g monofilament, TBI and TcPO₂ procedures), on a population with type 2 diabetes, but without active ulceration, and fulfilling in the inclusion criteria in section 4.5. Any participants who decline or fail to complete all of the primary outcome data will be excluded from the final analysis.

4.5 Inclusion and Exclusion Criteria

The study consisted of a sequence of seven experimental investigations, which altogether recruited from participants who were healthy (Chapters 5.1; 5.2; 5.4) , and from those with type 2 diabetes (Chapters 5.3; 5.5; 6 and 7), as summarised in figure 4.5.1 :

Figure 4.5.1: Showing an overview of the study participants profiles



4.5.1 Inclusion criteria for healthy participants

The inclusion criteria for experimental study 5.1 (DPNCheck® reliability), experimental study 5.2 (Medicap validity) and experimental study 5.4 (TBI reliability), was for healthy adult participants, between 18-65 years of age, able to attend the University of Southampton for assessment, and had no known medical treatments affecting their neurovascular status. The criteria are outlined in Appendix A21.

4.5.2 Inclusion criteria for participants with type 2 diabetes

The inclusion criteria for experimental study 5.3 (Medicap reliability) was for adults with type 2 diabetes, classified as at low risk of ulceration according to NICE NG19 (2015). Experimental study 5.5 (DPNCheck® reliability, Medicap reliability, 10g monofilament reliability, TBI reliability), experimental study 6 (DPNCheck® effectiveness against the 10g monofilament), and experimental study 7 (Medicap effectiveness against TBI) recruited

participants with type 2 diabetes from across the low-medium-high risk stratifications according to NICE NG19 (2015), including healed previous ulcerations, but excluding those with current ulcers, and those without the right hallux. Further exclusions, are outlined in section 4.5.3.

4.5.3 Exclusion criteria that applied to all the experimental studies

From across all the studies, potential participants were excluded if they:

- were suspected of having other possible cause of nerve dysfunction, such declaring a history of drug or alcohol abuse, vitamin deficiency, traumatic leg or spinal injury or harmful chemical exposure
- declared pre-existing conditions that affect nerve function such as history of polio, Charcot-Marie-Tooth;
- had an active non-healed ulcer or surgical wound
- had right 1st digit amputation
- were unable to give informed written consent in English

4.6 Statistical Principles

4.6.1 Sample Size Calculation for Chapter 5.5; Chapter 6 and Chapter 7

From the literature review, diabetes neuropathy is clinically detectable earlier (Alavi *et al.*, 2014; Anderson 2017). Therefore with a focus on earlier detection at assessment, it was the prevalence of diabetic neuropathy that was used to estimate the required sample size to answer the primary research questions. However, as shown in Figure 1.3.2 neuropathy prevalence proved difficult to estimate given the divergent diagnostic criteria and absence of a consensus. Dyck *et al.* (2013) estimated prevalence of 45% diagnosed through quantitative sensory testing (QST) and autonomic function tests; and the same estimate was used by (Sharma *et al.* 2015). Across these studies, neuropathy prevalence increased with age and the duration of diabetes, however there is no agreement on estimated prevalence. Since it is assumed that autonomic dysfunction sets in before other types of neuropathy (Malik *et al* 2008 ; Freeman 2014 ; Tesfaye 2019) and QST is the most objective of these studies, an estimated prevalence of 45% was therefore chosen. Values for the required sensitivity (0.9) were based on previous studies (Dyck *et al.* 2013;

Sharma *et al.* 2015). Gathering this, and with the assistance from a statistician (Appendix A16), the calculation was undertaken with the following assumptions: the probability of achieving the required sample size is 90% (0.9), a 20 % width of the 95% confidence interval, 90% sensitivity and a 45% prevalence. This gave 83 participants. To account for missing primary outcome data, withdrawal, or other exclusion from the final analysis, a 10% overrun was included, giving an overall sample of 92 participants for the study. This recruitment target was supported by a statistician (Appendix A16).

4.6.2 Statistical Significance Levels

All applicable statistical tests will be two-sided and at the 5% significance level, with two-sided 95% confidence intervals presented whenever possible.

4.6.3 Collection of Demographic Data and Baseline Measurements

The main demographic measurements collected were as follows in Table 4.6.1

Table 4.6.1. Showing main demographic and baseline information

Name	Date of Birth (and age on date of assessment)
Study Site (Southampton or Manchester)	Gender
Duration of diabetes (months)	Glycaemic Control (HbA1c)
Previous Ulceration	Previous Amputation
Current Medication List	Ankle circumference

4.6.4 Assessment of Primary Outcome Measures

The following 4 primary outcome measures were determined for each participant as shown in Table 4.6.2

Table 4.6.2: Showing main outcome measures

Neuropathy

1 DPNCheck®	Nerve conduction velocity and amplitude
2 10g monofilament	from 10 foot sites as per protocol (Appendix A1)

Ischaemia

3 Medicap	mean TcPO ₂ level between 10-15 minutes
4 TBI(R1st toe pressure) ÷ (Brachial Pressure)	

4.6.5 Protocols for the primary outcome measures

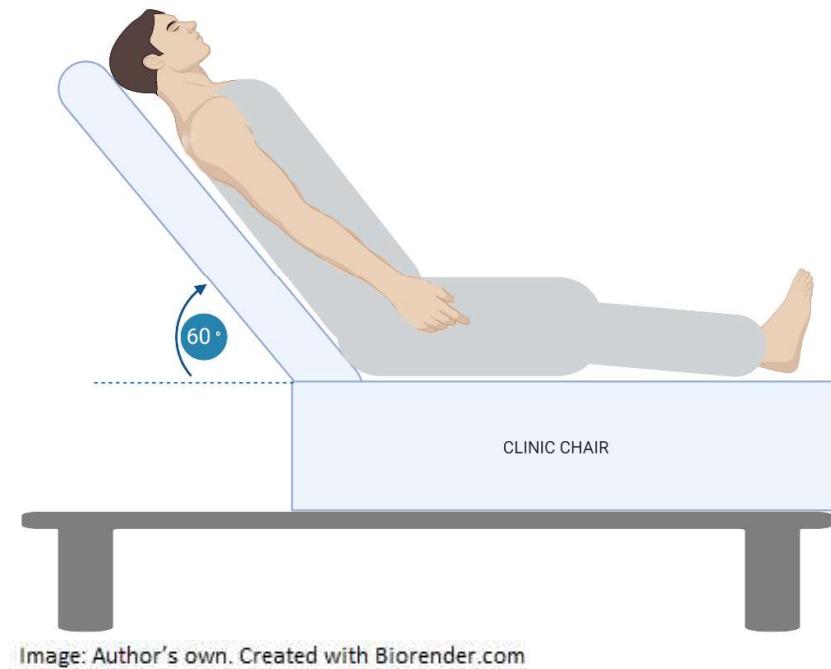
a) Assessment environment

At both sites (Southampton and Manchester), participants were assessed in a clinical room that would otherwise be used for clinical treatment, with no special adjustments made. The temperature of the rooms ranged from 18.5 °C to 31.2 °C (Southampton), and 22°C to 25°C (Manchester), through the different seasons over the recruitment period (22 months).

b) Participant positioning

All participants were positioned in the clinic treatment chair and rested for 10 minutes assessment, adopting a posture similar to Fowler's position, and with inclination kept at about 60° for all 92 participants as shown in Figure 4.6.1:

Figure 4.6.1: Showing position for all participants, for the assessment of all primary outcome measures



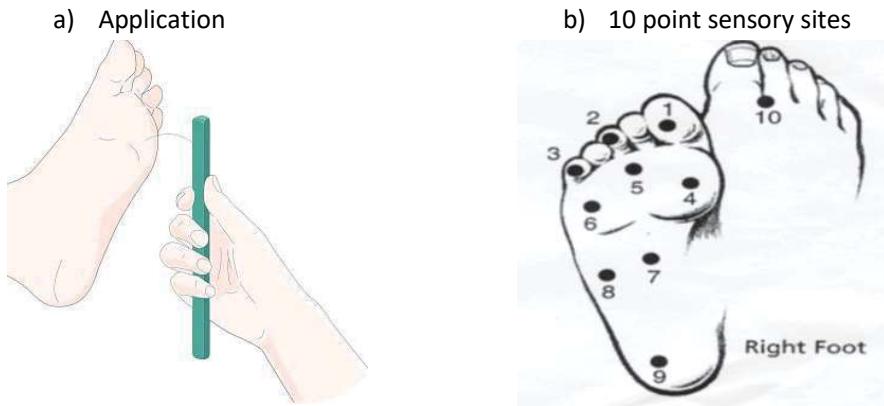
c) Order of assessments

With the exception of recording demographic information, there was no particular order used in the assessments of the primary outcome measures. On arrival, all participants emptied their pockets, and removed heavy clothing such as coats and jackets, and any footwear in order to expose the feet. A set of calibrated digital scales was used to record participant mass, and a height meter attached to the wall to record height, before they seated as shown in Figure 4.6.1. Whilst resting for 10 minutes, their demographics (Table 4.6.1) were recorded, before commencing assessments of the primary outcomes.

d) 10g monofilament

The protocol adopted for the 10g monofilament followed the suggested application to control for pressure (Figure 4.6.2(a)), on 10-point sensory sites (Figure 4.6.2(b)), as shown.

Figure 4.6.2: Showing 10g monofilament assessment



The detailed protocol is outlined in Appendix A1. The 10g monofilament was applied with minimal pressure until it buckled (Figure 4.6.2 (a)) ; to 9 plantar and one dorsum sites.

Participants were instructed to close their eyes, and to indicate verbally by saying “yes” if they felt the monofilament at each site. The total number of sensate sites out of 10 was recorded, and classified as no neuropathy ($\geq 8/10$); mild neuropathy (6-7/10); moderate neuropathy (3-5/10) and severe neuropathy ($< 3/10$)

e) DPNCheck®

The DPNCheck® assessment is outlined in Appendix A2, and the device was positioned as shown in Figure 4.6.3.

Figure 4.6.3; Showing DPNCheck® assessment

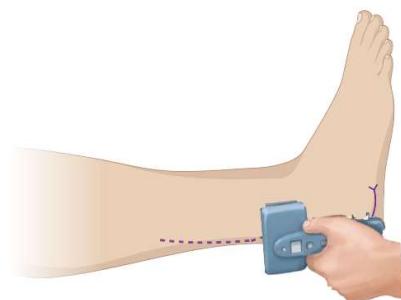


Image: Author's own. Created with Biorender.com

Once appropriately positioned, (Figure 4.6.1), the lateral aspect of the right leg was cleansed with a sterile wipe, covering an area about 5cm wide, and 10 cm proximal and 2 cm distal to the lateral malleolus, along the approximate site over the sural nerve (Figure 4.6.3). This was left to dry at room temperature. During the time the biosensor was removed from its protective packaging and attached to the sensor “receiving head” according to the manufacturer’s instructions (Appendix A2). Conductive gel was then applied to the 2 pins at the “sending head”, and small amount of conductive gel was also applied just below the lateral malleolus. The DPNCheck® was placed in firm contact with the lateral aspect of the leg , with the “sending head” distal to the lateral malleolus, and the “receiving head” with the biosensor proximal, as shown in Figure 4.6.3. The activating button was then pressed to send the charge, during which the DPNCheck® would flash a green light for about 10 seconds. After this, it would display 2 number on the LCD screen – to give the amplitude (amount of charge in μ V) and the velocity (m/s). in addition to this, the DPNCheck® also comes with software that can be loaded onto a computer, and a cable with which to attach the DPNCheck® after taking the recordings. The software would automatically upload the readings and display them on a chart with normative values for no neuropathy, and mild, moderate and severe neuropathy; as shown in Appendix A2. The DPNCheck® operates at foot temperatures $\geq 23^{\circ}\text{C}$, below which it would indicate an error and shut down. If a test failed due to low temperatures, or sural nerve anatomical variation, the foot was warmed with the participant’s clothing, recleaned, and the test was repeated after 5 minutes. Since participants had the assessments simultaneously, and all gave DPNCheck® readings, this aspect of the DPNCheck® acted as a de facto foot temperature control for the entire study.

f) TBI

The protocol for the TBI is outlined in Appendix A3. Figure 4.6.4 shows the DMX Dopplex with PPG probe from the ATP kit supplied by Huntleigh Healthcare. Following protocol, the brachial systolic pressures were taken for both right and left arms, and the higher one selected for calculating the TBI.

Figure 4.6.4: Showing the toe attachments and Dopplex for the TBI



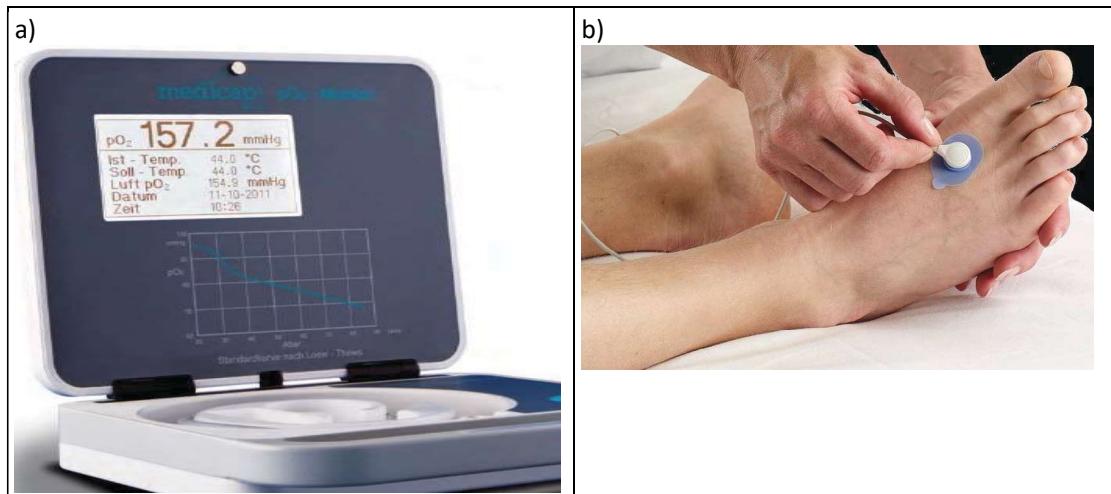
For the toe pressures, the red photoplethysmography (PPG) probe was attached to the plantar-apex of the right hallux, ensuring that the pulse wave was visible on the doppler screen. The toe cuff was then fixed loosely, and attached to both the sphygmomanometer lead tube and doppler unit. Pressure was then increased until the no pulse was detected by the PPG, at which point the pressure in the toe cuff was gradually released until the pulse returned. The pressure at which this was recorded gave the toe pressure, and TBI was determined by dividing the brachial pressure with the toe pressure. Values more than 1.1 or less than 0.7 were taken to indicate ischaemia with increasing severity from mild (0.65 -0.7), moderate (0.4- 0.64) severe (<0.4) and calcification (> 1.1)

g) Medicap

The protocol for the Medicap is outlined in Appendix A4, with the device (4.6.5(a)) and probe attachment (4.6.5(b)) shown: For each participant, the dorsum of the right foot was cleansed with a sterile wipe and allowed to dry naturally at room temperature. An area of

the foot in between the first and second metatarsals was chosen to attach the fixation ring, as shown in Figure 4.6.5.

Figure 4.6.5: Showing the Medicap device and attachment on foot



After this a single drop of the contact fluid was put inside the ring, and the oxygen sensor probe head was gently screwed into fixation ring. A light theraband bandage was attached lightly around the fixation ring, probe head and foot: this was necessary to maintain firm attachment, since the foot would gradually warm and weaken the fixation ring adhesive, which could loosen and be pulled away by the big probe head, thereby introducing air bubbles and invalidating the readings.

Once firmly attached the Medicap was set to “start measurement” and left to run for 15 minutes. TcPO₂ levels would stabilise by 10 minutes, and were recorded every 30 seconds. The readings between time 600 – 900 seconds (10 – 15 minutes) were used to calculate mean TcPO₂. After 15 minutes, the Medicap was turned off, all attachments removed.

After all the measurements were completed (10g monofilament, DPNCheck®, TBI and Medicap) all gel was removed from the arms and right foot by cleansing with sterile wipes and drying with blotting paper. The participant would then be free to redress and leave.

4.6.6 Risk stratification:

The outcomes from the main outcome measures (4.6.2) will be used in the risk stratification of each participant, based on the combined neurological and ischaemic components as follows:

Table 4.6.3: Showing the criteria used to determine risk stratification

	Neurological Function	Vascular Function
LOW RISK	No sensory deficit and no ischaemia	
INCREASED RISK	Either neuropathy or ischaemia , in the absence of other factors	
HIGH RISK	Neurological and Vascular deficit Neurological or Vascular deficit in combination with other factors (Previous ulceration; Previous amputation)	

4.6.7 Data Handling and Reporting

- a) *Data Transformation.* Variable data will be assessed to determine conformity to a “Gaussian distribution”, and any variables that do not will be \log_{10} transformed, and retested again for conformity.
- b) *Data reporting:* Variables that conform to a Gaussian distribution will be reported as means (\pm standard deviation); and those that conform to skewed distributions, depending on type, will be reported percentages or as medians (inter quartile range).
- c) *Missing Data:* Due to factors such as anatomical variation in nerves and blood vessels, withholding of demographic data, or otherwise withdrawal from the study, it is possible that there may be some missing data at trial conclusion. There will be no imputation of missing data. Any missing primary or secondary outcome data will be excluded from the final analysis.

4.7 Statistical Analyses – (outlined in Appendix A17)

4.7.1 Outcome Variables

- a) **The numbers of people suspected of having sensory neuropathy: (primary outcome)** based on DPNCheck®, will be counted, and compared to those suspected based on the 10g monofilament.

b) The numbers of people suspected of having ischaemia: (primary outcome) based on Medicap, will be counted, and compared to those suspected based on the TBI.

4.7.2 Primary Analysis of the Primary Outcomes

a) Neuropathy:

Each assessment (DPNCheck®; and 10g monofilament) will initially determine whether or not a participant is suspected of sensory neuropathy. **Frequency Counts** will be presented for the primary outcome, counting the number of people diagnosed for each category (no neuropathy/ neuropathy) as shown in Table 4.7.1.

Table 4.7.1: Neuropathy Frequency Counts: Primary Outcome Measure

	NO	YES
DPNCheck®	No impairment; n =	Neuropathy n =
10g monofilament	No impairment; n =	Neuropathy n =

Validity: Table 4.7.1 will be used to determine validity, based on sensitivity, specificity, and diagnostic accuracy of the 10g monofilament when compared to the DPNCheck®.

Agreement: Cohen's kappa will be used to estimate the extent of agreement between nerve conduction and the 10g monofilament. Agreement will be based according to the classification of Landis and Koch (1977) as ; Poor if $\kappa < 0.00$; Slight if 0.00 to 0.20; Fair if 0.21 to 0.40; Moderate if 0.41 to 0.60; Substantial if 0.61 to 0.80; Almost perfect if $\kappa > 0.80$. (Sim and Wright, 2005).

b) Ischaemia:

Each assessment (TcPO₂; and TBI) will initially determine whether or not a participant is suspected of ischaemia. **Frequency Counts** will be presented for the primary outcome, counting the number of people suspected of ischaemia as follows:

Table 4.7.2: Ischaemia Frequency Counts: Primary Outcome Measure

	NO	YES
Medicap	No ischaemia n =	Ischaemia n =
TBI	No ischaemia n =	Ischaemia n =

Validity: Table 4.7.2 will be used to determine the sensitivity, specificity, and diagnostic accuracy of TcPO₂ when compared to the TBI.

Agreement: Cohen's kappa will be used to estimate the degree of agreement between the two devices, based on Landis and Koch (1977).

4.8 Hypotheses and Interpretation of primary analysis results

The primary analysis will test the following null and alternative hypotheses:

4.8.1. Neuropathy:

H_{NR 0}: *There is no difference in frequency* (the number of people) between those suspected of having neuropathy based on the DPNCheck®, compared to those suspected based on the 10g monofilament. The 10g monofilament will have acceptable validity in diagnosing diabetic neuropathy.

H_{NR 1}: *There is a difference in frequency*, with nerve conduction suspecting more people of having neuropathy than the 10g monofilament.

If the results of the primary analyses suggest that there is sufficient evidence to reject the null hypothesis, it will be concluded that there is a difference in the number of people suspected of having neuropathy, that nerve conduction is more effective at the assessment of diabetes neuropathy; and the 10g monofilament will be deemed to lack adequate validity to assess for diabetes foot neuropathy.

4.8.2. Ischaemia:

H_{ISC 0}: *There is no difference in frequency* (the number of people) suspected of having ischaemia using the Medicap, compared to those suspected based on the TBI.

H_{ISC 1}: *There is a difference in frequency* with the Medicap suspecting more people of ischaemia than the TBI.

If the results of the primary analyses suggest that there is sufficient evidence to reject the null hypothesis, it will be concluded that the Medicap lacks adequate validity in the assessment of diabetes foot ischaemia when compared to the TBI.

4.9 Secondary analyses of the primary outcomes

4.9.1 **Neuropathy:** The severity of neuropathy will be categorised as mild-moderate or severe, with the frequency counts recorded. The discriminant ability of the DPNCheck® will be compared to that of the 10g monofilament, as shown in Table 4.9.1 .

Table 4.9.1 Showing classification of neuropathy severity

	No Neuropathy	Mild	Moderate	Severe
DPNCheck®				
10g monofilament				

Agreement: Weighted kappa will estimate the degree of agreement between the instruments; taking into account their respective ability to identify participants into the 4 categories. Agreement will be based according to the classification of Landis & Koch (1977) as described in section 4.8.2 .

4.9.2 **Ischaemia:** The severity of ischaemia will be categorised as mild, moderate or severe, with the frequency counts recorded. The discriminant ability of the Medicap will be compared to that of the TBI as shown in Table 4.9.2

Table 4.9.2: Showing classification of ischaemia severity

	No Ischaemia	Mild	Moderate	Severe	Calcified
Medicap					
TBI					

Agreement: Weighted kappa will estimate the degree of agreement between the instruments; taking into account their respective ability to identify participants into the 5 categories. Agreement will be based according to the classification of Landis & Koch (1977).

4.10 Analyses of the secondary outcomes

4.10.1 Comparison of risk stratification frequencies for each category, based on combined (DPNCheck® + TcPO₂) compared to combined (10g monofilament + TBI) (objective 2.7.1), as shown :

Table 4.10.1: showing tabulation of risk stratification frequencies for each combined approach

	Low Risk	Increased Risk	High Risk
DPNCheck® + Medicap			
10g monofilament + TBI			

The extent of agreement: The two stratification methods will be compared based on weighted kappa; taking into account their respective ability to stratify participants into the 3 categories. Agreement will be based according to the classification of Landis & Koch (1977).

4.10.2 **The ability of the DPNCheck® to identify risk on its own, when compared to the combined recommended methods (10g monofilament + TBI), (objective 2.7.2).** The numbers of people suspected of being 'at risk' – based on DPNCheck® alone, will be compared to those identified using the combined 10g monofilament and TBI as shown in Table 4.10.2 :

Table 4.10.2: Showing tabulation of risk identification based on the DPNCheck® alone compared to the combined (10g monofilament + TBI).

	Low Risk	'At Risk'
DPNCheck® alone		
10g monofilament + TBI		

The extent of agreement: The two stratification methods will be compared based on kappa; taking into account their respective ability to stratify participants into the 2 categories. Agreement will be based according to the classification of Landis & Koch (1977).

4.10.3 The ability of the Medicap to identify risk on its own, when compared to the combined recommended methods (10g monofilament + TBI), (objective 2.7.3). The numbers of people suspected of being 'at risk' – based on the Medicap alone, will be compared to those identified using the combined 10g monofilament and TBI as shown in Table 4.10.3 :

Table 4.10.3: Showing tabulation of risk identification by the Medicap alone, compared to the combined (10g monofilament + TBI)

	Low Risk	'At Risk'
Medicap alone		
10g monofilament + TBI		

The extent of agreement: The two stratification methods will be compared based on *kappa*; taking into account their respective ability to stratify participants into the 2 categories. Agreement will be based according to the classification of Landis & Koch (1977).

4.10.4 Whether the DPNCheck® can distinguish between people with different levels of ischaemia. The mean or median nerve conduction values based on Medicap or TBI ischaemia stratification, and the group differences analysed by the t-test or chi-square.

Table 4.10.4. DPNCheck® values between different states of macro or micro ischaemia

	No Ischaemia	Mild	Moderate	Severe
DPNCheck®	amplitude	amplitude	amplitude	amplitude
	velocity	velocity	velocity	velocity

4.10.5 Whether the Medicap can distinguish between people with different levels of neuropathy. The mean or median Medicap TcPO₂ values based on DPNCheck® or 10g monofilament neuropathy stratification, and the group differences analysed by the t-test or chi-square.

Table 4.10.5: Showing Medicap scores for different levels of neuropathy.

	No Neuropathy	Mild Neuropathy	Moderate Neuropathy	Severe Neuropathy
Medicap				

4.10.6 **Whether ankle circumference affects DPNCheck® values.** Depending on distribution, the strength and significance of the Spearman σ or Pearson r correlation coefficients will determine the extent to which ankle size affects DPNCheck® parameters.

4.11 Further Statistical Analyses

4.11.1 Depending on the shape and distribution of data, either the Spearman σ (non-parametric) or the Pearson r (parametric) correlation was used to determine the strength of linear correlations. The Kappa statistic was used to assess the level of agreement between devices.

4.11.2 For the validity investigations (Experimental Studies 5.2 and 5.3), it was important to examine and determine the extent of measurement bias, which was done through Bland-Altman analysis (Bland and Altman 1986).

4.11.3 For the reliability investigations (Experimental Studies 5.1, 5.4 and 5.5) the extent of variability was determined through Bland-Altman analysis, and the extent of reliability was examined based on the appropriate version of the intraclass correlation coefficient, as outlined in sections 4.11.4, 4.11.5 and 4.11.6.

4.11.4 For DPNCheck reliability on healthy participants (Experimental Study 5.1), analysis was based on statistical accuracy comparisons using average measures. The intra-class correlation coefficient (version 2,1) (ICC), on the continuous variables from the DPNCheck® (velocity and amplitude) was used to determine intra-rater reliability. Correlation coefficients greater than 0.75 were considered to have excellent reliability, based on Koo and Li, (2016). A single measures, two-way mixed model, type absolute intra-class correlation coefficient was used to calculate ICCs.

4.11.5 For TBI inter and intra-rater reliability on healthy participants (Experimental Study 5.4), the raters were assumed to have been randomly selected from a larger group of students, and results intended to be generalisable, which gave ICC Model 2. Reliability was calculated on mean values from the first two measurements for each rater, which gave an ICC form for average measures.

- a) For each individual rater: The version of ICC was ICC (2,2).
- b) Between two raters: The version of ICC was ICC (2,2).
- c) Between three raters: The version of was ICC (2,3).
- d) A Bland-Altman plot was constructed to determine potential bias between assessments.

4.11.6 For the intra-rater reliability of all 4 devices when used together on people with type 2 diabetes (Experimental Study 5.5) reliability was based on the strength of the intraclass correlation coefficient. Although the results were intended to be generalisable, and the rater was a podiatrist, the additional research training implies the rater was 'fixed' and could not be assumed to have been drawn from a general sample of podiatrists. The participants who returned for reassessment were randomly drawn from a larger population of 92 participants. Reliability was calculated for: absolute agreement, on 'two way mixed' effects, for single values from the first measurements only for each device. The version of ICC selected, for consistency using on single values, was therefore ICC (3,1).

4.12 Statistical Software

The statistical analyses will be undertaken using SPSS v26, supplemented where required by Microsoft Excel and the R statistical packages.

Chapter 5 VALIDITY AND RELIABILITY EXPERIMENTAL STUDIES.

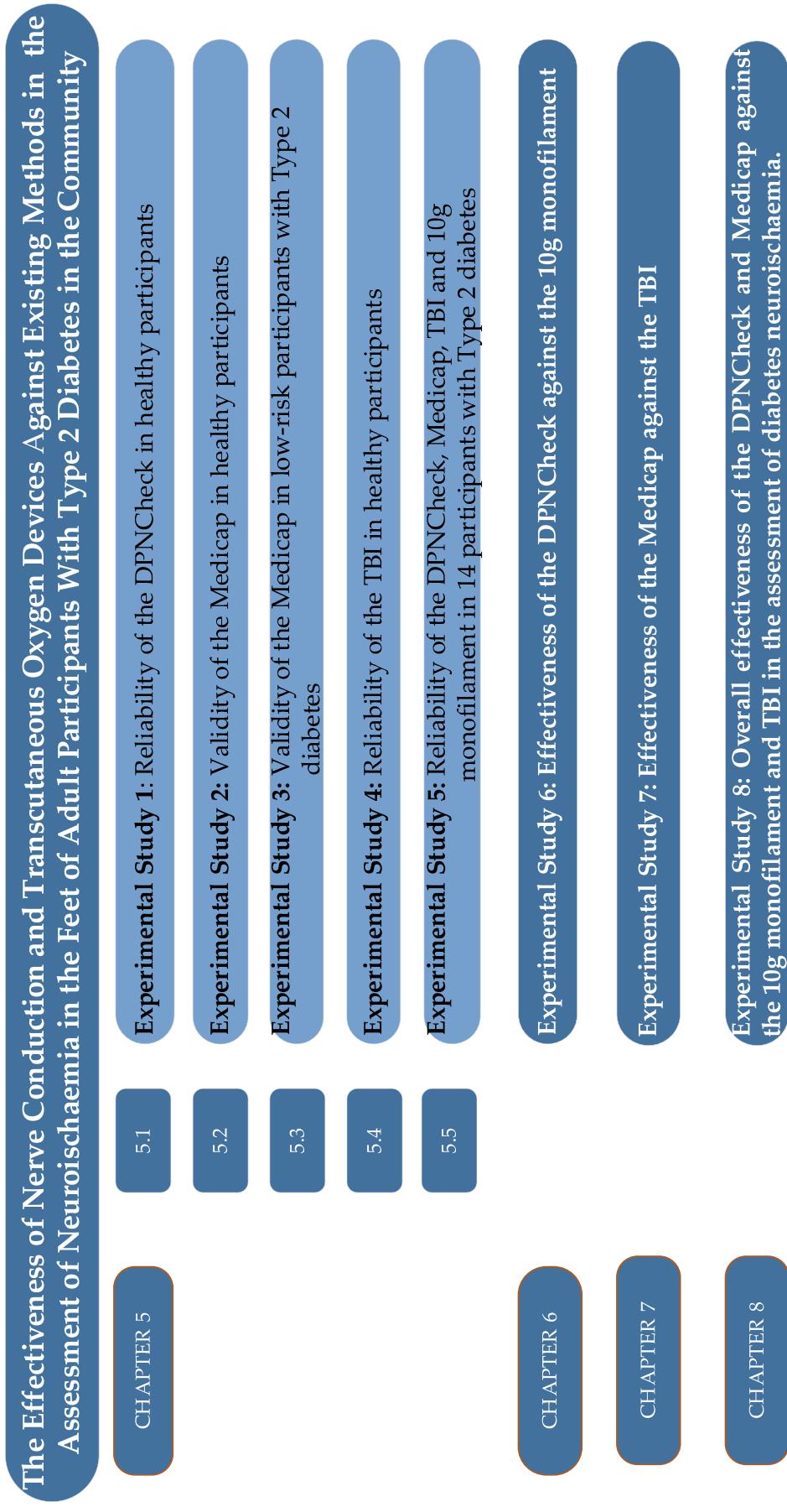
From the literature review (Chapter 3) the DPNCheck® has more validity literature supporting its use in neuropathy assessment, whilst the Medicap is a more novel device in determining microischaemia. Building on this, and as shown in Figure 5.1, the main aim of this chapter is to investigate the reliability of the DPNCheck®, the validity and reliability of the Medicap, and overall reliability of the four devices (DPNCheck®, Medicap, 10g monofilament and TBI), before progressing to the effectiveness investigations.

Figure 5.1: Showing the validity and reliability investigations within the context of the overall thesis.



This provides an outline experimental studies done to investigate the reliability of the DPNCheck® (section 5.1), and the validity of the Medicap in healthy (section 5.2) and ‘low risk’ type 2 diabetes participants (section 5.3). It also outlines experimental studies to investigate the reliability of the TBI in healthy participants (section 5.4), and concludes by investigating the reliability of all four devices when used together in participants with type 2 diabetes (section 5.5). A summary of the experimental investigations is shown in Figure 5.2:

Figure 5.2: Showing a summary of the experimental investigations



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5.1 EXPERIMENTAL STUDY 1: The Reliability of the DPNCheck® in healthy participants

5.1.1 Introduction.

Despite the reliability of the DPNCheck® having been investigated in previous studies (Chapter 3.3, page 68), it was important to investigate its reliability whilst familiarising with the operation of the device, beginning with healthy participants before introducing it to a clinic setting. Figure 5.1.1. Shows where this investigation of the DPNCheck® reliability, lies within the context of the thesis overall.

Figure 5.1.1: Showing reliability of the DPNCheck investigation within context of overall thesis



5.1.2 Research Question

- a) What is the intra-rater reliability of the DPNCheck® as a nerve conduction device over the sural nerve in the feet of healthy participants?

5.1.3 Objectives

To determine the intra-rater reliability of the DPNCheck® in assessment sural nerve conduction in the feet of healthy participants.

5.1.4 Method

a) *Study Design and sample recruitment*

As the DPNCheck® gives a snapshot of sural nerve health status at a point in time, this was designed as a cross sectional study. A convenience sample of 20 healthy participants, due to time and ethical constraints, was recruited from staff and students at the University of Southampton. Healthy participants aged between 18 – 40 years responding to poster adverts and who met the inclusion criteria (Appendix A21); were recruited, excluding those that may have a compromised sensory function of the lower limb. Testing this only this cohort limited the influence of external variables, producing more definitive conclusions on intra-rater reliability based on a single population. The health assessment questionnaire (Appendix A21) based on a modified version of the MNSI instrument used to identify peripheral neuropathy (Moghtaderi, Bakhshipour and Rashidi, 2006), was used to determine the subject's suitability for the study.

b) *Ethical approval*

The study was part of a larger student project investigating nerve function including vibration perception with the biothesiometer, in the Faculty of Health Sciences at the University of Southampton. Ethical approval was granted by the University of Southampton Ethics Committee via the Ethics and Research Governance Online system (ERGO ID 29998) (Appendix A5). All participants gave full written consent before participating in the study.

c) *Test Protocol*

Participants: Participants were screened in accordance with the inclusion and exclusion

criteria (Appendix A21) before participating in the study using the health assessment questionnaire (Appendix A22). Each participant had the nerve conduction test repeated on only the right leg over two visits, following the DPNCheck® protocol (Chapter 4.6.5(e), pages 95-96; and more detailed on Appendix A2).

d) Outcome Measures

The primary outcome measures were the nerve conduction velocity (m/s) and amplitude (μ V) from the DPNCheck®.

e) Data Analysis

Types of Data: Continuous data were reported as mean \pm standard deviation (SDs); and categorical data as numbers and percentages (%). Data was assessed for normality (Chapter 4.11.1), and two-tailed paired t- and chi-squared variants applied to study the significance of continuous and categorical data, respectively, with a significance level for all tests set at 5 %.

Determination of intra-rater reliability of the DPNCheck®: Following Chapter 4.11.4 (page 105), reliability was determined in two ways; over the same day and over two different days, 14 days apart. At the first visit, nerve conduction, following the DPNCheck® protocol (Chapter 4.6.5 (e) pages 95-96; and Appendix A2) was assessed twice across the outside of the right ankle along the sural nerve, and a mean of the two readings taken. This was repeated 14 days later in the same individuals, on the same leg. Testing and retesting were carried out in the same room with similar conditions – including time of assessment (all in the morning), kept as stable as possible. Repeating the nerve conduction test as described made it possible for DPNCheck® test-retest reliability to be determined, as described in section 4.11.4 (page 105) of the Methods Chapter.

5.1.5 Results

a) Demographic information.

The demographic information on the participants is shown in Table 5.1.1.

Table 5.1.1: Demographics for healthy participants (n=20, after 1 withdrawal)

Demographics	mean (SD)
Age (years)	22.8 (4.7)
Gender Male % (Male/Female)	40% 8/12
Mean Body Mass (kg)	67.1 (12.9)
Mean BMI (kg/m ²)	23.8 (3.5)
Smoking History (%) (current / previous) (never)	0 % 0 20

This shows that 20 participants (8 males; 12 females) were included in the study, with an average age of 22.8 +/- 4.7 years, a BMI = 23.8 kg/m² and with no smoking history. In total, 21 participants volunteered for the study, with one excluded in the final analysis, as shown in Table 5.1.2.

b) Raw nerve conduction data for participants.

The raw data collected are shown in Table 5.1.2. Of the 21, data was incomplete for 4 participants due to declining follow-up (**a**); or missing the initial day testing (**b**). One participant had to be withdrawn from the study as a result of later declaring having type 1 diabetes (*w).

Table 5.1.2: Raw DPNCheck® participant data for healthy participants

		Day 1				Day 2			
Volunteers		Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
Gender		Velocity (m/s)		Amplitude (µV)		Velocity (m/s)		Amplitude (µV)	
1	F	54.0	54.0	15.0	15.5	56.0	55.0	16.0	16.1
2 <i>a</i>	F	56.0	56	22.0	22	Declined follow-up			
3	M	57.0	55.0	29.0	25.0	55.0	56.0	27.0	27.0
4 <i>b</i>	F	Missed day 1 testing				52.0	53.0	8.0	7.0
5	F	49.0	48.7	21.8	21.2	55.0	59.0	7.0	8.0
6	M	47.0	48.0	6.0	5.0	46.0	45.0	4.0	5.0
7 <i>b</i>	F	Missed day 1 testing				63.0	63.0	27.0	25.0
8 <i>a</i>	F	59.0	59.0	8.0	7.0	Declined follow-up			
9	M	65.0	62.0	27.0	25.0	65.0	62.0	28.0	27.0
10	F	57.0	56.0	18.0	17.0	64.0	64.0	16.0	17.0
11	F	62.0	63.0	17.0	18.0	65.0	64.0	13.0	12.0
12	F	52.0	51.0	23.0	23.0	51.0	51.0	23.0	24.0
13	F	54.0	55.0	23.0	2.0	55.0	55.0	23.0	23.0
14	F	52.0	52.0	22.0	23.0	54.0	55.0	22.0	23.0
15	M	65.0	64.0	24.0	24.0	62.0	62.0	25.0	24.0
16	M	55.0	55.0	31.0	32.0	54.0	56.0	30.0	31.0
17	M	62.0	62.0	24.0	24.0	61.0	61.0	25.0	25.0
18	M	56.0	56.0	27.0	27.0	55.0	56.0	27.0	26.0
19	F	47.0	42.0	23.0	23.0	58.0	55.0	7.0	15.0
20	M	51.0	50.0	21.0	22.0	42.0	42.0	14.0	17.0
*21 <i>w</i>	F	37	41	4	5	39	38	6	5

M = male; F = female

a Declined follow-up. Data included in analyses; *b* Missed day 1 testing. Data included in analyses

* *w* Withdrawn due to declaring diabetes diagnosis. Data not included in analyses

c) *Primary outcome measures.*

The summary data from the primary outcome measures, is shown in Table 5.1.3 :

Table 5.1.3: Summary data of primary outcome measures for the DPNCheck®

	Day 1				Day 2			
	Velocity (m/s)		Amplitude (µV)		Velocity (m/s)		Amplitude (µV)	
	Test 1	Test 2						
Mean (+/- SD)	55.6	54.9	21.2	19.6	56.3	56.3	19	19.6
	55.3 (5.6)		20.4 (7.3)		56.3 (6.1)		19.3 (8)	

d) *DPNCheck® reliability.*

The test – retest reliability of the DPNCheck® was determined based on the intra-class correlation coefficient (2,1) with the results shown in Table 5.1.4.

Table 5.1.4: Intra-class correlation coefficient for reliability of the DPNCheck®

Single measures ICC (2,1) for DPNCheck®		
	Day 1	Day 2
Velocity (m/s)	0.97 (95% CI = 0.91 - 0.99)	0.97 (95% CI = 0.95 – 0.98)
Amplitude (µV)	0.76 (95% CI = 0.63 – 0.86)	0.96 (95% CI = 0.95 – 0.99)

5.1.6 Discussion

The results show that the DPNCheck® had excellent intra-rater reliability, with all parameters > 0.75 (Koo and Li 2016). From table 5.1.4, on day 1, the velocity coefficient was 0.97 (95% CI = 0.91- 0.99), and for amplitude 0.76 (95% CI = 0.63 – 0.86); whilst on day 2 it showed an ICC (2,1) = 0.97 (CI = 0.95 – 0.98) for velocity, and 0.96 (95% CI = 0.95 – 0.99) for amplitude. On day 1, the mean conduction velocity was 55.3 m/s (+/- 5.6), with an amplitude of 20.4 µV (+/- 7.3); and on day 2, mean velocity was 56.3 m/s (+/- 6.1) and 19.3 µV (+/- 8) amplitude. These parameters are consistent with previous studies, including Lee *et al* (2014) who, from 80 healthy participants, found the DPNCheck® to have excellent test-retest reliability with ICC(2,1) for velocity = 0.94 (Median 54 ; IQR 45 – 58); and for amplitude = 0.97 (Median 5; IQR 3-13). They also reported mean conduction velocity of 50.2 m/s (+/- 5.7), at a mean amplitude of 18.5 µV (+/- 4.1), which corroborate the reliability findings from the present study as shown in Table 5.1.4. Lee *et al* (2014), further speculated on the potential of ankle size in affecting nerve conduction values,

which was considered in the design of the neurological experimental study (Chapter 6).

a) Limitations. Intra-rater reliability was determined from a relatively healthy and small (n=20) university cohort, thereby limiting the generalisability of the results, which cannot be extended to a population of diabetes participants.

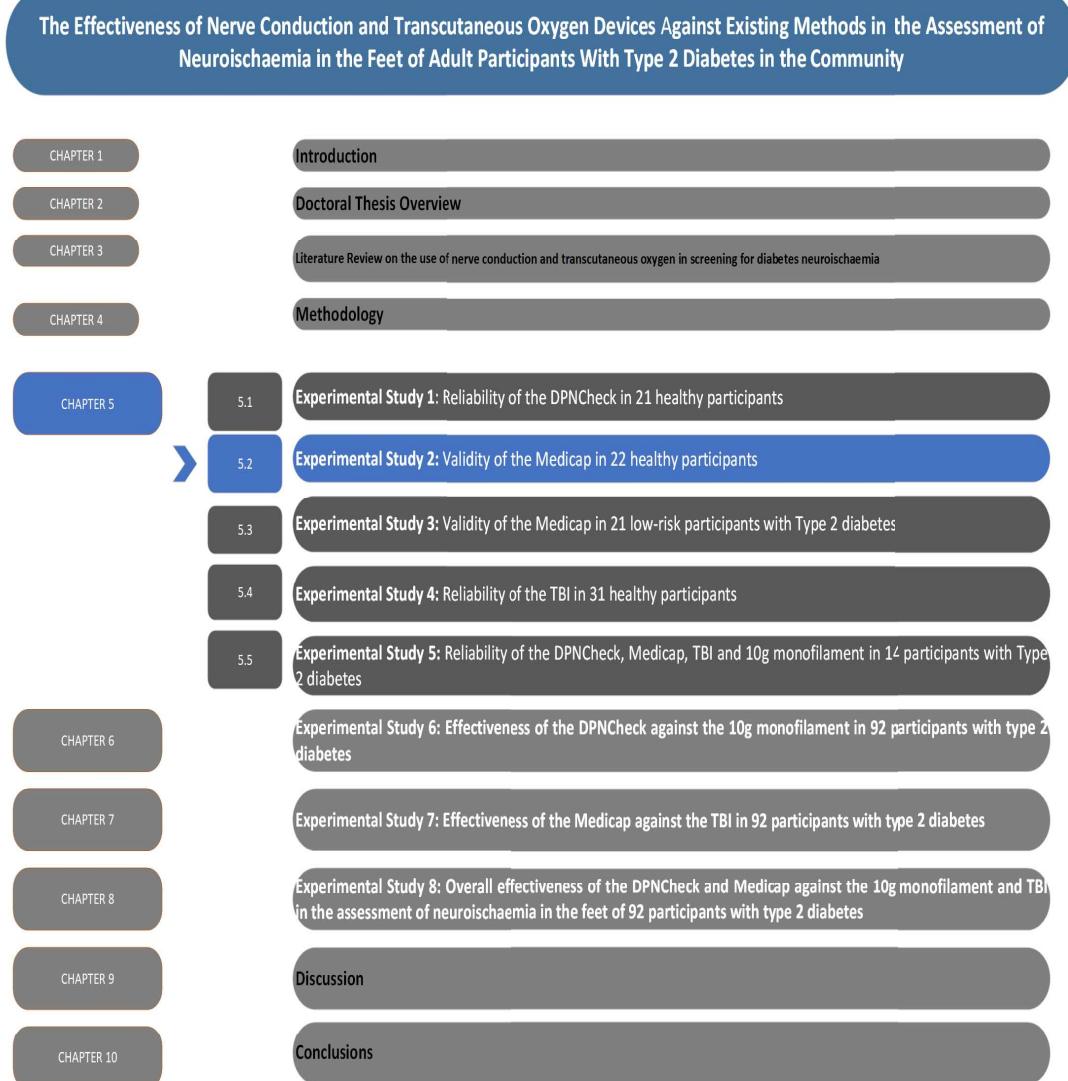
b) DPNCheck® reliability. In summary, the DPNCheck® demonstrated excellent intra-rater reliability, and the findings from this study agree with those of previous investigations discussed in section 5.5 of this chapter. Building on these reliability results from healthy participants, the reliability of the DPNCheck® was further investigated in people with type 2 diabetes (Section 5.5), as well as investigating the potential effect of ankle size on DPNCheck® parameters (Chapter 6).

5.2 EXPERIMENTAL STUDY 2: The Validity of the Medicap in healthy participants

5.2.1 Introduction

This section investigates the validity of the Medicap as a TcPO₂ monitoring device when compared to a reference standard (TCM 400 Radiometer) on healthy participants, and its relevance within the context of the thesis is shown in Figure 5.2.1.

Figure 5.2.1: Showing Medicap validity investigations within the thesis context



This section investigates the validity of the Medicap as a TcPO₂ monitoring device when compared to a reference standard (TCM 400 Radiometer) on healthy participants. The Medicap uses a different detection method (photochemical), when compared to established reference devices (electrochemical), and it is therefore important to determine the validity of the photochemical (Medicap) against the reference electrochemical method (TCM 400) of TcPO₂ detection.

5.2.2 Background: The electrochemical Clark type (TCM400) and photochemical probes (Medicap)

The established method of TcPO₂ detection, as used by the TCM400 (Radiometer[®]), employs a modified electrochemical Clark-type electrode, which heats the overlying skin to 43°C to create local hyperaemia and where TcPO₂ values are more representative of arterial oxygen saturation. However, Clark type electrodes are affected by lengthy setups, probe physical vulnerability to damage and time to stabilisation (Williams, Price and Harding, 2006). In a clinical setting they are less reliable and less practical as they are very sensitive to movement, moisture and temperature fluctuations (Oriani *et al.*, 1996; Kalani *et al.*, 1999; Deng *et al.*, 2014) and measurement drift (Eberhard *et al.*, 1975; Marsden *et al.*, 1985; Urban *et al.*, 2015). The nature of a Clark type electrode requires frequent and resource intensive membrane changes, complex calibration and specialised software to interpret the waveforms. In spite of this, the non-invasive assessment of TcPO₂ is still important as it gives a localised measure of arterial quality, and complements common macroischaemic measures in predicting ulcer outcomes. The Medicap Précise 8001 (Medicap Homecare GmbH, Ulrichstein, Germany; Moor instruments) is a novel device based on the photo-chemical measurement principle, as opposed to the more established electro-chemical based Clark type probe. The potential advantages of the photochemical technique are that the system comes readily calibrated, sensor cleaning is easy, does not require expensive membrane changes, and is quicker to set up and run.

5.2.3 Primary Research Question:

- a) What is the criterion validity of the Medicap in measuring transcutaneous oxygen in the feet of healthy participants?

5.2.4 Secondary Research Questions:

- a) Do the device outputs (Medicap and TCM400) reach a stable output at the same time?
- b) Do the two devices (Medicap and TCM400) warm the skin to a similar temperature?
- c) Do the two devices (Medicap and TCM400) induce a similar vasodilation (measured using VMSOXY)?
- d) Does $TcPO_2$ differ between placement sites (dorsum between 1st – 2nd metatarsal phalangeal joint (MTPJ); and dorsum 4th and 5th MTPJ) (Figure 5.2.3 on page 122)

5.2.5 Aims and Objectives

The objective of this study was to determine the criterion validity of the Medicap against the reference TM400 in detecting $TcPO_2$ on the dorsum of the feet of healthy participants.

5.2.6 Method

a) Study design and participant recruitment

As the Medicap and TCM400 devices gave a snapshot of nerve health status at a point in time, this was a cross sectional study design. $TcPO_2$ was measured simultaneously at two sites on the dorsum of the foot using the TCM400 and Medicap devices. 22 healthy adult participants, aged between 18-70 years were recruited from University of Southampton and Southampton University Hospitals Trust staff and students. All participants gave informed written consent. Potential participants were ineligible if they were pregnant; taking drugs that modify cardiovascular status (including nitroglycerin and prostaglandin analogues, statins, steroids and anti-inflammatory agents); had a history of cardiovascular disease, including Raynaud's phenomenon, and if they had diabetes mellitus or any other chronic condition.

b) Sample size determination.

A sample of 22 participants was determined by comparing paired differences in transcutaneous readings, given the expected mean of paired differences to be 10;

expected standard deviation to be 15, with the aim of achieving a power of 80% and a two-sided significance level of 5% (Dhand and Khatkar, 2014).

c) Ethical approval

Faculty Ethical approval was granted through the University of Southampton, ERGO (ethics and research governance online) system under the Faculty of Health Science Research Ethics Committee number 17598 (Appendix A6).

d) Test Protocol

All investigations took place in a temperature controlled (21.5 °C – 25 °C) laboratory, Faculty of Health Sciences at University Hospital Southampton.

TCM400 machine preparation. This included preparation of the Radiometer TCM400, with the insertion of new membranes (according to manufacturer's instructions) and calibration of the Clark type probe (as per instructed on device screen). All machines were then switched on (The Radiometer TCM400; the Medicap, the VMS-OXY and laptop computer with VMS software) as the TCM400 completed calibrating.

Participant preparation. Participants were asked to refrain from strenuous exercise for 24 hours prior to the study visit, and from smoking and consuming caffeine-containing drinks for at least 2 hours prior to the study visit. Acclimatisation occurred whilst the participant was seated as shown in Figure 5.2.2., over 15 minutes in the temperature controlled room ($22.1 \pm 0.4^\circ\text{C}$). The study was conducted with the participant sitting on a clinical chair with their back upright and with their feet and legs straightened (as shown in Figure 5.2.2). This imitates the position patients would adopt in a usual clinical chair for podiatry assessment and treatment.

Figure 5.2.2. Showing participant position during acclimatisation and TcPO₂ assessment.

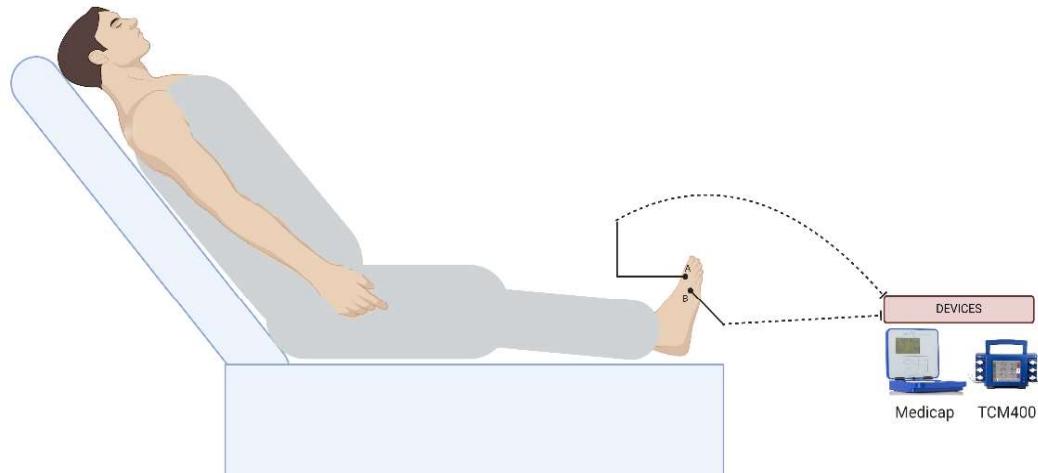
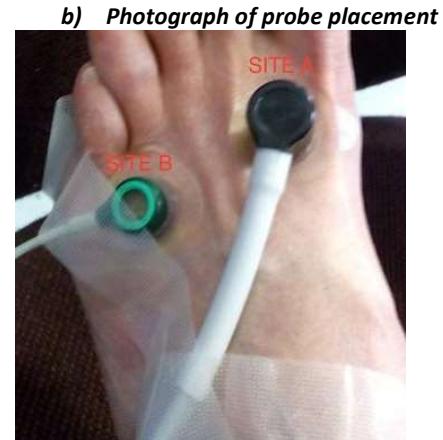
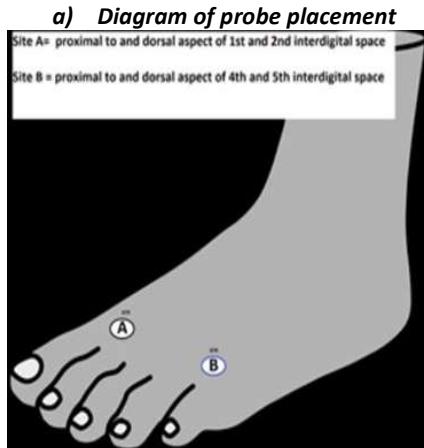


Image: Author's own. Created with Biorender.com

Demographics: Whilst acclimatising, information regarding age, recent exercise, medication (such as recent NSAIDS) and blood pressure, height and mass was collected.

Probe placement: Sites were randomised for placement of the two TcPO₂ sensors, avoiding bony prominences and visible veins between the dorsal 1st and 2nd (Site A) and the 4th and 5th (Site B) inter-metatarsal spaces (Figure 5.2.3). The Medicap and Radiometer TCM400 (combined TcPO₂/CO₂) sensors were approximately 5 cm apart. Both were held in place using sticky discs/fixation rings as described by the manufacturers. To avoid air bubbles the required amount of contact fluid was added to the each holder and the sensor secured in the holder with the dorsum of the foot held horizontally.

Figure 5.2.3. Diagram (i) and photograph (ii) of probe placement sites between 1st-2nd (Site A) and 4th-5th (Site B) inter-metatarsal spaces.



Measurements: Participants were instructed to sit quietly without talking or moving their feet throughout the study. Both the TCM400 and Medicap TcPO₂ probes were left to reach the required temperature (43.5°C) and readings from both sensors were taken for up to 20 minutes. Blood flux, skin temperature and tissue oxygenation (SO2%) were additionally measured at both sites on removal of the TcPO₂ sensors using the VMSOXY (Moor Instruments, UK) and combined laser Doppler (LD) and white light reflectance probe (moorCP1T-1000, Moor Instruments Ltd, Axminster, UK) with a single point 785 nm, 1 mW low power red laser light source (moorVMS-LDF2, Moor Instruments Ltd, UK) and a 400-700 nm, <6 mW white light source (moorVMS-OXY, Moor Instruments Ltd, UK) (LD fibre separation of 0.5 mm and SO2 separation of 1 mm).

Flux measurement at the fixation sites: (VMS-OXY). At the end of the TcPO₂ measurement period, one of the sensors was removed along with the fixation ring and any excess contact fluid gently blotted with paper. To measure flux, the VMS-OXY probe was attached with a sticky O-ring at the TcPO₂ sensor site. Blood flow and OXY signals [oxygenated haemoglobin (oxyHb), deoxygenated haemoglobin (deoxyHb), total haemoglobin (totalHb) and tissue oxygen saturation (SO2)] were recorded continuously for up to 3 minutes. It was important that whilst the VMSOXY output was recorded at the first sensor site, the other sensor remained in place to maintain skin temperature at that site. After 3 minutes, the second TcPO₂ sensor was removed, the skin site dried and the VMS-OXY reading repeated over the second heated sensor site. After the readings were taken, all attachments were removed and participants asked to sit up slowly and were free to leave. The whole study data collection time per person was took approximately 40 minutes.

e) Outcome Measures

The main outcome measure was the TcPO₂ (mmHg) on each device on each foot site, with secondary outcomes measuring flux and time to stabilisation.

f) Data handling and analysis

VMSOXY data were saved directly onto the recording computer and analysed using the manufacturer's software (Moorsoft v4.0). Radiometer data were saved onto the device and transferred to an encrypted USB memory stick. Since the Medicap saves directly to

the device with no means of exporting data, this was read and manually recorded onto a spreadsheet onto an encrypted computer. All USB memory sticks and the camera are stored in compliance with the Data Protection Act (1998) and the University of Southampton policy for the storage of data

<http://library.soton.ac.uk/researchdata/retention>). Unlinked anonymised data (identified by participant study number and date of birth) were stored on the software system under investigation and transferred to computers housed within the clinical academic facility at Southampton General Hospital, and University of Southampton secure password protected laptops for analysis. Data were analysed in Microsoft Excel, SPSS Statistics version 22.0 (SPSS Inc., Chicago, IL, USA) software and GraphPad Prism. Data are presented as raw data plots of the two machine outputs for each individual. Steady state values of $TcPO_2$ were calculated over the period 10-15 min after the start of recording ($TcPO_2$ 10-15). Data are expressed as mean (SD) or median (range).

Types of Data: Continuous data were reported as mean \pm standard deviation (SDs); and categorical data as numbers and percentages (%). Outputs from the two sensors and variations between probe placement sites were compared using non-parametric statistics and a Kappa statistic used to assess the level of agreement between devices (Bland and Altman 1986), with a significance level for all tests set at 5 %.

Determination of Medicap Criterion Validity: the extent of agreement and correlation at 'steady state' will be analysed between the $TcPO_2$ values from the Medicap and TCM400. Analysis will also be done on the time it takes for each device to reach stable output ('steady state').

Potential sources of variability: Since it is not possible to attach both probes simultaneously to the same site at the same time, attaching them to different sites (site A or site B) could be a potential source of variability. In addition, it is also possible that the different probes heat the skin to different extents, which in turn would affect flux and $TcPO_2$. It was therefore important to investigate the potential effects of site variability, and effects of heating (flux).

5.2.7 Results

a) Demographics

Despite recruiting 22 participants, data from the first 4 individuals were incomplete due to machine failure (n=1) or flawed owing to probe detachment or poor sensor contact with the skin resulting in unusable readings (n=3). The demographics of the remaining 18 healthy adult individuals are shown in Table 5.2.1.

Table 5.2.1: Demographics for healthy adult study sample (n=18)

Demographics mean(SD) for n = 18	
Age (years)	34.2 (9.4)
Gender (Male / Female)	11 / 7
Mean Body Mass (kg)	86.6 (23.9)
Mean BMI (kg/m ²)	27.1 (5.3)
Smoking History (%)	11.1 %
(current)	2
(previous)	0
(never)	16

b) Site randomisation.

The results from where each probe was placed (Site A and Site B) for each participant, are shown in Table 5.2.2.

c) Primary Outcome - Raw *TcPO₂* outputs from Medicap® vs TCM400® devices

The outputs from the two devices for all 22 healthy individuals are shown in Appendix A.

Inspection of these outputs showed that data from the first 4 individuals were incomplete due to machine failure (n=1) or flawed owing to probe detachment or poor sensor contact with the skin (fluid bubble) (n=3), and therefore excluded from analysis.

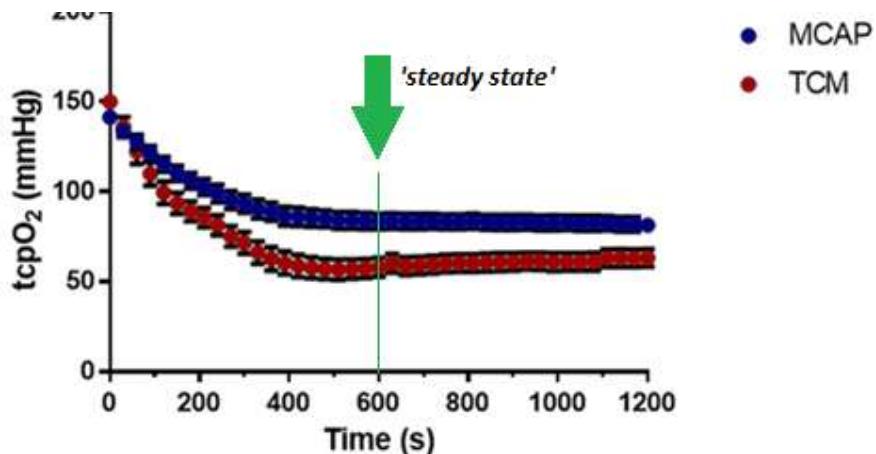
Table 5.2.2: Randomisation to site and order for VMS-OXY assessment

<u>Case ID</u>	<u>MCP site</u>	<u>TCM site</u>	<u>VMS-Oxy 1st placement</u>
1, 2, 3, 4	Data from the first 4 individuals were incomplete due to machine failure (n=1) or flawed owing to probe detachment or poor sensor contact with the skin (fluid bubble) (n=3).		
5	B	A	over TCM 1st site B
6	A	B	not recorded
7	A	B	not recorded
8	A	B	over TCM 1st site B
9	B	A	over TCM 1st site A
10R	A	B	over MCP 1st site A
10L	B	A	over TCM 1st site A
11	A	B	over TCM 1st site B
12	B	A	over TCM 1st site A
13	B	A	over TCM 1st site A
14	B	A	over MCP 1st site B
15	A	B	over TCM 1st site B
16	B	A	over MDCP
17	A	B	over MDCP
18	B	A	over MDCP
19	B	A	over MDCP
20	A	B	over TCM
21	A	B	over TCM
22	B	A	over MDCP

d) Secondary Outcome: Time to Steady State.

Figure 5.2.4 shows a summary of the time course of the simultaneous measurements from the two sensors for the remaining 18 individuals. The raw traces are shown in Appendix B4. Both devices recorded an initial rapid decline in $TcPO_2$ to reach a steady state at approximately 10 min after the start of recording.

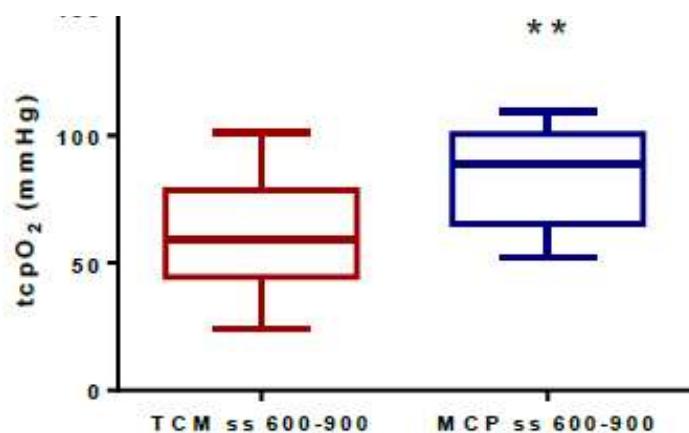
Figure 5.2.4. Time course of TcPO₂ measured using Medicap and TCM400



e) Secondary Outcome: Steady State TcPO₂ values:

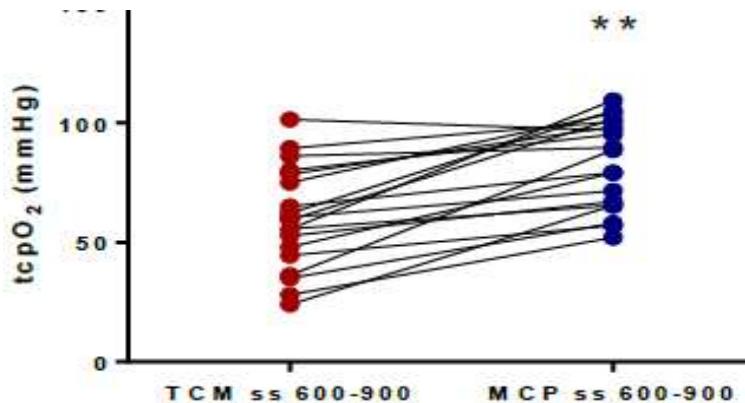
The steady state values TcPO₂ 10-15 min are shown in Figure 5.2.5.

Figure 5.2.5. Mean TcPO₂ steady state of Medicap and TCM400 between 10-15 minutes.



The mean steady state of TcPO₂ between 10-15 minutes estimated across the two sites measured using the Medicap (mean \pm Std Dev), was 82.15 (\pm 18.35 mmHg) ; and using the TCM400 was 60.39 (\pm 21.9 mmHg). The difference between the means is 21.76 mmHg (p < 0.0001).

Figure 5.2.6. Paired data of mean TcPO₂ at steady state for the Medicap and TCM400.

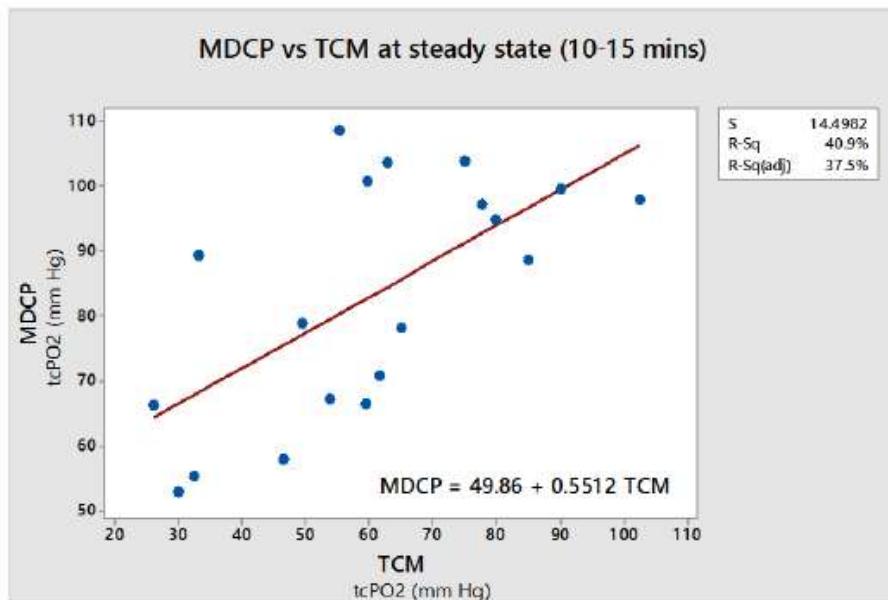


Paired data analysis further confirms that the Medicap consistently measured higher TcPO₂ (+22.8 mmHg) than the reference TCM400, which was significant ($p < 0.0001$).

f) Correlation at steady state.

The scatter plot shows there was a linear correlation between TcPO₂ values (steady state 10-15min) for TCM400 and Medicap (Spearman rho for Medicap against TCM = 0.621, $p = 0.005$) (Figure 5.2.7).

Figure 5.2.7. Linear TcPO₂ steady state correlation between Medicap and TCM400

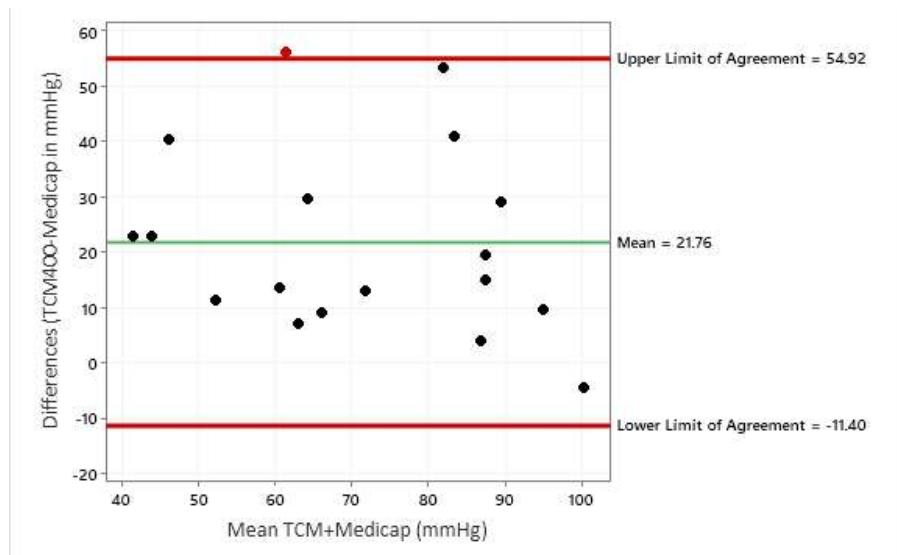


g) Measurement bias

Following section 4.11.2 (page 105) Bland-Altman analysis (Figure 5.2.8), determined the extent of measurement bias, with the Medicap overestimating TcPO₂ by 21.76 mmHg

when compared to the TCM400

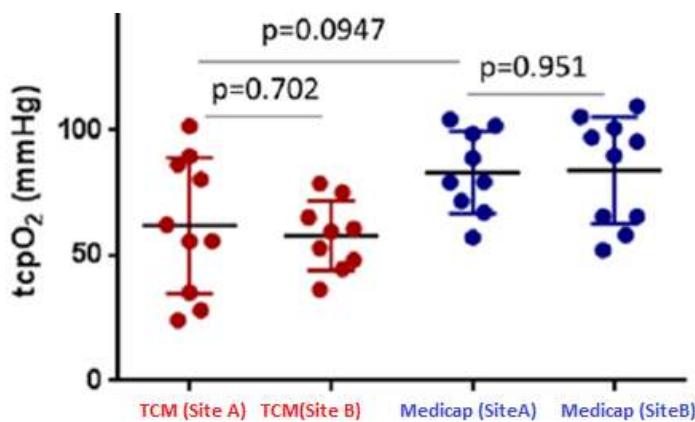
Figure 5.2.8. Bland-Altman Analysis of $TcPO_2$ at steady state between Medicap and TCM400



h) Site $TcPO_2$ Variability

As the probes were randomised to site, the impact of site on the outputs measured was analysed. Figure 5.2.9 summarises the data from the probes at the two fixation sites between the 1st - 2nd (Site A) and 4th - 5th (Site B) inter-metatarsal spaces. There were no significant difference between the mean steady state $TcPO_2$ based on site location for either probe. The $TcPO_2$ measured did not depend on which site the probe was located.

Figure 5.2.9 Mean steady state (10-15 min) $TcPO_2$ using Medicap and TCM400 randomised to site.

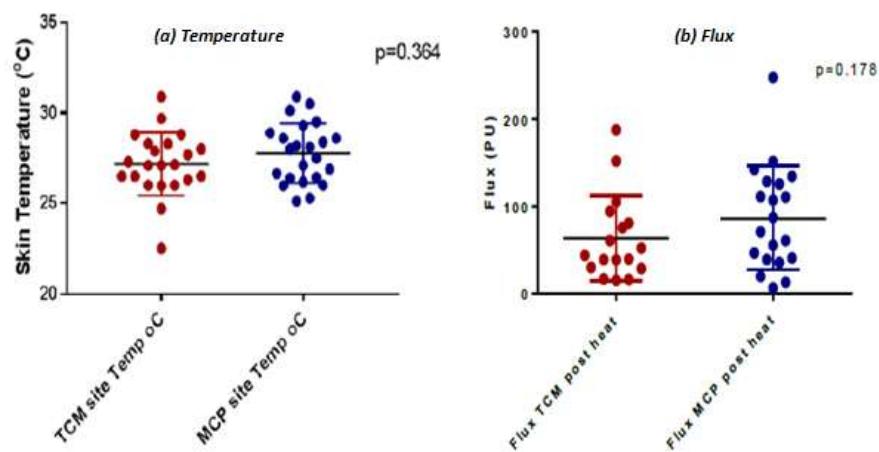


Probe fixation sites between 1st - 2nd (Site A) and 4th - 5th (Site B) inter-metatarsal spaces.

i) *Variability in Probe Skin Temperature and Probe Flux Induction.*

Both device probe temperatures were set to 42.5°C. There was no significant difference in the skin temperature or blood flux measured at the two sites immediately after removal of the heated (43°C) TcPO₂ probes (Figure 5.2.10). Mean skin temperature measured at the Medicap and TCM400 sites using the VMSOXY integrated probe was 27.8 ± 1.7 °C and 27.2 ± 1.7°C respectively, with no significant difference (p=0.36). Skin blood flux for the Medicap was 86.7±159.4 PU, and 63.4±48.5 PU for the TCM, again with no significant difference between the flux induced by the different probes (p = 0.18). In summary both probes heated the skin to the same extent, and induced similar levels of blood flux.

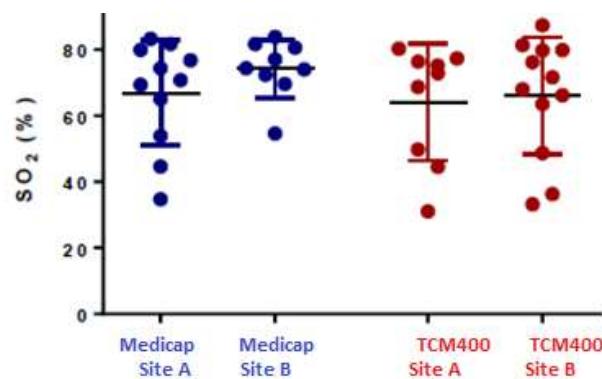
Figure 5.2.10: Skin temperature and flux at the heated TcPO₂ sites following probe removal



j) *Site Flux Variability*

This was determined on the extent of oxygen saturation (SO₂), as shown in figure 5.2.11., which shows no significant difference in SO₂ (%) measured at the previously heated TcPO₂ sites.

Figure 5.2.11: Tissue oxygenation (SO₂, %) measured at the heated TcPO₂ sites following probe removal



5.2.8 Discussion

The results show that in the feet of healthy individuals, the time course of $TcPO_2$ to reach steady state recorded using the Medicap and TCM400 devices was similar. Both devices reach steady state at approximately 10 min after the start of recording. The skin temperature and blood flux at the previously heated sites of the two probes did not show significant differences, and the extent of oxygen saturation was similar regardless of probe or site. There was no significant difference between the mean steady state $TcPO_2$ measured at the two sites, for either probe. Having excluded these potentially confounding effects, the two devices (TCM400 and Medicap) can therefore be directly compared. There was a good correlation between the steady state outputs of the two devices (Spearman $\sigma = 0.621$, $p = 0.005$). Despite this, the steady state value of $TcPO_2$ measured using the Medicap (83.13 ± 18.33 mmHg) was consistently and significantly higher than that recorded by TCM400 (60.35 ± 21.29 mmHg) with a measurement bias from the Medicap, determined Bland-Altman analysis, of $+21.76 (+/- 16.9)$ mmHg. The TCM400 measurement of $TcPO_2$ employs a planar modified Clark electrode which heats the skin to generate a local hyperaemia to bring oxygenated blood to the site and to permeabilise the cornified epithelium. It works by extracting oxygen from the skin and uses it to determine oxygen pressure polarographically. A fundamental limitation of the TCM400 technique is the oxygen consumption during measurement, which makes long-term measurements impossible and overestimates pO_2 values as the electrode 'sucks' oxygen through the tissue, and potentially depletes the remaining oxygen amount in the underlying tissue, and could possibly account for the discrepancy when compared to the Medicap values.

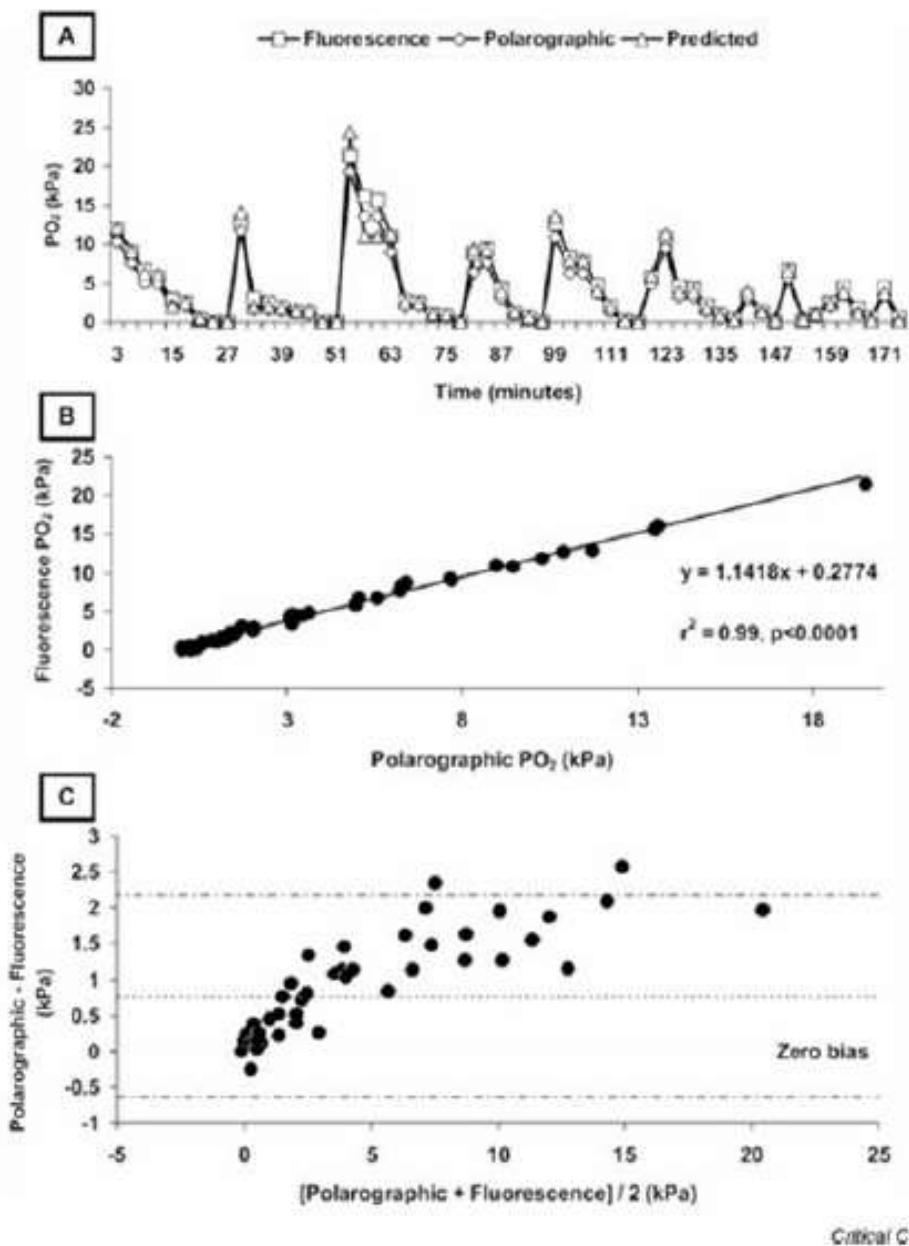
By contrast, the Medicap generates a local hyperaemia by heating but does not consume oxygen during measurement and has no stirring effects. This allows both a more physiologically accurate estimation of pO_2 values compared with the TCM400 and other 'Clark type' devices.

These observations are consistent with the concept that the TCM400 records lower values than the Medicap due to oxygen consumption, and the two $TcPO_2$ detection principles have been compared previously (Shaw *et al.*, 2002). These authors used a dynamic fluorescence quenching electrode and a polarographic Eppendorf needle

electrode with an in vitro saline tonometer in which the PO₂ could be controlled. They also tested the fluorescence quenching system in a rodent model of skeletal muscle ischaemic hypoxia. They found that both systems measured pO₂ accurately in the tonometer, and there was excellent correlation between them ($r^2 = 0.99$) (Figure 5.2.12).

Figure 5.2.12 Showing Polarographic vs Fluorescence Oxygen sensing techniques (from Shaw *et al.*, 2002).

- (A) Plot of fluorescence, polarographic and predicted partial oxygen tension (PO₂) against time.
- (B) Correlation plot of polarographic and fluorescence measurement techniques.
- (C) Bland– Altman plot of polarographic and fluorescence techniques.



Critical Care

They also found that polarographic system exhibited proportional bias that was not evident with the fluorescence method. *In vivo*, the fluorescence quenching technique provided a readily recordable signal that varied as expected. The experiment data are consistent with this demonstrated relationship (Figure 5.2.6 and Figure 5.2.7; page 128), showing a similar correlation to Shaw *et al.*, (2002), between the two devices measured at two skin sites on the dorsum of the foot across the 18 healthy individuals. The findings are also similar to those of Urban *et al.*, (2015), who recorded values for TcPO₂ on the calf and buttocks of patients with intermittent claudication before and during an exercise test using TCM400 and Medicap probes. They reported good concordance between the devices with absolute values of TcPO₂ at rest being 13.7 ± 12.7 mmHg higher with the Medicap compared to the TCM400.

a) Validity of the Medicap in healthy participants.

The Medicap shows measurement bias, consistent with previous studies, but accounting for this shows that the Medicap has criterion validity in measuring TcPO₂ when compared to a reference device (TCM400) in healthy participants. Having established the validity of the Medicap in healthy participants, it was important to investigate its use in volunteers with type 2 diabetes determined to be at low risk of ulceration, and compare the observations. This was done in experimental study 3 (Section 5.3, page 134).

5.3 EXPERIMENTAL STUDY 3: The Validity of the Medicap in individuals with type 2 diabetes at low risk of foot ulceration.

5.3.1 Introduction

Following the study in healthy participants, it was necessary to see if the observations were consistent in participants with type 2 Diabetes. Figure 5.3.1, shows where Experimental study 3 sits within the thesis context.

Figure 5.3.1: Showing Medicap validity investigation in people with type 2 diabetes, within the overall thesis context.



5.3.2 Primary Research Question:

What is the criterion validity of the Medicap in measuring transcutaneous oxygen in the feet of people with type 2 diabetes at low risk of foot ulceration.

5.3.3 Secondary Research Questions:

- a) Do the device outputs (Medicap and TCM400) reach a stable output at the same time?
- b) Do the two devices (Medicap and TCM400) warm the skin to a similar temperature?
- c) Do the two devices (Medicap and TCM400) induce a similar vasodilation (measured using VMSOXY)?
- d) Does $TcPO_2$ differ between placement sites (dorsum between 1st – 2nd metatarsal phalangeal joint (MTPJ); and dorsum 4th and 5th MTPJ) (Figure 5.2.3 on page 122)

5.3.4 Aims and Objectives

The objective of this study was to determine the criterion validity of the Medicap against the reference TM400 in detecting $TcPO_2$ on the dorsum of the feet of participants with type 2 diabetes at low risk of foot ulceration.

5.3.5 Method

The methodology was as described in Section 5.2.6 (page 120)

a) Participants and Ethical Approval.

Faculty Ethical approval was granted as an amendment under the Faculty of Health Science Research Ethics Committee number 24500, to include low risk diabetes participants (Appendix A6).

b) Inclusion Criteria.

Adults aged 18-70 years, with type 2 diabetes of any duration at low risk of ulceration (as determined by NICE NG19 (2015)), were recruited from University of Southampton and Southampton University Hospitals Trust staff, students and patients. All participants gave informed written consent. If any of the following applied; pregnant, suffering from other chronic conditions, or otherwise was at higher risk of ulceration; the potential participant was ineligible for the study. The protocol followed that on healthy participants from

5.3.6 Results

a) Participants

Table 5.3.1 Demographics and probe placement for the assessment of TcPO₂ in individuals with type 2 diabetes

	Gender	Age (yrs)	Diabetes duration (months)	BMI (kg.m ⁻²)	Smoking	MCP site	TCM site
23	M	51	48	35.3	N	A	B
24	F	39	26	30.5	Y	B	A
25	M	51	180	28.4	Y	B	A
26	F	49	6	22.6	Y	B	A
27	M	60	16	33.2	N	B	A
28	M	55	8	29.4	N	B	A
29	M	57	12	20.8	N	B	A
30	M	37	12	39.0	Y	A	B
31	F	52	6	35.88	N	A	B
32	M	41	14	27.55	Y	A	B
33	F	50	3	29.85	N	A	B
34	M	62	160	44.83	N	A	B
35	M	55	4	33.96	N	A	B
36	M	48	10	38.14	Y	A	B
37	M	55	120	27.91	Y	A	B
38	F	55	6	40.09	Y	A	B
39	M	56	50	29.34	Y	A	B
40	M	51	264	29.57	Y	A	B
41	F	39	42	44.99	Y	A	B
42	F	51	122	30.17	Y	A	B
43	F	49	3	24.46	N	A	B

b) Summary demographics

A summary of the demographics of the 21 adult participants with type 2 diabetes are shown in Table 5.3.2.

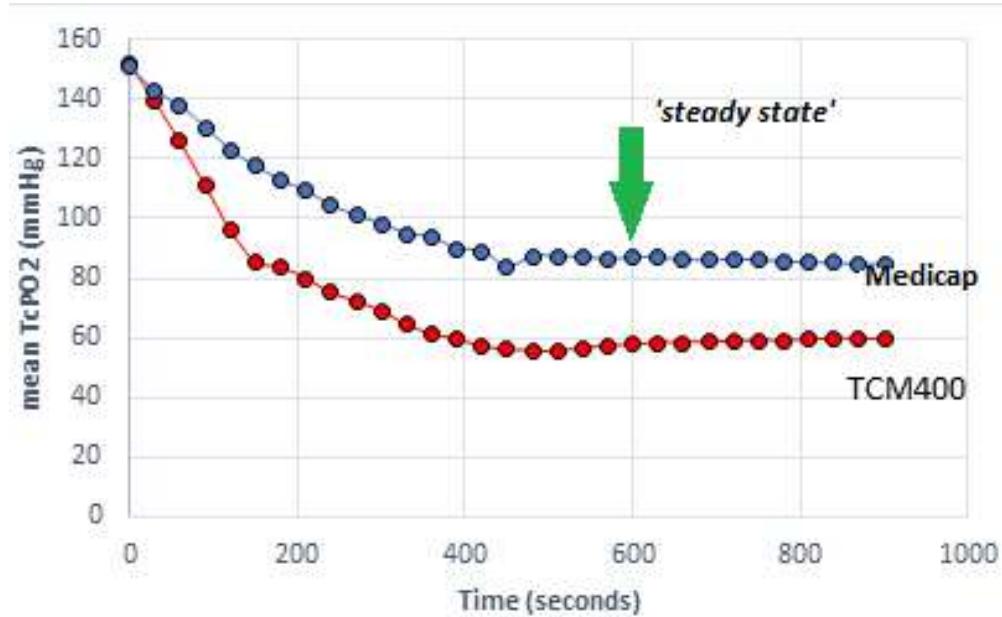
Table 5.3.2 Summary demographics for participants with low risk type 2 diabetes(n=21)

<u>Low risk study population with Type 2 diabetes; n=21</u>	
Age (years)	50.3 (8.6)
Gender (Male / Female)	13/8
Mean BMI (kg/m ²)	32 (6.5)
Diabetes Duration (months) (median - range)	14 (3-264)
Current Smokers (%)	57.1%

c) *Raw TcPO₂ outputs from Medicap vs TCM400 devices*

The outputs from the two devices for the 21 individuals with T2DM are shown in Appendix B5. Figure 5.3.2 shows a summary of the time course of the simultaneous measurements from the two sensors for the 21 participants. Similar to 5.2.3 in healthy participants, both devices recorded an initial rapid decline in TcPO₂ to reach a steady state at approximately 10 min after the start of recording. The Q-Q plots of both Medicap and TCM400 led to the assumption that TcPO₂ output followed a Gaussian distribution.

Figure 5.3.2. Time course of TcPO₂ measured using Medicap and TCM400 in people with Type 2 diabetes.



d) Time to Steady State:

As shown in Figure 5.3.2, both devices reached steady state within 600 seconds (10 minutes). The steady state values $TcPO_2$ 10-15 min are also shown in Figure 5.3.3. The mean steady state values of $TcPO_2$ 10-15 min estimated across the two sites measured using the Medicap (85.81 ± 21 mmHg) were significantly higher than those measured using TCM (59.03 ± 14.84 mmHg), with a difference of 26.78 mmHg, ($p < 0.0001$; Wilcoxon matched pairs signed rank test). The Medicap consistently gave higher $TcPO_2$ reading regardless of site; by a mean of $26.78 (\pm 19.8)$ mmHg; ($p < 0.0001$).

Figure 5.3.3: Mean steady state values of $TcPO_2$ for the Medicap and TCM400 in people with type 2 diabetes.

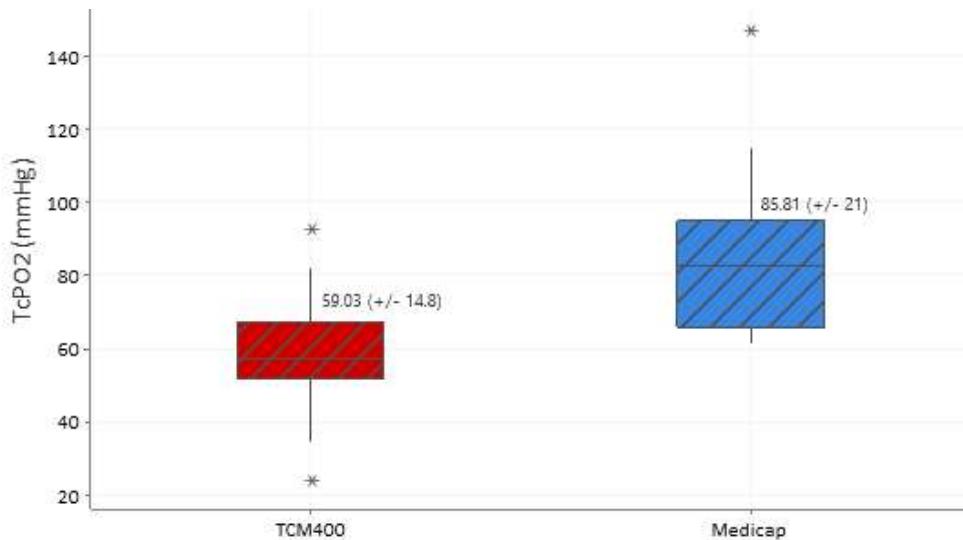


Figure 5.3.4: Paired data of mean steady state $TcPO_2$ for the Medicap and TCM400 in people with type 2 diabetes.

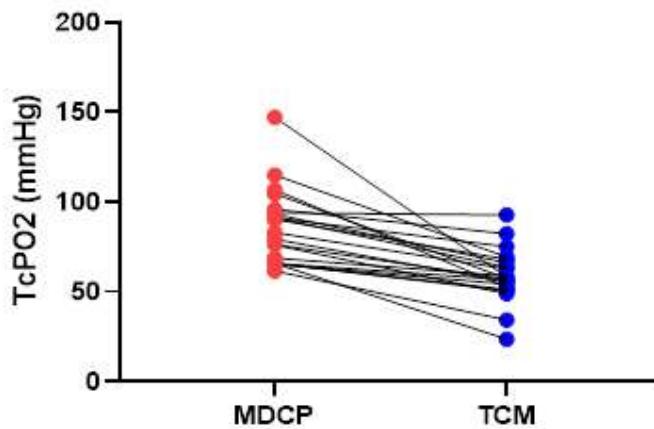
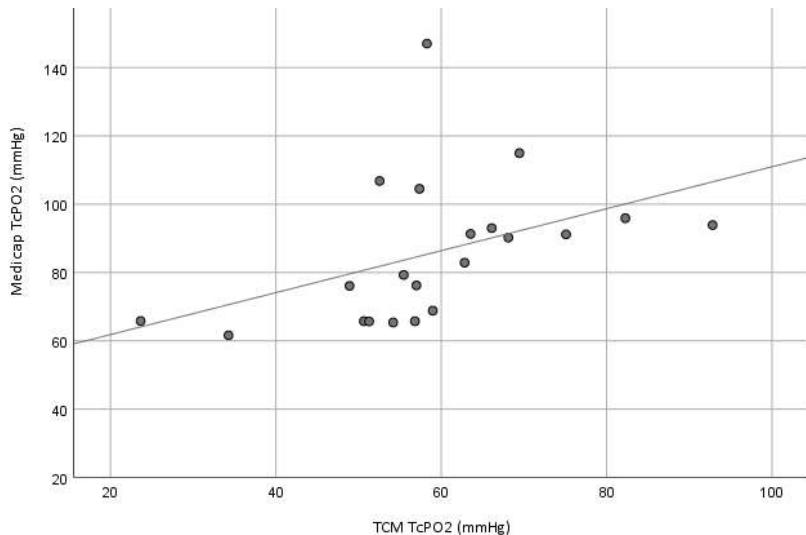


Figure 5.3.4 shows paired steady state data from the two probes for each individual, and confirms the mean data from Figure 5.3.3, with the Medicap consistently measuring higher $TcPO_2$ than the reference TCM400 in all participants with type 2 diabetes.

e) Correlation between Medicap and TCM400.

The scatter plot shows there was a linear correlation between $TcPO_2$ values (steady state 10-15min) for TCM and Medicap (Figure 5.3.5), with Spearman $\sigma = 0.64$ ($p = 0.002$); Pearson $r = 0.43$ (95% CI = 0.003 – 0.73) ($p < 0.05$) ; $R^2 = 0.19$, $p=0.03$.

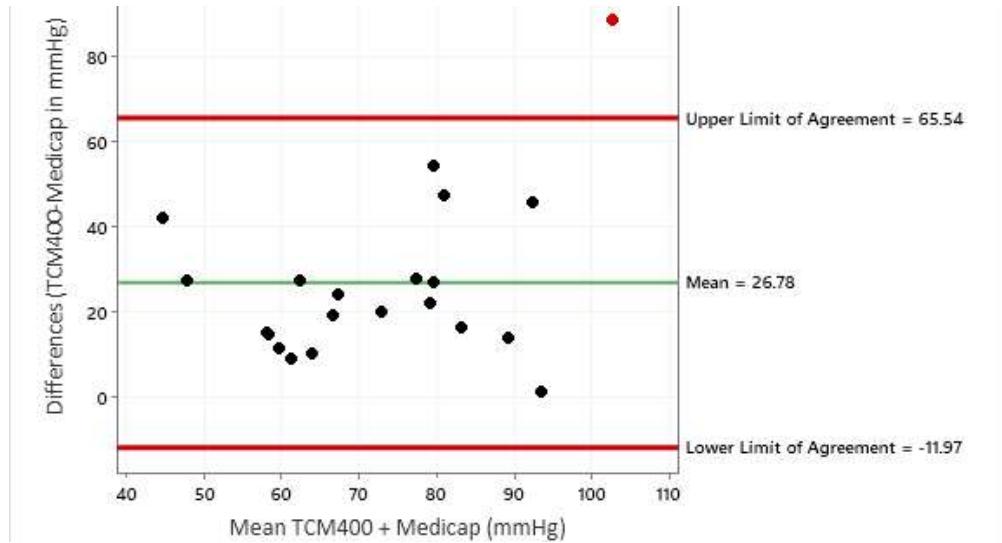
Figure 5.3.5: Linear correlation at steady state between the Medicap and TCM400 in people with type 2 diabetes.



f) Measurement bias

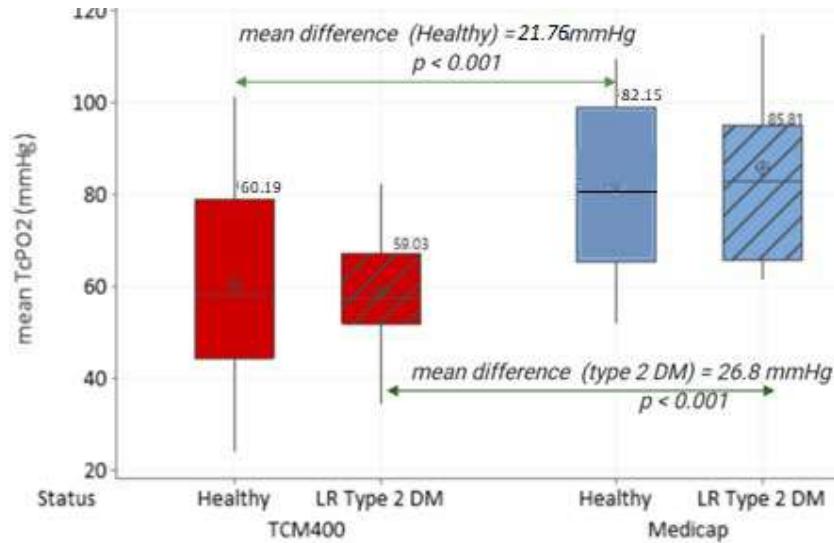
Following Chapter 4.11.2 (page 105) a Bland-Altman plot was constructed as shown in Figure 5.3.6. This confirmed measurement bias from the Medicap, with it measuring 26.78 mmHg higher than the reference TCM400.

Figure 5.3.6: Bland-Altman Plot of mean $TcPO_2$ between the Medicap and TCM400 in people with type 2 diabetes.



The difference in device readings was also consistent across the two different populations, as shown in Figure 5.3.7.

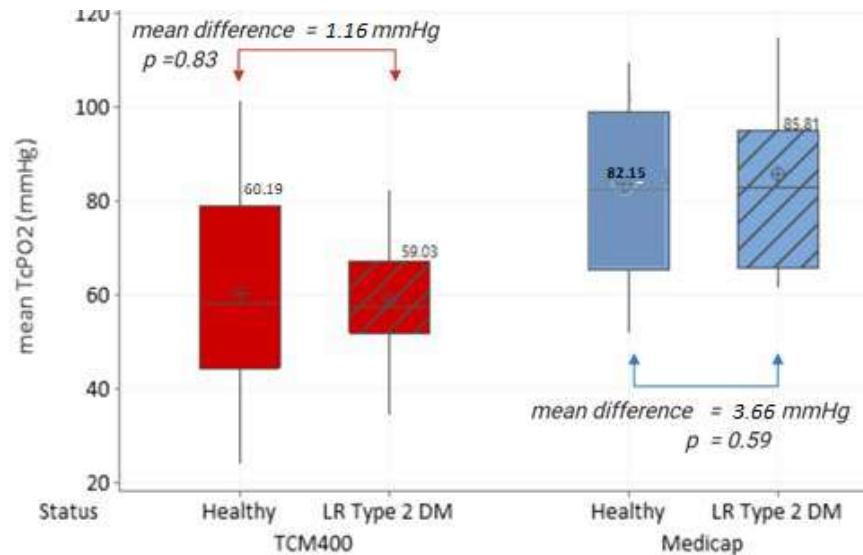
Figure 5.3.7: Showing device differences (TCM400 vs Medicap) in $TcPO_2$ is consistent across healthy and low risk type 2 diabetes participants.



g) *TcPO₂ in Healthy vs Low Risk Type 2 diabetes participants.*

Comparison with data from healthy individuals in study 5.2 (Experimental study 2) showed that for each individual device, there was no significant difference in TcPO₂ between the two study populations.

Figure 5.3.8: Showing TcPO₂ consistent for each device in healthy and low risk type 2 diabetes participants.



Therefore the devices themselves could not distinguish between healthy, and low risk type 2 diabetes participants (Figure 5.3.8).

5.3.7 Discussion

The study population were recruited as individuals with type 2 diabetes mellitus at 'low risk' of tissue breakdown according to NICE NG19 (2015). The duration of diabetes from diagnosis ranged from 3-264 months (median 14 months). The results show that in the feet of individuals with type 2 diabetes at low risk of foot ulcers, the time course of TcPO₂ to steady state recorded using the Medicap and TCM devices was similar. Both devices reach steady state at approximately 10 minutes after the start of recording. The results also show that steady state value of TcPO₂ measured using the Medicap (85.8 ± 21 mmHg) were consistently and significantly higher than those measured using the TCM400 (59 ± 14.8 mmHg) with a difference in means of $26.8 (\pm 19.8)$ mmHg ($p < 0.0001$). There was also a correlation between the steady state outputs of the two devices (Pearson $r = 0.43$; $p < 0.05$). The values for TcPO₂ measured in the feet using the two devices in people

with type 2 diabetes mellitus at low risk of tissue breakdown did not differ significantly from those obtained in healthy individuals. The results show slightly larger TcPO₂ differences shown by the Medicap between the healthy vs diabetes participants (Figure 5.3.8), suggesting a higher discriminative power in the Medicap, but this did not reach significance ($p = 0.59$).

a) Medicap threshold for ischaemia

Before progressing to the doctoral ischaemia investigation (Chapter 7), it is necessary to determine the Medicap threshold for ischaemia based on healing potential. Whilst it is not possible to establish this directly from these investigations, it is clear that the Medicap overestimates TcPO₂ compared to the reference TCM400 by 24.3 (± 18.4) mmHg. This is derived from averaging the Medicap TcPO₂ overestimations between the two investigations, with 21.8 mmHg in healthy, and 26.8 mmHg in 'low risk' diabetes, giving a mean overestimate of 24.3 (± 18.4) mmHg. TCM400 diagnostic studies can therefore stand as a reference in establishing Medicap thresholds for ischaemia. Earlier, Pecoraro *et al.*, (1991) had used a TCM3 device, and found those with TcPO₂ less than 27 mmHg and failed to heal; and the difference between the healing and non-healing groups was significant ($p = 0.003$). Pawlaczyk-Gabriel *et al.*, (2014) used a TCM4 and Periflux 5000 system, and found that participants with ischaemia Rutherford class 3-4, had a mean TcPO₂ level of 19.8 mmHg. From the literature review (Chapter 3.4, page 75) Yang *et al* (2008) found 25mmHg on the TCM400 had best diagnostic performance, based on AUC = 0.8 (95% CI = 0.7 – 0.98) with a sensitivity of 88.6% and specificity of 82.4%. In both their studies, Pardo *et al* (2010; 2015) found that TcPO₂ detected by the TCM400 increased from 27 ± 8.1 mmHg in those with ischaemia; to 48 ± 8.4 mmHg after revascularisation. Fagher *et al* (2018) used a Periflux 5000 system – which relies on a Clark-type electrode found in the TCM400, and found that a TcPO₂ of 25mmHg was predictive of 1 year cardiovascular mortality. It is therefore reasonable to establish the ischaemia threshold for the TCM400, based on healing potential, at 25 mmHg. In adjusting for the Medicap overestimate, the diagnostic threshold taken forward to the doctoral experimental study (Chapter 7), will be 50mmHg for the Medicap.

b) Limitations

The main limitations from experimental studies 5.2 and 5.3, were the relatively healthy and low risk cohort, with no diagnosed ischaemia, which limits applicability of results. The bias between Medicap and TCM400 readings increased from 21.8 mmHg (healthy) to 26.8 mmHg (low risk) cohorts, but this did not reach statistical significance ($p = 0.6$). However it is unclear how this extends to higher risk diabetes populations more likely to have ischaemia, therefore assumptions on Medicap criterion validity are limited to the healthy and low risk cohorts. It was also not practical to recall participants for reliability investigations for comparison. Given the relatively modest samples in both healthy ($n = 18$) and low risk ($n = 21$) studies, in addition to recruiting in people with no diabetes complications, it is therefore not surprising that no significant differences were detected in $TcPO_2$ between healthy individuals and those with type 2 diabetes at low risk of ulceration.

5.3.8 Summary of Medicap Validity.

Section 5.2 and 5.3 outlined the two experimental studies that attempted to determine the Medicap's validity against the reference standard in healthy and low risk type 2 diabetes participants, respectively. They have shown that regardless of the health status, the Medicap measures higher than the TCM400. The studies also show that the sites chosen for placing the probes had no significant effect on $TcPO_2$ readings and could be interchanged. Both the TCM400 and Medicap heated the skin to the same extent, took similar time to reach stable output, and induced similar levels of flux. Therefore the devices could be directly compared having excluded the variations of where they were placed, the temperature to which they heated the skin, the extent of flux induced and saturated oxygen that was drawn to the heated sites.

Any differences therefore would be due to the devices themselves, which could potentially be explained by the different underlying technologies in transcutaneous oxygen detection and extraction between the Medicap (photochemical detection without consuming the oxygen) and the TCM400 (electro-chemical processing which involves oxygen consumption). As such, the TCM400 "consumes" some of the oxygen as part of its electrochemical detection process, hence what is left over would read lower than for the Medicap, which does not consume any oxygen. It is possible that, without correcting for

this “consumption”, and despite being the reference device, it could be the TCM400 itself that underestimates the actual $TcPO_2$. It has previously been found that Clark type electrodes, such as those used by the TCM400, suffer from ‘measurement drift’ which affects their reliability (Eberhard *et al.*, 1975; Marsden *et al.*, 1985; Urban *et al.*, 2015).

van Weteringen *et al.*, (2020) has suggested improving the Clark type probes by developing a unified sensor that combines electrochemical and optical techniques.

Despite their study being limited through being conducted in-vitro and later validated on 12 healthy volunteers, their unified probe did minimise measurement drift, which ranges from about 10% (Marsden *et al.*, 1985) down to 0.6% (van Weteringen *et al.*, 2020). What is of relevance is it suggests that the limitations introduced by this ‘measurement drift’ on the TCM400 could have been responsible for the consistent differences observed against the Medicap, and it is possible the Medicap values are more valid. One way of further investigating this would be to benchmark TCM400 and Medicap longitudinal performances against gold standard capillary blood oxygen measurement, in each relevant population with type 2 diabetes.

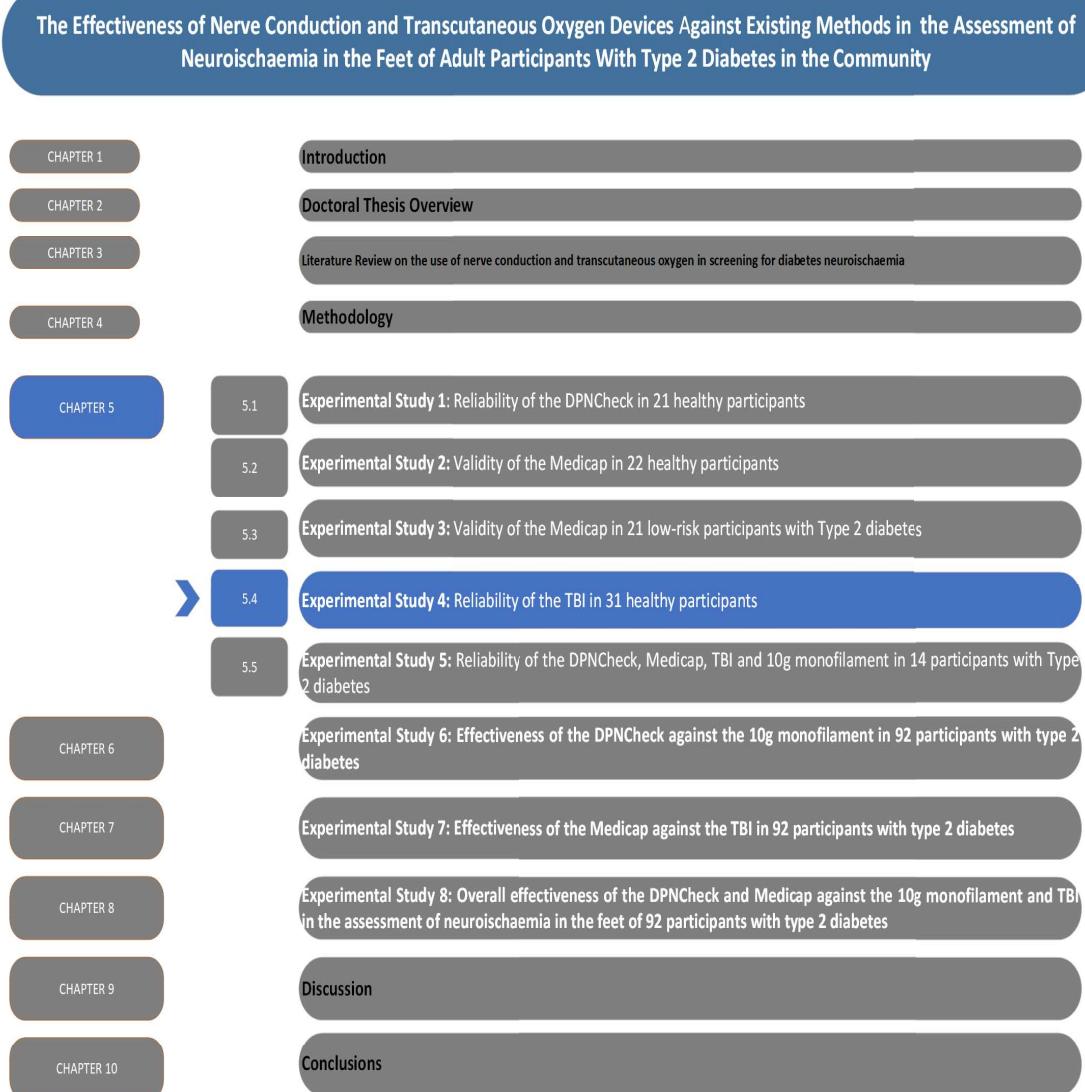
In summary, when adjusting for the detected bias, it is possible to establish the Medicap’s criterion validity against the TCM400. The clinical implications for the Medicap are that instead of relying on published $TcPO_2$ reference ranges based on Clark-type electrodes, the Medicap would need to have its own unique reference values to identify microischaemia, as also suggested by Urban *et al.*, (2015).

5.4 EXPERIMENTAL STUDY 4: Reliability of the TBI in healthy participants

5.4.1 Introduction

As discussed in Chapter 1.4, early detection of ischaemia is important to determine ulceration risk and healing potential. Ischaemia commonly coexists with diabetes, but ischaemia prevalence itself varies widely from about 3% - 67% as previously shown in Figure 1.4.3 (page 36). This section aims to investigate TBI reliability, and is placed within the thesis context as shown in Figure 5.4.1

Figure 5.4.1: Showing the investigation on TBI reliability within the thesis context.



Whilst the ABI is recommended by NICE CG147 (2018) for suspected cases of ischaemia, it is less reliable in people with diabetes. As discussed previously (pages 40-42; pages 75-83), the TBI is more reliable than the ABI, but there is no definitive agreement on its diagnostic threshold, which ranges from >0.6 -0.75, with the most commonly used diagnostic threshold of ischaemia being present if the TBI < 0.7 . In addition, due to the brachial and toe components of the TBI, there is variability in their measurement and in its determination. Earlier, Kranenburg *et al.*, (2017) found that for every 5mmHg difference between brachial pressures, a 12% increase risk of vascular event occurs. It was therefore important to determine the extent of variability in the TBI.

5.4.2 Primary Research Question:

- a) What is the intra and inter-rater reliability of the TBI in healthy participants?

5.4.3 Secondary Research Questions:

- a) To what extent does prior practice (familiarity) with equipment affect TBI variability?

5.4.4 Aims and Objectives

The main aim was to determine the intra and inter rater reliability of the TBI in healthy participants.

5.4.5 Method

a) Sample size.

A convenience sample of 32 was calculated for an intra-class correlation coefficient (ICC) of 0.8 with a confidence interval of ± 0.11 .

b) Participants and Ethical Approval.

This was part of a student project, involving three students who were the assessors (3 raters). Ethical approval was granted under ERGO II: 45964 (Appendix A7). The study recruited healthy participants from amongst staff and students from the University of

Southampton, without any chronic or vascular complications. All participants agreed to refrain from smoking, drinking coffee or alcohol an hour prior to data collection.

c) Study Protocol.

Participants had their demographics (gender, age, mass, height) recorded on arrival after giving written consent. All testing was carried out in a clinical skills room at the University of Southampton. Just prior to assessment, participants lay supine for 10 minutes. The toe pressure kit (Dopplex ATP Ankle & Toe Pressure Kit) was supplied by Huntleigh Healthcare, which includes a photoplethysmography (PPG) probe. The bilateral brachial and right 1st toe pressures were taken following the recommended protocol outlined under section 4.6.5 (f) (page 96), and in Appendix A3, and this was repeated twice within the same session. Measurement sessions occurred two weeks apart. To control for bias, all 3 raters were blinded to other rater results, but not to their repeated measurements.

d) Experience.

Two raters (raters 1 and 2) had 3-4 sessions with the principal investigator and clinical supervisor to familiarise with the equipment and run through the protocol before testing on volunteers. Rater 3 did not familiarise or practice with the TBI equipment.

e) The Intraclass Correlation Coefficient.

TBI reliability was determined based on the strength of the intraclass correlation coefficient (ICC) as earlier outlined in section 4.11.5 . To summarise, since various versions of ICC exist, the appropriate one was selected based on the *model* and the *form*. The raters were assumed to have been randomly selected from a larger group of students, and results intended to be generalisable, which gave ICC Model 2. Reliability was calculated on mean values from the first two measurements for each rater, which gave an ICC form for average measures.

- For each individual rater: The version of ICC selected, using the mean values from each testing session, was ICC (2,2).
- Between two raters: The version of ICC selected, using their mean values was therefore ICC (2,2).
- Between three raters: The version of ICC selected, using their mean values was therefore ICC (2,3).

5.4.6 Results

a) Demographics

Due to time constraints, 31 participants were enrolled, consisting of 20 females and 11 males, with a mean age of 26.5 years (± 10.13), and a mean BMI of 24.08 (± 3.99). These are shown in Table 5.4.1.

Table 5.4.1 Showing demographics of healthy participants (n = 31)

Characteristics		\pm Standard Deviation
Age (years)		26.55 \pm 10.13
Session 1 BMI (kg/m ²)		24.10 \pm 3.91
Session 2 BMI (kg/m ²)		24.06 \pm 4.12
Mean BMI (kg/m ²)		24.08 \pm 3.99
Toe pressure (mmHg)		81.77 \pm 22.29
Brachial pressure (mmHg)		118.18 \pm 9.09
TBI [†]		0.68 \pm 0.18

b) Intra-Rater variability

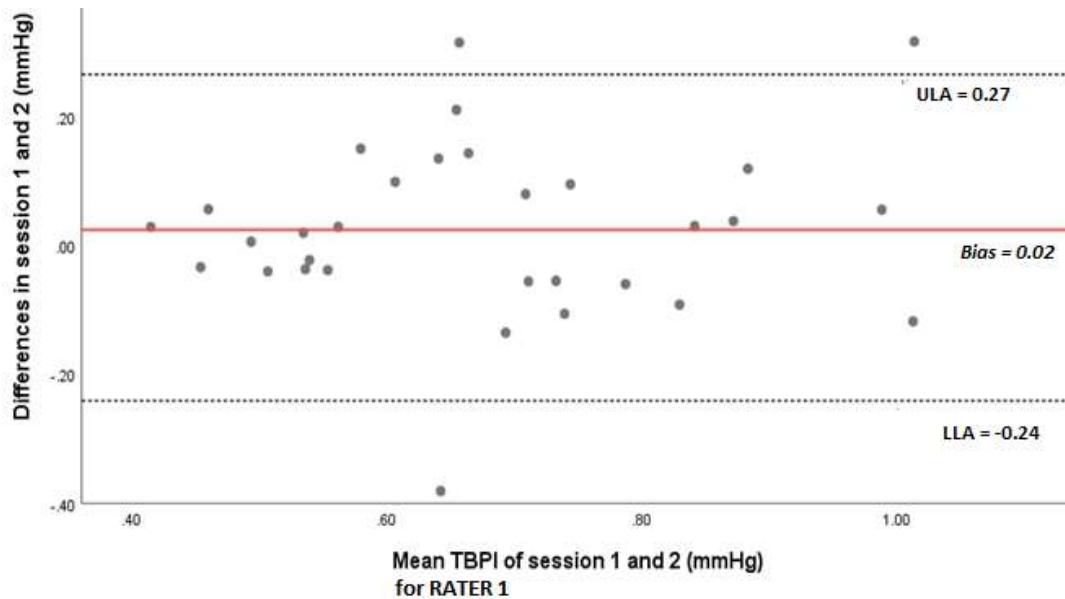
The results from intra-rater variability analysis are shown in Table 5.4.2 .

Table 5.4.2 Showing results from the intra-rater variability analyses

Intra-rater Agreement for the TBI				
Rater (R)	Mean (SD)	ICC (2,2) (95% CI)	SEM	95% Limits Of Agreement (mmHg)
R1 (Session 1)	0.69 (0.18)	0.92 (0.87 to 0.96)	0.03	-0.23 to 1.05 (mean diff of 0.69)
R1 (Session 2)	0.67 (0.17)	0.98 (0.97 to 0.99)	0.03	-0.22 to 0.45 (mean diff of 0.67)
R1	0.68 (0.16)	0.79 (0.68 to 0.88) ICC (2,2)	0.03	-0.21 to 1.00 (mean diff 0.68)
R2	0.70 (0.14)	0.98 (0.95 to 0.99) ICC (2,2)	0.26	-0.28 to 0.28 (Mean diff - 0.004)
R3	0.69 (0.20)	0.99 (0.97 to 0.99) ICC (2,2)	0.35	-0.39 to 0.39 (mean diff of 0.001)

A Bland-Altman plot was constructed to determine potential bias between assessments, as described in section 4.11.3 (page 105). One rater was chosen for this (rate one = R1), with their values from sessions 1 and 2 selected for analysis. This would also help to determine intra-rater agreement for the TBI between testing sessions for a single rater. The results are shown in Figure 5.4.2.

Figure 5.4.2. Showing intra-rater agreement for single rater between testing sessions



c) Inter-rater variability

The interrater variability analysis is shown in Table 5.4.3 :

Table 5.4.3. showing inter-rater agreement analyses

Inter-rater Agreement for the TBI				
Raters	Mean (SD)	ICC(2,k) (95% CI)	SEM	95% Limits Of Agreement (mmHg)
R1 and R2	0.68 (0.17)	0.98 (0.95 to 0.99) ICC (2,2)	0.03	-0.75 to 0.75 (mean diff of -0.008)
R2 and R3	0.68 (0.18)	0.81 (0.649 to 0.91) ICC (2,2)	0.03	-0.22 to 0.23 (mean diff 0.004)
R1 and R3	0.67 (0.18)	0.81 (0.65 to 0.91) ICC (2,2)	0.03	-0.23 to 0.23 (mean diff of -0.004)
R1, R2 and R3	0.68 (0.17)	0.96 (0.93 to 0.98) ICC (2,3)	0.03	-0.22 to 0.46 (mean diff of 0.67)

5.4.7 Discussion

a) Intra-rater variability.

The results show that intra-rater reliability for the TBI was good to excellent for all 3 raters (Table 5.4.2), with ICC (2,2) for each rater ranging from 0.79 – 0.99 (SEM = 0.03; 95% CI; 0.68 – 0.99). These results are better than those from Scanlon *et al.*, (2012), who determined TBI reliability in 60 people with diabetes, and found intra-rater reliability fair-good, with ICC (3,1) ranging from 0.51-0.72 (SEM 0.08). The difference with Scanlon *et al* (2012) could potentially be down to differences in cohorts as they investigated people with diabetes, the type of ICC that took only the first reading, the wholly automated equipment (Hadeco Smartdop 30EX) which did not allow clinician input in determining systolic pressure, and the less controlled environment.

b) Inter-rater variability.

Inter-rater reliability (Table 5.4.3) was also good - excellent with ICC (2,2) for any two raters 0.81 – 0.98 (SEM 0.03; 95% CI; 0.65 – 0.99) ; and was excellent for the three raters with ICC (2,3) =0.96 (95% CI; 0.93 – 0.98). Scanlon *et al.*, (2012) also found an excellent ICC (2,2) = 0.85 (SEM 0.07; 95% CI = 0.74 - 0.91).

c) Effect of rater experience on TBI variability.

The rater with the lowest ratio of training and experience, (R3) also had the highest standard deviation (0.2) and error of mean (0.35) (Table 5.4.2). Measurements involving Rater 3 also had the lowest inter-rater agreement with ICC (2,2) = 0.8 (95% CI 0.65 – 0.91) with the other 2 raters. Though this is not definitive, it is suggestive that rater experience could have an effect on TBI variability, and agrees with the review by Trevethan, (2019) and the earlier work by Romanos, Raspovic and Perrin, (2010). Further research would need to be undertaken with a larger cohort of raters, with varying experience and training.

The results also show that, on average, the group as a whole was below an assumed threshold for ischaemia of 0.7, with a TBI = 0.68 (± 0.18), although taking the upper limit of the standard deviation would classify them as non-ischaemic. This is still in contrast to a similar study by Quong *et al.*, (2016) on 73 healthy participants in Canada with a mean

age of $24.3 \pm (2)$ years, who found mean right TBI of $0.96 (\pm 0.17)$, which is above the $0.68 (\pm 0.18)$ from the Southampton study. The difference could be due to the effects of seasonal temperature variation – as the Southampton students were assessed during the winter months (December – February) which could have vasoconstricted the digital arteries and lowered the toe pressure, compared to the Canadian study who were assessed between February and May; however neither study measured foot temperatures. This could also be due to the resting time for participants prior to assessment being longer for Southampton (10 minutes), which could have lowered the toe pressures more when compared to the Canadian study who rested for 5 minutes prior to assessment. Sadler *et al* (2015) found a significantly higher systolic toe pressure (3.66 mmHg; 95% CI: 1.44–5.89; $p \leq 0.001$) and TBI (0.03; 95% CI: 0.01–0.05; $p \leq 0.001$) in PAD participants who rested for 5 minutes compare to those who rested for 10 minutes. Further variation could also be due to differences in toe cuff sizes, which vary between suppliers from 15mm – 30mm in width, which in turn vary toe pressures by over 20 mmHg and have an index variation of 0.2 on the TBI (Pahlsson *et al* 2007). It can be speculated that a combination of foot temperature, resting time prior to assessment and equipment variation (toe cuffs) could therefore explain the discrepancy in TBI between the studies with similar participants.

As to the components of the TBI, the systolic toe pressures showed the broadest variation, with a mean deviation between the three raters of 23.92 mmHg (range: 22.09 – 26.65 mmHg). Despite the good-excellent ICC's for intra and inter-rater reliability, the range of error was broad. This shows the vulnerability of the individual components of the TBI to subjective application and interpretation.

d) Limitations.

The study managed to recruit 31 out of the 32 due to time and recruitment constraints, particularly as less people were willing to commit to reassessment with multiple raters. The results are from a fairly homogeneous healthy sample in an academic setting, and therefore cannot be generalised to community patients with diabetes or PAD. The clinical experience of the assessors is also different compared to qualified clinicians, so the ICC values would only be generalisable to clinicians – perhaps newly qualified, that fit a similar profile to the assessors. It is important to remember that the TBI is an assessment

approach, to exclude people from suspicion of ischaemia. People with systolic brachial hypertension can also have reduced TBIs, yet the toe perfusion pressure in isolation would exclude ischaemia. The TBI therefore is not diagnostic, and this study did not set out to establish normative values for the TBI.

In summary, this study has shown that the TBI, using the toe pressure kit, has excellent intra and inter rater reliability in healthy participants. Future research needs to be conducted to investigate the reliability of TBI measurements in people with diabetes in a clinical setting.

5.5 EXPERIMENTAL STUDY 5: Reliability of the DPNCheck®, 10g monofilament, Medicap and TBI in participants with Type 2 diabetes.

5.5.1 Introduction

The previous sections sought to establish reliability of the DPNCheck® in healthy participants, the validity of the Medicap in low risk diabetes and healthy participants, and reliability of the TBI in healthy populations. This section aims to investigate the reliability of the 4 devices used for the primary outcomes and on similar participants as those for the main investigations. Its value within the thesis context is shown in Figure 5.5.1.

Figure 5.5.1: Showing investigation on devices' reliability, within the thesis context.

The Effectiveness of Nerve Conduction and Transcutaneous Oxygen Devices Against Existing Methods in the Assessment of Neuroischaemia in the Feet of Adult Participants With Type 2 Diabetes in the Community



This section therefore adds to the previous studies in setting out to determine the reliability of the DPNCheck®, Medicap, TBI and 10g monofilament in low, medium and high risk, non-ulcerated diabetes participants, in preparation for the final investigations in Chapters 6 and 7.

5.5.2 Primary Research Questions:

- a) What is the intra-rater reliability of the DPNCheck® in participants with type 2 diabetes?
- b) What is the intra-rater reliability of the 10g monofilament in participants with type 2 diabetes?
- c) What is the intra-rater reliability of the Medicap in participants with type 2 diabetes?
- d) What is the intra-rater reliability of the TBI in participants with type 2 diabetes?

5.5.3 Aims and Objectives

The main aim was to determine the intra-rater reliability of the devices used for the doctoral investigation (DPNCheck®; 10g monofilament; Medicap; TBI) in people with type 2 diabetes.

5.5.4 Method

a) Sample size.

Based on previous reliability studies (Romanos *et al*, 2010) and the healthy reliability study (section 5.4), a convenience sample of 30 was calculated to determine the intra-class correlation coefficient (ICC) for the four instruments.

b) Participants and Ethical Approval.

This was part of the final doctoral research project, where the original project under IRAS 170265, was granted ethical approvals on ERGO 13474 (Appendix A8), Research Ethic Committee 17/LO/2033 (Appendix A9) and the Health Research Authority (Appendix A10). To include North Manchester General Hospital as an additional site, minor amendments were forwarded to the relevant authorities, for which further approvals were granted (Appendix A12; Appendix A13), as well as local approval under R&I Ref

P19DIAB05 (Appendix A14). The study aimed to recruit participants with type 2 diabetes, but without active ulceration as described in the Methods section (Chapter 4.3.5, page 88 and Chapter 4.5.2, pages 90-91).

c) Protocol.

Participants had their demographics (gender, age, mass, height) recorded on arrival after giving written consent. All testing was carried out by the same rater, in a dedicated clinical room at either the Royal South Hants Hospital or North Manchester General Hospital diabetes centre, following the protocols in Chapter 4.6.5 (pages 93-98) described in the Methods section, and repeated 12-16 weeks apart. The protocol for each individual device was followed as described in sections 4.6.5 (d) (10g monofilament, page 94-95), 4.6.5 (e) (DPNCheck®, page 95-96), 4.6.5 (f) (TBI, page 96) and 4.6.5 (g) (Medicap, page 97-98).

d) The Intraclass Correlation Coefficient.

Intra-rater reliability was based on the strength of the intraclass correlation coefficient (ICC), as earlier described in section 4.11.6 (page 106). To summarise, the results were intended to be generalisable, the rater was 'fixed', and the 14 participants who returned for reassessment were randomly drawn from a larger population of 92 participants. The version of ICC selected, using 'absolute agreement' on single values, was therefore ICC (3,1).

Variability analyses were also done using Bland-Altman plots for each device as earlier described in section 4.11.3 (page 105)

5.5.5 Results

a) Demographics

Table 5.5.1. Showing participant demographics from n = 14

	Test - Retest		
	Assessment 1	Assessment 2	p - value
Gender % (M 10/ F 4)	Male = 71.4%	Male = 71.4%	ns
Age years	mean ($\pm SD$)	53.4 (± 9.2)	
BMI kg/m ²	mean ($\pm SD$)	27.4 (± 3.9)	0.12
Diabetes Duration months	median (IQR)	25 (4 - 97.5)	w 0.001*
HbA1c mmol/mol	median (IQR)	54 (50.3 - 69)	w 0.07
Smoking History	n = 2	n = 2	ns
Previous Ulceration	n = 1	n = 1	ns
Previous Amputation	0	0	ns
R Ankle size cm	mean ($\pm SD$)	22.2 (± 2.6)	0.43
TBI	0.94 (± 0.17)	0.92 (± 0.17)	t 0.02
Medicap (TcPO ₂)	mean ($\pm SD$)	84.7 (± 2.6)	0.13
10g monofilament	median (IQR)	10 (10 - 10)	w 0.04*
DPNCheck®	Velocity m/s median (IQR)	51.5 (46.8 - 55.8)	w 0.04*
	Amplitude μV median (IQR)	7.5 (4 - 11.8)	w 0.6
* significant at p < 0.05; w Wilcoxon signed rank test; t paired samples t-test IQR = inter quartile range ns = not significant			

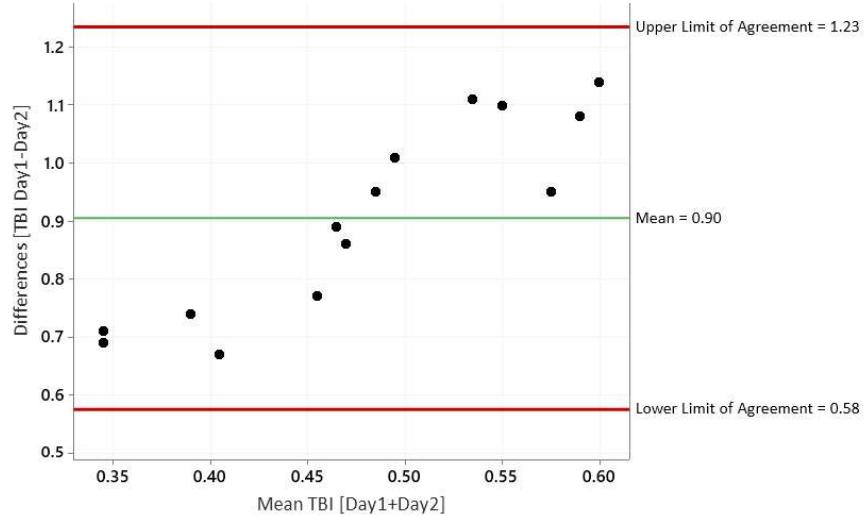
b) Intra-rater variability

Table 5.5.2. Showing intraclass correlation coefficients between assessments

	Intra-rater Agreement	
	ICC (3,1)	(95% CI)
TBI	0.97	(0.84 - 0.99)
Medicap (TcPO ₂)	0.66	(0.24 - 0.87)
10g monofilament	0.38	(-0.08 - 0.73)
DPNCheck®		
Velocity m/s	0.96	(0.87 - 0.99)
Amplitude μV	0.96	(0.89 - 0.99)

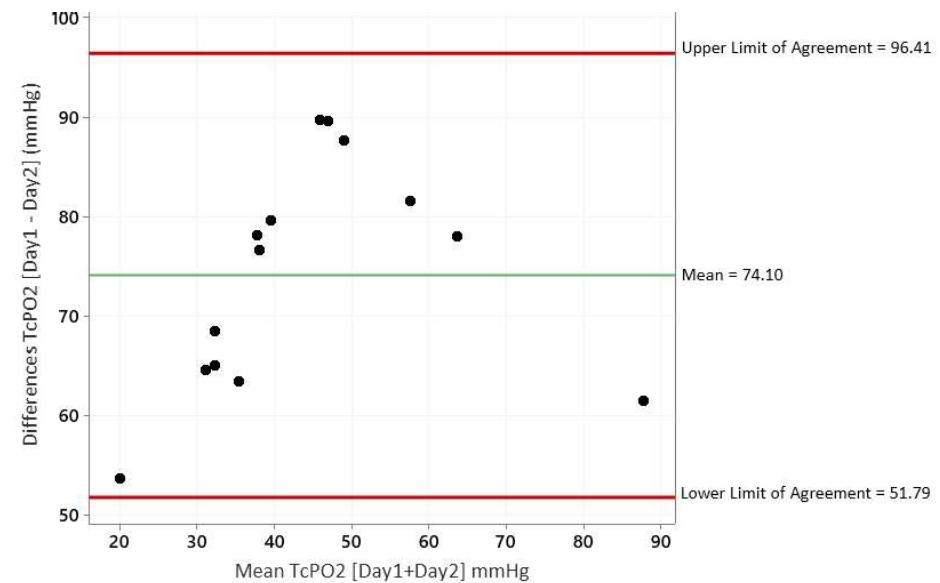
c) *Intra-class variability for the TBI*

Figure 5.5.2: Bland Altman plot of TBI intra-rater agreement.



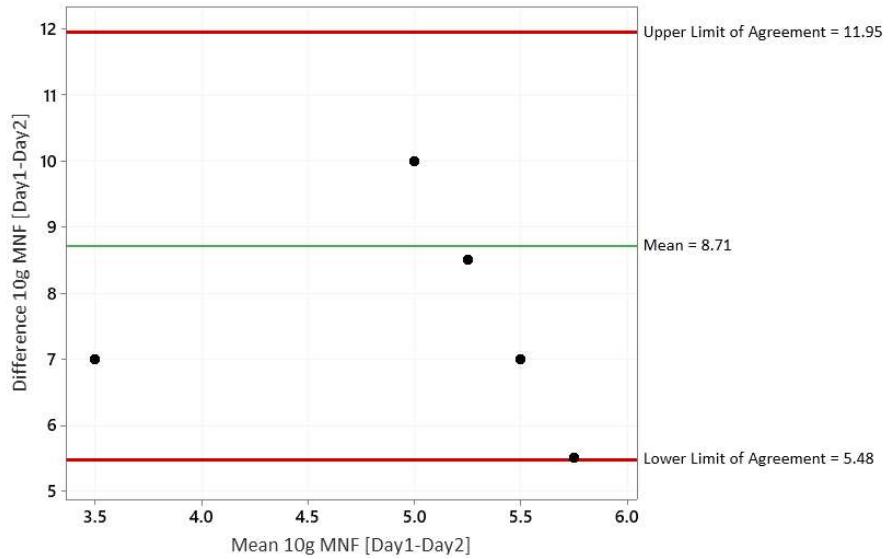
d) *Intra-class variability for the Medicap*

Figure 5.5.3. Bland-Altman plot of TcPO₂ Intra-rater agreement.



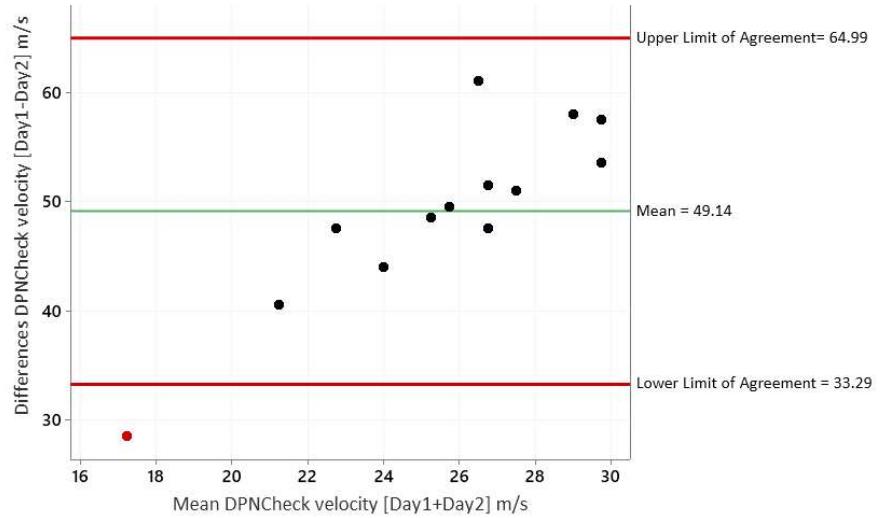
e) Intra-class variability for the 10g monofilament

Figure 5.5.4. Bland-Altman plot of 10g monofilament Intra-rater agreement.



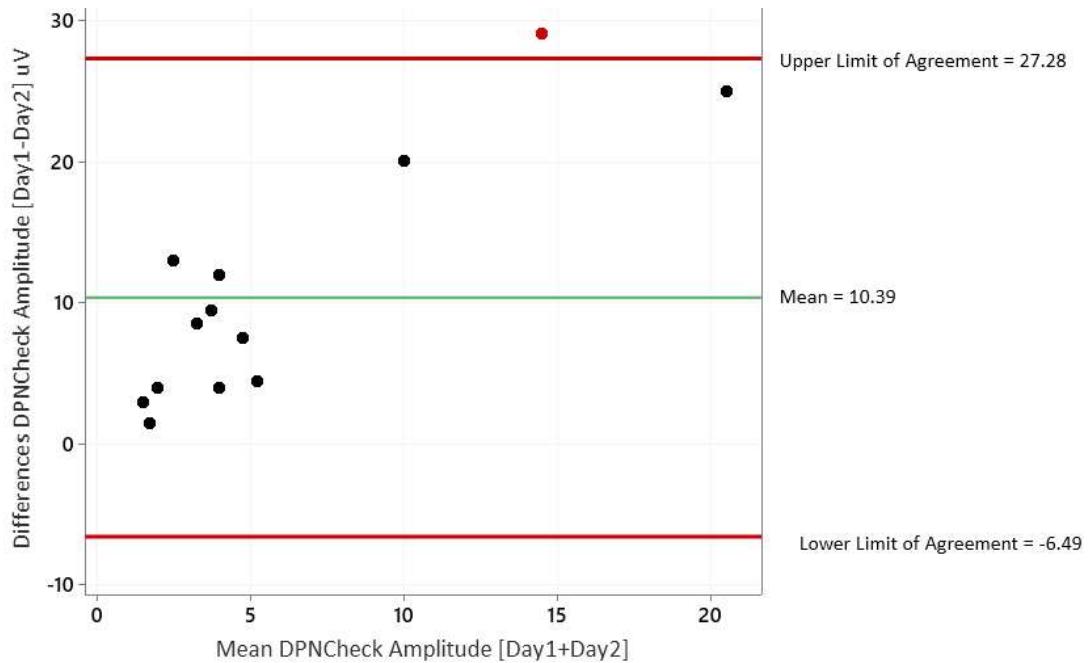
f) Intra-class variability for the DPNCheck® conduction velocity

Figure 5.5.5. Bland-Altman plot of DPNCheck® conduction velocity Intra-rater agreement.



g) *Intra-class variability for the DPNCheck® conduction amplitude*

Figure 5.5.6. Bland-Altman plot of DPNCheck® conduction amplitude intra-rater agreement.



5.5.6 Discussion

The main assumptions underpinning intrarater reliability are that neither the instrument used nor the participant health parameters being examined have changed between assessments, and therefore any variability observed in this scenario – were both the participant health status and instrument are ‘static’- will be due to the rater. Ideally this variability will be small, so that, assuming no change in the patient or instrument, the same rater using the same instrument on the same patient should get similar results for each assessment. The small differences will be due to intra-rater variability. This provides useful information in reaching clinical decisions, particularly on the extent of change that is detected by the instrument. It was therefore important to determine whether the participants health status had changed significantly enough between assessments to undermine the calculation of intrarater variability.

a) Participants

Out of an intended sample of 30, only 14 (10 male and 4 female) participants, who had a mean age of 53.4 (± 9.2) years, returned for reassessments, which occurred about 4 months following initial testing. The demographics of the 14 participants who returned are shown in Table 5.5.1.

b) Change in the health status of participants.

This shows that between the first and second assessments, apart from diabetes duration, the main diabetes characteristics (BMI, HbA1c) did not change significantly within the 4 months. There were however significant differences in the mean TBI, which reduced from 0.94 to 0.92 ($p = 0.02$), but no difference was detected by the Medicap ($p = 0.13$). For the 10g monofilament, 5 participants had reduced scores than on initial testing despite no change in the median scores, (Wilcoxon signed-rank test $Z = -2.1$, $p = 0.04$), whilst 11 participants had reduced DPNCheck® velocities, with overall median velocity reducing from 51.5 to 50 m/s (Wilcoxon signed-rank test $Z = -2$, $p = 0.04$). The data therefore suggests that according to some of the main outcome measures, the participants health status significantly changed within the 4 months.

c) Intrarater variability as shown in Table 5.5.2.

Intrarater variability was excellent for the TBI with $ICC(3,1) = 0.97$ (95% CI = 0.84-0.99), and for DPNCheck® velocity and amplitude ($ICC(3,1) = 0.96$ ((95% CI = 0.87-0.99)), with narrow ranges of confidence intervals. Intrarater reliability for the Medicap showed moderate agreement, with $ICC(3,1) = 0.66$ (95% CI = 0.24 – 0.87). The 10g monofilament showed poor reliability with $ICC(3,1) = 0.38$ (95% CI = -0.08 – 0.73). Whilst the distribution of data points around the mean line for each of TBI (Figure 5.5.3), 10g monofilament (Figure 5.5.4), DPNCheck® velocity (Figure 5.5.5) and DPNCheck® amplitude (Figure 5.5.6) suggest systematic errors; the distribution for the Medicap (Figure 5.5.3) suggest random error, however with less than half of data points ($n=14$) this is not definitive.

d) Comparisons with other studies

TBI: The intrarater reliability of 0.97 is better than that of previous studies. Romanos, Raspovic and Perrin (2010) found good reliability from 30 participants, deriving an ICC (2,1) of 0.75 (95% CI = 0.55 – 0.87), with the limits of agreement between 0.2 and 0.3. From 60 participants, Scanlon *et al.*, (2012) found reliability ranged from fair (ICC (3,1) = 0.51 ; 95% CI 0.30 - 0.68) to good (ICC 3,1= 0.72, 95% CI 0.57 - 0.82). With 2 raters, and retesting within 7-10 days, Sonter, Chuter and Casey (2015) found good intra-rater reliability, with ICCs (version not described) of 0.72 (95% CI = 0.5-0.85), and 0.75 (95% CI = 0.57 – 0.84). All these studies had larger samples, with much shorter retest intervals, making their findings less comparable to, but more robust than the current study.

Medicap: No studies were identified that investigated the Medicap intrarater reliability, therefore the ICC (3,1) = 0.66 (95% CI = 0.24 – 0.87), is a novel finding, notwithstanding the limitations outlined in section 5.5.7 (e).

10g monofilament: Collins *et al.*, (2010) found poor to moderate reliability, from 57 participants retested after 22 days, with right foot ICC scores (version of ICC not described) = 0.52 (IQR = 0.42 – 0.58). More recently, Lanting *et al.*, (2020), from 50 participants retested after 1 week, found intra-rater reliability ranging from κ = 0.44 to 0.77 (overall range of 95% CI from 0.09 – 0.99). However the κ is a categorical comparison score which is less sensitive to continuous scale changes than the ICC, which weakens the results of their study and makes them less comparable.

DPNCheck®: Lee *et al.*, (2014) assessed 44 participants with diabetes, and found the DPNCheck® had excellent intrarater reliability, with ICC (2,1) values of 0.97 (IQR 43-58) velocity; and 0.94 (IQR 3-11) for amplitude; which are similar to those found in the current study. Scarr *et al.*, (2018) assessed 139 participants (68 with Type 1 diabetes) and found the DPNCheck® had reduced ICC (2,1) = 0.7 for velocity (no CI / range provided) and 0.77 for amplitude (no CI / range provided). By not conducting same leg measurements, and instead comparing to measurements from the contralateral leg, intrarater variability

was incorrectly determined, and their findings cannot be compared to the current study. Shibata *et al.*, (2019) assessed 57 participants with diabetes, and found excellent intrarater repeatability of the DPNCheck®, with ICC _{velocity} (version not declared) = 0.88 (95% CI 0.79 -0.93); and ICC _{amplitude} (version not declared) = 0.84 (95% CI 0.76–0.89). Whilst it is not possible to determine the extent to which their results are generalisable, DPNCheck® reliability was similar to this study. Therefore, from the four devices, the DPNCheck® is the only one whose intrarater reliability agrees with previous investigations.

e) ***Limitations.***

The study's limitations derive from a combination of the extended recall time and the modest sample, with less than half of intended returnees. In the context of type 2 diabetes, retesting at 12-16 weeks was too long to determine intrarater reliability, during which time the ratees health status changed to such an extent that it is not possible to attribute any observed variations exclusively to the rater. An additional aspect to consider with the DPNCheck® and Medicap, as novel instruments, is that by 4 months considerable additional experience would have been gained by the rater as he continued to recruit and assess for the main study, and this would have a further effect on intrarater variability. But these conclusions are drawn from a reduced sample, and with the current levels of significance from some of the outcome measures not far below the threshold of $p < 0.05$, it can be postulated that the change in health status might not have reached statistical significance from a complete dataset with the intended 30 participants. However, the main limitations of an extended recall time, given the nature of type 2 diabetes, on a reduced sample (14), deserve focused consideration. Therefore, for the 10g monofilament, TBI, and Medicap, it is not possible to draw definitive conclusions from the limited dataset, and their reliability results should be seen from the perspective of these limitations. Despite these, the DPNCheck® emerges with reliability results that are consistent with findings from other studies.

f) Summary of validity and reliability investigations

In summary, Chapter 5 has shown that for the devices used for the doctoral investigations:

Reliability of the DPNCheck® in healthy participants. The DPNCheck® has excellent intrarater reliability in healthy participants.

Validity of the Medicap in healthy participants. The Medicap demonstrated criterion validity but overestimates TcPO₂ compared to a reference TCM400 device.

Validity of the Medicap in low risk diabetes participants. The Medicap retained criterion validity and overestimated TcPO₂ compared to a reference TCM400, and the extent of validity and bias across low risk diabetes is similar to that shown across healthy participants.

Reliability of the TBI in healthy participants. The TBI had excellent inter and intrarater reliability in healthy participants

Reliability of the TBI, Medicap, 10g monofilament and DPNCheck® in participants with type 2 diabetes. The TBI and DPNCheck® had excellent intrarater reliability, whilst the Medicap has moderate intrarater reliability and the 10g monofilament had poor intrarater reliability.

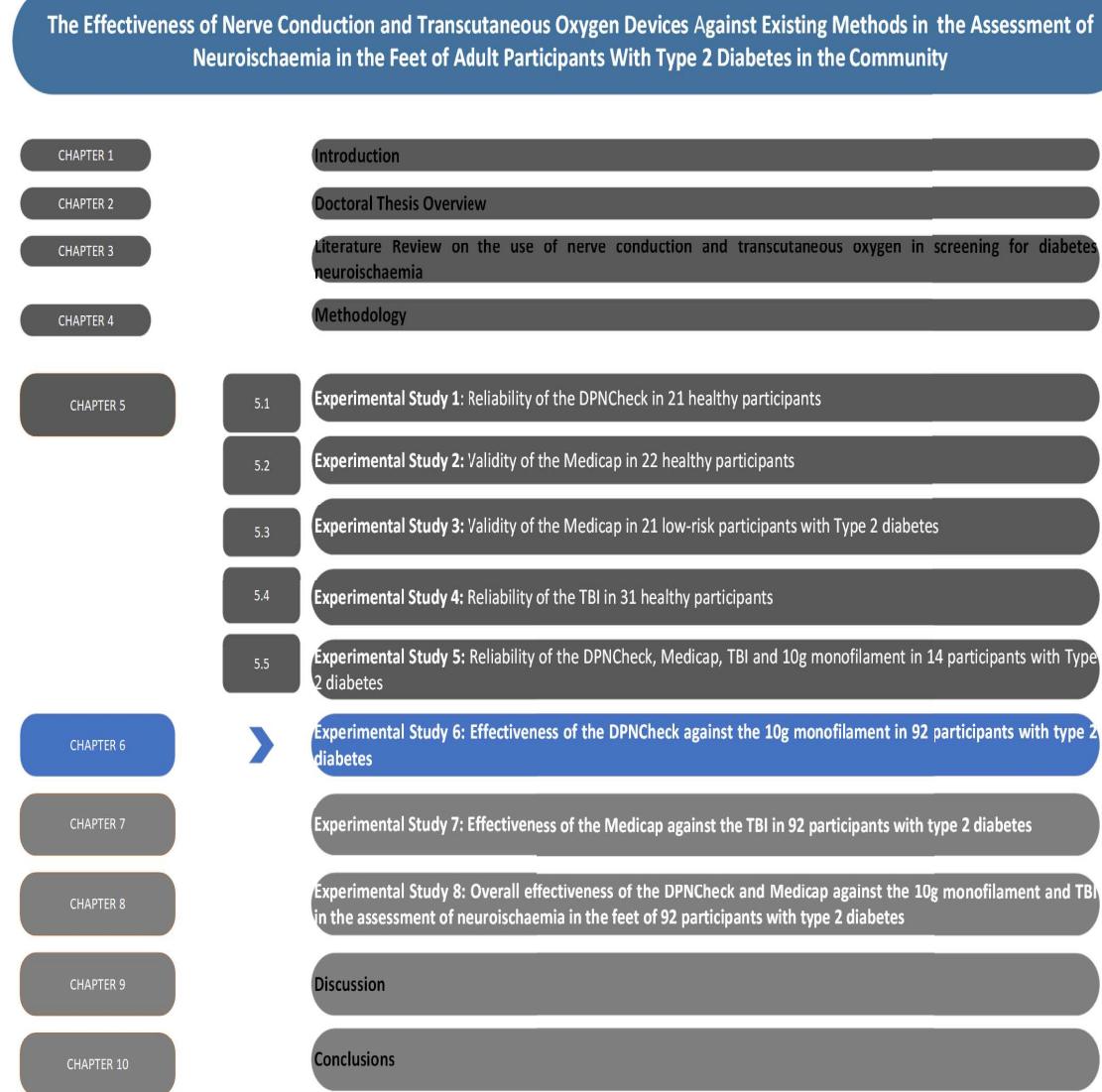
Methodological limitations with recall time and a reduced sample make the findings less comparable; however, DPNCheck® findings are supported by and consistent with current literature.

Chapter 6 NEUROLOGICAL EXPERIMENTAL STUDY

6.1 Introduction

This chapter compares the effectiveness of portable nerve conduction (DPNCheck®) to the 10g monofilament, in neuropathy assessment in people with type 2 diabetes in a routine podiatry clinic. As Experimental Study 6, its placement within the thesis context is shown in Figure 6.1

Figure 6.1: Showing investigation on DPNCheck® effectiveness within the thesis context



As previously discussed in Chapter 1.3.9, nerve conduction is considered an emerging reference standard, providing an objective quantitative assessment of neuropathy. However as outlined in Chapter 1.3.10, its use has faced adoption barriers when compared to established tools such as the 10g monofilament, due to equipment complexity, interpretation of findings, and studies that are largely laboratory based. Recent advances in technology and design have led to the development of more portable versions of nerve conduction devices, such as the DPNCheck® (NC-Stat DPNCheck®, Neurometrix Inc., Waltham, MA), capable of detecting early signs of sensory nerve damage (Lee *et al.*, 2014; de Souza, de Souza and Nagvekar, 2015; Georgia Chatzikosma *et al.*, 2016). The validity and reliability of the DPNCheck® in detecting sensory neuropathy has been established based on previous studies as described in Chapter 3.3, and DPNCheck® reliability for this thesis has been investigated in Chapter 5.5.

6.2 Aims and Objectives

This experimental study will assess whether the use of the DPNCheck® is more effective at the assessment of sensory neuropathy in the feet of people with type 2 diabetes attending a podiatry clinic, when compared to the 10g monofilament.

6.2.1 Primary Research Question

- a) Is the DPNCheck® more effective at the assessment of sensory neuropathy in a podiatry clinic when compared to the 10g monofilament?

6.2.2 Secondary research question

- a) Is the DPNCheck® more effective at stratification, i.e. (identifying the severity of neuropathy) than the 10g monofilament.

6.2.3 Hypothesis.

Interpretation of results was based on the following null and alternative hypotheses

***H_{NR} 0:** There is no significant difference in frequency (the numbers of people) suspected of having sensory neuropathy when assessed using the DPNCheck®, compared to using the 10g monofilament. The 10g monofilament will have acceptable validity in the assessment of diabetic sensory neuropathy.*

***H_{NR} 1:** There is a significant difference in frequency, with more people suspected of sensory neuropathy using the DPNCheck®, than on the 10g monofilament.*

If the results of the primary analyses suggest that there is sufficient evidence to reject the null hypothesis, it will be concluded that there is a difference in the number of people suspected of having sensory neuropathy, that nerve conduction is more effective at the assessment of diabetes neuropathy; and the 10g monofilament will be deemed to lack adequate validity to assess diabetes foot neuropathy.

6.2.4 Primary Outcome Measure

The primary outcome measure is the numbers of people suspected of having sensory neuropathy, based on either the DPNCheck®, or the 10g monofilament, as described in Chapter 4.7.2(a) and Table 4.7.2 (page 100).

6.2.5 Secondary Outcome Measure

The secondary outcome measure will determine the numbers of people classified into 4 categories depending on neuropathy severity; (no neuropathy; mild-moderate-severe neuropathy) based on the DPNCheck® and the 10g monofilament, as described in Chapter 4.9.1 and Table 4.9.1 (page 102).

6.3 Method

6.3.1 Study design and sample recruitment

As the DPNCheck® will give a snapshot of nerve health status at a point in time, this is a cross sectional study design. The eligibility and recruitment criteria are as outlined in Chapter 4.5 (page 88-91), and ethical approvals are outlined in Chapter 5.5.4(b) (page 154-155)

6.3.2 Test Protocol

Each participant had both neuropathy assessments at the same time, according to each devices respective protocol, for the DPNCheck® (Appendix A2) and 10g monofilament (Appendix A1).

6.3.3 Data Analysis

For the primary outcome, data was recorded as frequency counts (numbers of people) suspected with and without neuropathy for each device. For other measures, data was assessed for conformity to a Gaussian distribution, with parametric data reported as mean \pm standard deviations (SDs); and non-parametric data as median (range) and as numbers and percentages (%). Agreement between the DPNCheck® and 10g monofilament was determined using Cohen's kappa. In all cases, significance level for all tests set at 5 %.

6.4 Results

6.4.1 Demographics of study participants.

The demographic information on the participants is shown in Table 8.1.1 in Chapter 8. Overall, 93 participants (58 males; 35 females) were recruited for the study. Despite giving written consent, 1 female participant later declined to have the nerve conduction assessment, and was therefore excluded from the final analysis. This left 92 participants who were included in the overall analysis, with a median age 56 (range 25-65) years, BMI

of 30.8 (21.2-48.5) kg/m², median HbA1c of 60 (38-141) mmol/mol, and diabetes duration of 75 (2-360) months. The rest of the demographics are as shown in Table 8.1.1 in Chapter 8.

The overall results from the assessment of sensory neuropathy show that from the DPNCheck®, 45 participants were suspected of having neuropathy, compared to 21 participants from using the 10g monofilament, as summarised in Figure 6.4.1.

Figure 6.4.1. Results from DPNCheck® and 10g monofilament in the assessment of sensory neuropathy.

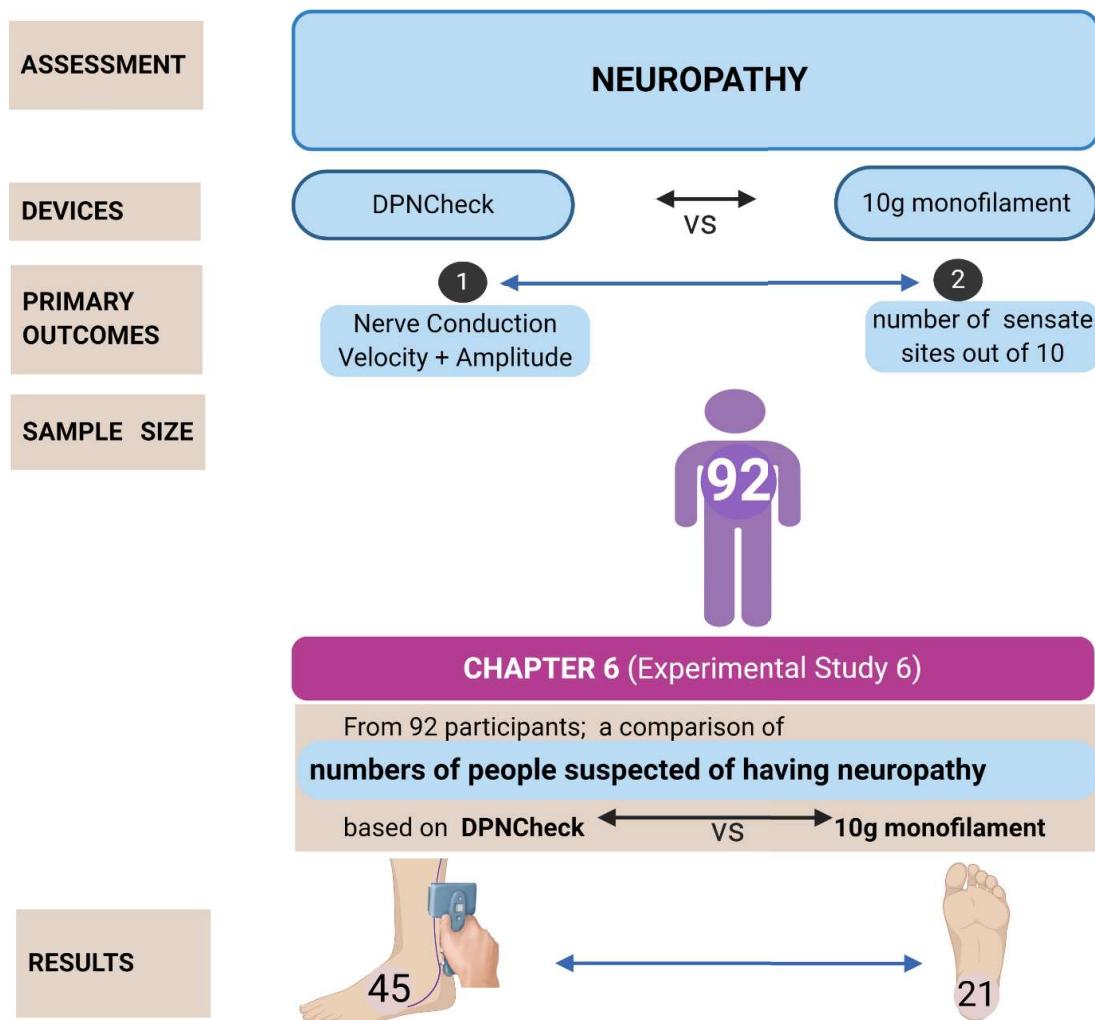


Image: Author's own. Created with Biorender.com

6.4.2 Primary outcome – numbers of people suspected of having with neuropathy

Table 6.4.1: Frequency table showing numbers of people suspected of having sensory neuropathy

		DPNCheck® (Nerve Conduction)		
		Neuropathy	No neuropathy	TOTAL
10g monofilament	Neuropathy	20	1	21
	No neuropathy	25	46	71
	TOTAL	45	47	92

From Table 6.4.1, the DPNCheck® suspected 45 participants of having neuropathy, compared to 21 by the 10g monofilament, giving an overall neuropathy prevalence of 48.9% and 22.8% respectively. The validity and diagnostic accuracy of the 10g monofilament compared to the DPNCheck®, was determined by its sensitivity of 44.4% (95% CI = 30.9 – 58.8%); specificity of 97.9% (95% CI = 88.9 - 99.6%) and diagnostic accuracy of 71.7% (95% CI = 61.8 - 79.9%).

6.4.3 Comparison of the effectiveness of DPNCheck® to the 10g monofilament in the assessment of sensory neuropathy

Cohen's κ estimated moderate agreement between the two instruments ($\kappa = 0.43$, $p < 0.001$), and because DPNCheck® is "gold standard"; this also shows the degree of measurement error for the 10g monofilament.

From section 6.2.3, the null hypothesis ($H_{NR\ 0}$) is therefore rejected, and the alternative hypothesis ($H_{NR\ 1}$) is accepted. The DPNCheck® is more effective than the 10g monofilament at the assessment of sensory neuropathy in the feet of people with type 2 diabetes.

6.4.4 Secondary Outcomes: the effectiveness of the DPNCheck® at neuropathy stratification, i.e. (identifying the severity of neuropathy) when compared to the 10g monofilament.

The severity of neuropathy was categorised as mild, moderate or severe, with the frequency counts recorded as shown in Table 6.4.2.

Table 6.4.2: Table showing the DPNCheck® and 10g monofilament stratification of neuropathy severity.

		DPNCheck®				TOTAL
		No Neuropathy	Mild	Moderate	Severe	
10g monofilament	No Neuropathy	47	5	16	3	71
	Mild	1	0	8	1	10
	Moderate	0	0	2	3	5
	Severe	0	0	1	5	6
	TOTAL	48	5	27	12	92

a) *Weighted kappa* (κ_{weighted}), **with linear weighting**, was used to determine the extent of agreement between the instruments; taking into account their respective ability to identify participants with different neuropathy severity.

$\kappa_{\text{weighted}} = 0.4$ (95% CI: 0.26 - 0.54) $p < 0.001$, indicating fair agreement.

b) *Correlations*: Since data follows a non-Gaussian distribution, Spearman σ was used to determine the extent of correlation between the neuropathy scoring systems as follows;

- Correlation between the 10g monofilament and nerve conduction amplitude: Spearman $\sigma = 0.53$ ($p < 0.001$)
- Correlation between 10g monofilament and nerve conduction velocity: Spearman $\sigma = 0.48$ ($p < 0.001$)
- Correlation between nerve conduction amplitude and nerve conduction velocity: Spearman $\sigma = 0.69$ ($p < 0.001$)

This shows strong and significant correlations between nerve conduction velocity and amplitude. The 10g monofilament has significant, but fair to moderate correlations with nerve conduction parameters (velocity and amplitude).

6.5 Discussion

6.5.1 Effectiveness of the DPNCheck®.

The results show that the DPNCheck® was more effective in the assessment of sensory neuropathy and identifying neuropathy severity than the 10g monofilament. From

section 6.4.2, the 10g monofilament demonstrates very high ability in excluding those without neuropathy (specificity = 97.9%), but relatively poor at identifying those with neuropathy (sensitivity = 44.4%). The current findings also agree Vogt *et al* (2017), who found the level of agreement of $\kappa = 0.4$ in 90 participants between the 10g monofilament and the DPNCheck®. However in contrast they also found high false positives (23%), good sensitivity (86%) and moderate specificity (59%) from the 10g monofilament, probably due to the differences in ethnic demographics and thickened plantar callus due to extended time barefoot amongst the Zanzibar participants, compared to the current study. Current findings also broadly align with those by Brown *et al.*, (2017), who from 34 participants, found the 10g monofilament to have relatively poor sensitivity (47.4%) and good specificity (73.3%) in neuropathy assessment against the DPNCheck®. However, only 11 participants had type 2 diabetes, which could account for the differences in specificity, but overall this supports the finding that the 10g monofilament has poor sensitivity in the assessment of sensory neuropathy against the DPNCheck® in people with type 2 diabetes. With the stated aim of diabetes neuropathy assessment being its early identification, what is of interest from this study are the false negatives representing the 10g monofilament's potential "blind spot". From Table 6.4.1, the 10g monofilament ruled out 71 participants from having neuropathy, yet from these, 25 were suspected of neuropathy by the DPNCheck®, representing a false negative rate of 35.2%. The clinical implications of this are that, based on the 10g monofilament, more than 1 in 3 people ruled out, do in fact have sensory neuropathy that they themselves and the clinicians are not aware of. This then compounds the problems of late detection, which include delayed interventions and increased rates of ulcerations, amputations and deaths. It is therefore important to further investigate the magnitude of this potential "blind spot", and crossover thresholds between those who have neuropathy and those who do not from amongst the 71 participants that the 10g monofilament determined as unlikely to have neuropathy. Both these aspects of the discussion are continued in Section 8.6.2 of Chapter 8.

With the DPNCheck®, this investigation adds to current literature by demonstrating its effectiveness in a pragmatic and routine clinic setting. The DPNCheck® is not burdened by the constraints of fixed nerve conduction, which continues to face adoption challenges despite being a reference standard in the assessment of sensory neuropathy as outlined

in Chapter 1.3.10 (page 31). The DPNCheck® is considerably less complex than fixed nerve conduction devices, can be administered in more diverse settings away from specialised setups, has criterion validity and excellent repeatability (Chapter 3.3), and is more effective at the assessment of diabetes sensory neuropathy than the recommended NICE NG19(2015) approach. As with all sensory nerve conduction, the DPNCheck® outputs two parameters, velocity and amplitude, which it uses to determine neuropathy severity, but this potentially adds complexity to the interpretation of its findings. It is therefore important to investigate statistical approaches that could simplify the conduction velocity and amplitude into a single unified score which can help the interpretation of nerve conduction findings, and assist with its clinical adoption.

6.5.2 Limitations.

The main limitation affecting the study was the unilateral nature of the neuropathy assessments. This is based on the assumption that diabetes has symmetrical effects on the sural nerve in both limbs, which is supported by previous studies (Albers *et al.*, 1996; Perkins, Ngo and Bril, 2002; Lee *et al.*, 2014; Sharma, Vas and Rayman, 2015; Hamasaki and Hamasaki, 2017). Unilateral limb assessments were done for pragmatic reasons, particularly cost. The required DPNCheck® sensory electrodes for 113 participants (92 main study + 21 students), with one for each limb, would have exceeded 200 units and proved prohibitive. The research was made possible by the DPNCheck® manufacturer (Nuerometrics), kindly supplying 150 electrodes at no cost for the investigations.

6.5.3 Summary

In summary, this investigation adds support to the DPNCheck® as a portable nerve conduction device, in being more effective than the NICE NG19 (2015) method, in the assessment of sensory neuropathy. Given the importance of neuropathy assessment, from this chapter has emerged a need to determine a potential “no neuropathy”/“neuropathy” threshold using the more effective DPNCheck®, and in addition the potential for the DPNCheck® itself to have a simplified unified score for neuropathy. Both these discussion points are further explored in Chapter 8, after considering the ischaemia investigations in Chapter 7.

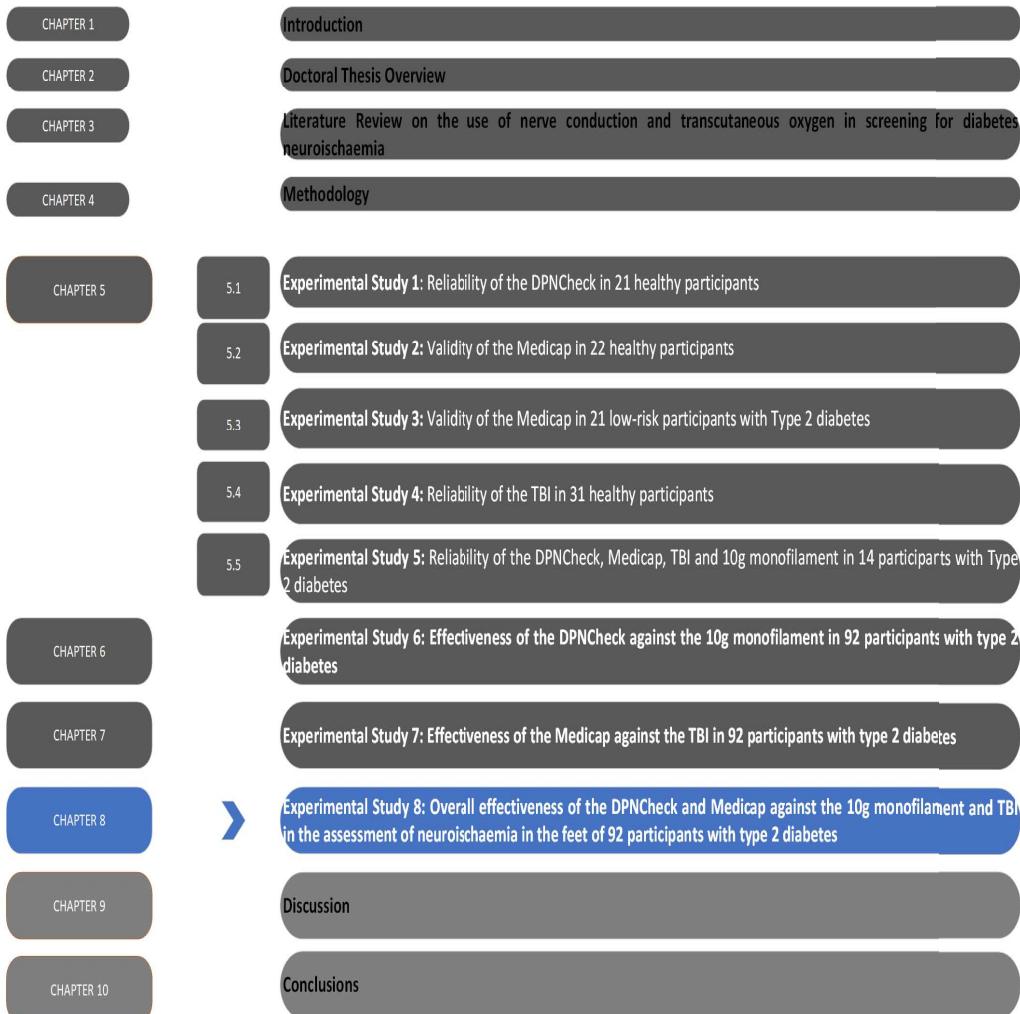
Chapter 7 ISCHAEMIA EXPERIMENTAL STUDY

7.1 Introduction

This chapter compares the effectiveness of microvascular ($TcPO_2$) and macrovascular (TBI) assessments in the assessment of ischaemia in the feet of people with type 2 diabetes patients in a routine podiatry clinic. The value of this chapter within the thesis context is shown in Figure 7.1

Figure 7.1: Showing investigation on Medicap effectiveness within the thesis context

The Effectiveness of Nerve Conduction and Transcutaneous Oxygen Devices Against Existing Methods in the Assessment of Neuroischaemia in the Feet of Adult Participants With Type 2 Diabetes in the Community



As previously discussed in Chapter 1.4.5, the TBI is more reliable than the ABI in the assessment of ischaemia in people with diabetes, but is a poor predictor of chronic ulceration and cannot be used if the toe has been amputated. TcPO₂ can be used even post-amputation and accounts for collateral circulation, but its role in the early assessment of ischaemia is not clear. The validity and reliability of TcPO₂ in detecting microischaemia has been established based on previous studies as described in Chapter 3.4, whilst Medicap validity has been established in Chapter 5.2 and 5.3, and Medicap reliability for this thesis has been investigated in Chapter 5.5.

7.2 Aims and Objectives

This experimental study will assess whether the use of the Medicap, is more effective at the assessment of ischaemia in the feet of people with type 2 diabetes attending a podiatry clinic, when compared to the TBI.

7.2.1 Primary Research Question

- a) Is the Medicap more effective at the assessment of ischaemia in a podiatry clinic when compared to the TBI?

7.2.2 Secondary research question

- a) Is the Medicap more effective at stratification, i.e. (identifying the severity of ischaemia) compared to the TBI.

7.2.3 Hypothesis.

Interpretation of results was based on the following null and alternative hypotheses

H_{1sc 0}: There is no difference in frequency of (the number of people suspected of having) ischaemia using the Medicap, and those diagnosed based on the TBI.

H_{1sc 1}: There is a difference in frequency with more people suspected of having ischaemia based on the Medicap when compared to the TBI.

If the results of the primary analyses suggest that there is sufficient evidence to reject the null hypothesis, it will be concluded that the Medicap has adequate validity in the assessment of diabetes foot ischaemia when compared to the TBI.

7.2.4 Primary Outcome Measure

The primary outcome measure is the numbers of people suspected of having ischaemia, based on either the Medicap or the TBI.

7.2.5 Secondary Outcome Measure

The secondary outcome measure is the numbers of people stratified into one of 5 categories depending on ischaemia severity; (no ischaemia, mild-moderate-severe ischaemia, calcification), based on either the Medicap, or the TBI.

7.3 Method

7.3.1 Study design and sample recruitment

As both the Medicap and TBI will give a snapshot of ischaemic status at a point in time, this is a cross sectional study design. The eligibility and recruitment criteria are as outlined in Chapter 4.5 (page 88-91), and ethical approvals are outlined in Chapter 5.5.4(b) (page 154-155)

7.3.2 Test Protocol

Each participant had both ischaemia assessments at the same time, according to each device's respective protocols, for the Medicap (Chapter 4.6.5(g), page 97-98; and Appendix A4) and TBI (Chapter 4.6.5(f), page 96-97 and Appendix A3).

Following earlier discussions, threshold values of $TBI \leq 0.7$ (Chapter 1.4.5, page 41), and Medicap $TcPO_2 \leq 50$ mmHg(Chapter 5.3.7(a), page 142); were set to suspect ischaemia for these investigations.

7.3.3 Data Analysis

For the primary outcome, data was recorded as frequency counts (numbers of people) suspected with and without ischaemia for each device. For other measures, data was assessed for conformity to a Gaussian distribution, with parametric data reported as mean \pm standard deviations (SDs); and non-parametric data as median (range) and as numbers and percentages (%). Agreement between the Medicap and TBI was determined using Cohen's kappa. In all cases, significance level for all tests set at 5 %.

7.4 Results

7.4.1 Demographics of study participants.

The demographic information on the participants is shown in Table 8.1.1 in Chapter 8. Overall, 93 participants (58 males; 35 females) were initially included in the study. Despite giving written consent, 1 female participant later declined to have the nerve conduction assessment, and was therefore all her measures were excluded from the final analysis. This left 92 participants who were included in the overall analysis, with a median age 56 (range 25-65) years, BMI of 30.8 (21.2-48.5) kg/m², median HbA1c of 60 (38-141) mmol/mol, and diabetes duration of 75 (2-360) months. The rest of the demographics are as shown in Table 8.1.1 in Chapter 8.

The overall results from the assessment of ischaemia show 10 participants each were suspected of having ischaemia by the Medicap and the TBI, as summarised in Figure 7.4.1.

Figure 7.4.1. Results from Medicap and TBI in assessment ischaemia.

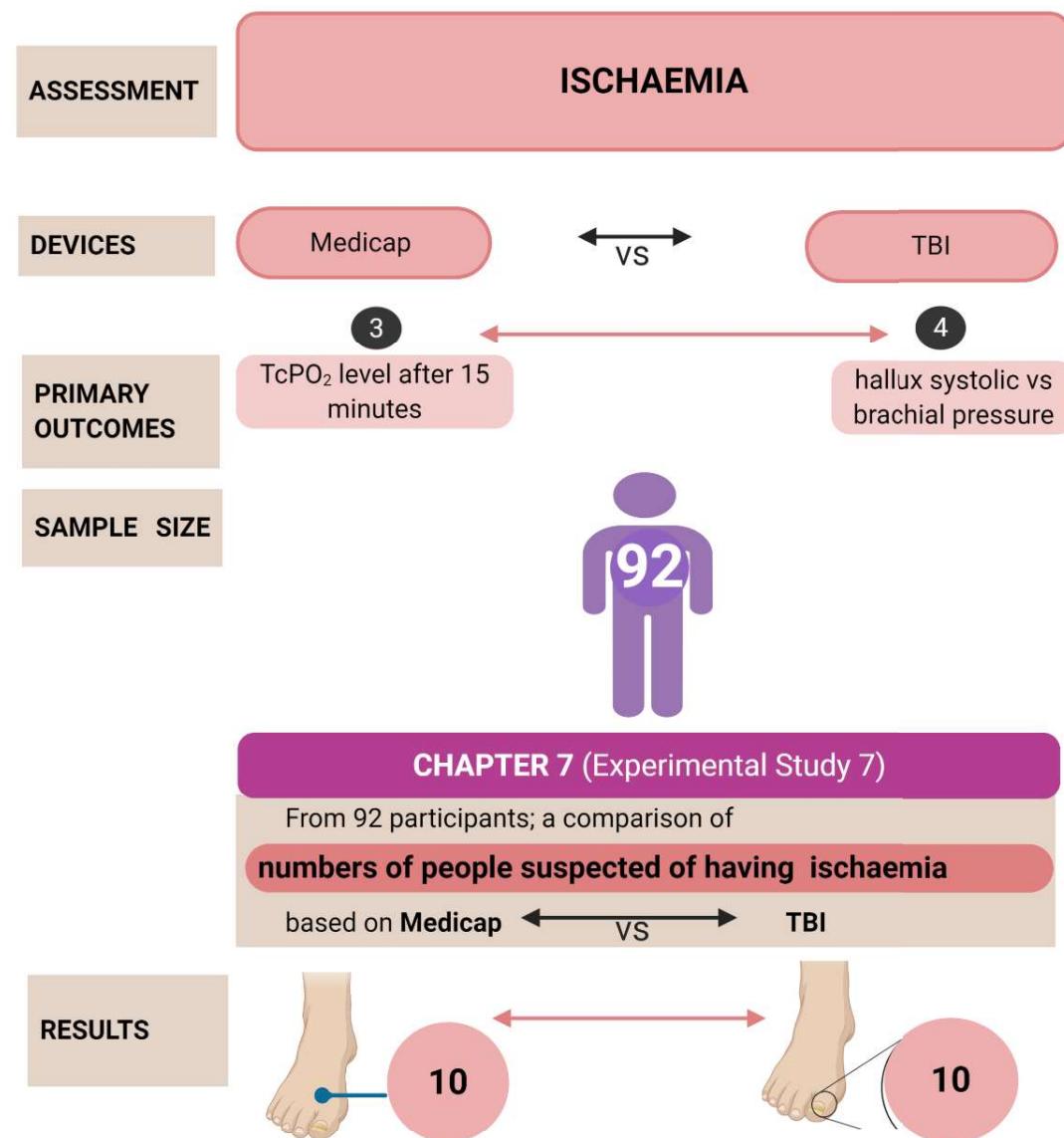


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7.4.2 Primary outcome – numbers of people suspected of having ischaemia

Table 7.4.1: Frequency table showing numbers of people suspected of having ischaemia

Medicap (TcPO ₂)	Ischaemia	TBI		TOTAL
		Ischaemia	No ischaemia	
	Ischaemia	0	10	10
	No ischaemia	10	72	82
	TOTAL	10	82	92

The overall prevalence of ischaemia, based on the TBI, was 10.9%. From Table 7.4.1, 10 participants were suspected of having ischaemia based on the TBI, and a further 10 by the Medicap. The instruments agreed on excluding ischaemia in 72 cases, but did not agree on a single suspected case. The validity and diagnostic accuracy of the Medicap compared to the TBI was determined by the Medicap's sensitivity 0% (95% CI = 0 – 30.9%); specificity 86.6% (95% CI = 77.3-93.1%) and a diagnostic accuracy of 77.2% (95% CI = 67.3-85.3%). Cohen's κ estimated moderate negative agreement between the two instruments which did not reach significance ($\kappa = -0.12$, $p = 0.24$).

7.4.3 Comparison of the effectiveness of the Medicap to the TBI

The results show no significant difference in the numbers of people suspected of having with ischaemia from the Medicap (10 participants), compared to the TBI (10 participants). The null hypothesis is therefore accepted, with the Medicap not being more effective at the assessment of ischaemia. Of interest is the finding that the Medicap and the TBI did not agree on any suspected cases of ischaemia, which will be discussed in section 7.5.

7.4.4 Secondary Outcomes: the effectiveness of the Medicap at ischaemia stratification

i.e. (identifying the severity of ischaemia) when compared to the TBI. The severity of ischaemia was categorised as no ischaemia, mild, moderate, severe or calcification, with the frequency counts recorded as shown in Table 7.4.2.

Table 7.4.2: Table showing the showing the TBI and TcPO₂ stratification of ischaemia severity

		TBI					
		No Ischaemia	Mild	Moderate	Severe	*Calcification	
Medicap (TcPO ₂)	No Ischaemia	72	8	0	0	2	82
	Mild	8	0	0	0	0	8
	Moderate	1	0	0	0	0	1
	Severe	1	0	0	0	0	1
	*Calcification	0	0	0	0	0	0
TOTAL		82	8	0	0	2	92

* TBI detected 2 people with incompressible digital arteries (calcification)

a) *Weighted kappa* was used to determine the extent of agreement between the Medicap and the TBI, taking into account their respective ability to identify participants into the 5 categories. Because of the “zero” count having failed to agree on a single case of suspected ischaemia, no weighted Kappa coefficient could be calculated. SPSS failed to report *Kweighted*, as the observed concordance was smaller than mean-chance concordance.

b) Correlation between Medicap and TBI was determined by the Spearman $\rho = 0.07$, ($p = 0.49$), showing poor correlation which did not reach statistical significance between the Medicap and TBI.

7.5 Discussion

The results show that the Medicap was not more effective at the assessment of ischaemia than the TBI. Whilst both the Medicap and TBI ruled out ischaemia in the same 72 participants, they failed to agree on any suspected cases, showing a lack of agreement between microischaemia and macroischaemia in this group of participants. From an ischaemia viewpoint, no participant presented with complications such as active ulceration, and even those with previous amputations had fully healed. It is possible that for this community outpatient cohort the two processes of macro and microischaemia were occurring independently and yet to overlap as they do in later diabetes. The possible discrepancies have been observed elsewhere:

7.5.1 **Normal TBI but with microischaemia (subnormal TcPO₂ from the Medicap)**

The TBI, as a macro-circulatory measure, gives an indication of the gross volume or quantity of arterial supply to the digit. The TBI however cannot determine the quality that is delivered to a specific angiosome. It is therefore possible that despite a good digital arterial supply with a normal TBI > 0.7 , a paradoxical defective microcirculation could be present, with subnormal TcPO₂ < 50 mmHg. This is consistent with previous studies identified in Chapter 3.4, that found a normal TBI but subnormal TcPO₂. For example Ezio *et al.*, (2010) found normal macrocirculation, with normal ankle pressures indicated in 50 participants (31%), yet TcPO₂ diagnosed microischaemia. Ezio *et al.*, (2010) could not obtain the toe pressures in over 70% of their participants, hence comparisons for macrocirculation relied on the ABI rather than the TBI. Pardo *et al.*, (2015), also found that in 17.5% participants, the ABI increased whilst the TcPO₂ did not. Whilst both these studies used the ABI rather than the TBI, they show that the macroarterial supply can be intact despite the presence of microischaemia.

7.5.2 **Normal TcPO₂ from the Medicap, but with macroischaemia (subnormal TBI)**

Because of the Medicap's ability to account for the collateral circulation, it is also possible that despite a defective macroarterial supply with an abnormal TBI < 0.7 , an angiosome can have normal TcPO₂ > 50 mmHg. This too is consistent with the literature, as demonstrated by Pardo *et al.*, (2015) who found that in 12.5% the ABI suspected macroischaemia despite normal TcPO₂.

7.5.3 **Limitations**

The study's limitations include:

- a) *Participant positioning.* It has been recommended that the TBI protocol follows that of the ABI, in stipulating that the participant should lie supine with the ankles at heart level, as shown in Figure 7.5.1.

Figure 7.5.1: Showing the recommended protocol for participant positioning when taking the TBI.



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The reasons for this include to minimise the effects of the veno-arteriolar reflex (VAR), which reduces arterial flow to the foot. The VAR mechanism is activated by changes in posture, and operates through a feedback mechanism under autonomic control, therefore a further aspect to consider is its impairment in the presence of diabetes neuropathy. If the feet become dependent relative to the heart, the pooling of blood in the veins constricts the arteries, thereby restricting pedal arterial flow. The VAR effect relies on the vertical distance between the heart and the ankle, and is more pronounced with the legs in full dependency when the venous columns of blood are vertical, as shown in Figure 7.5.2.

Figure 7.5.2 Showing the venous blood orientation in triggering the VAR.

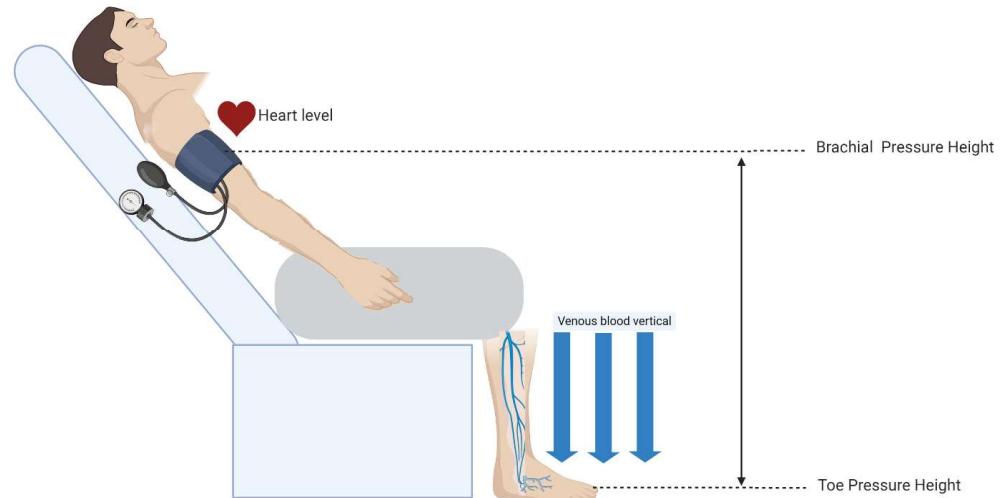


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By contrast, the TBI position for this study (Fowler's position) is as shown in Figure 7.5.3.

Whilst this did not exclude the VAR effects on peripheral circulation, it can be argued that these effects were not as pronounced since the legs were not in full dependency, although this was not measured.

Figure 7.5.3: Showing Fowler's position used for this study, and potential effects on VAR

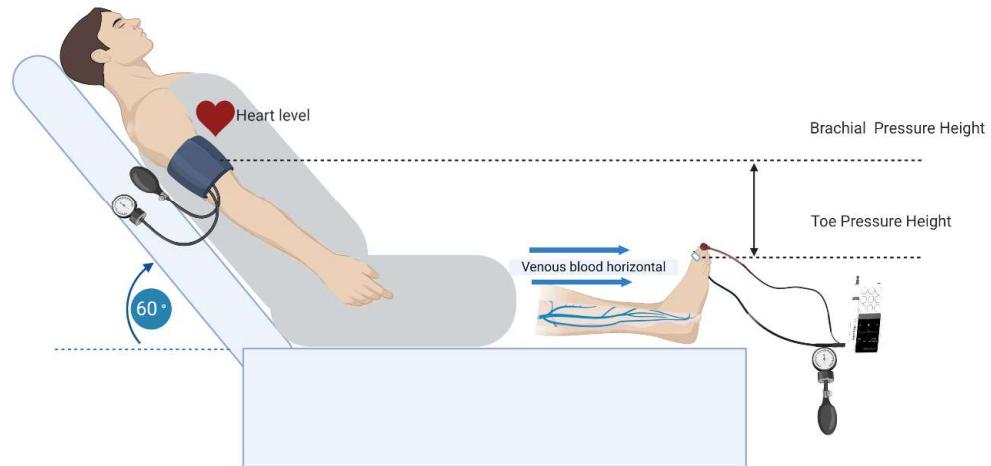


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The literature is also inconsistent regarding the effects of changing posture on ABI/TBI, finding both increases and decreases in blood pressure (Kallioinen *et al.*, 2017). Privšek *et al.*, (2018) suggested that the sequence of posture changes and pressure measurements, in the same session, has a determinant role. Studies that investigated changes from *seated* → *supine* found higher seated pressures (Krzesiński *et al.*, 2016; Lacruz *et al.*, 2017; Privšek *et al.*, 2018); compared to those that investigated *supine* → *seated*, finding higher supine pressures (Gornik *et al.*, 2008; Cicolini *et al.*, 2011).

Additional consideration ought to be given to the overall effects on the TBI itself. Since it is a ratio, if both brachial and toe pressures change to the same extent, then this would not adversely affect the overall TBI. This study did not investigate changes in perfusion pressure relative to posture, so the effects of taking the participants from *standing* → *seated* in the Fowler's position (Figure 7.5.3) on the TBI are unclear. The overall effect on brachial pressure is unknown, with divergent opinion on whether it changes (Vrachatis *et al.*, 2014; Yoloğlu and Ulus, 2018), but it can be assumed to not have changed as it was level with the heart. What cannot be ignored, is that the participant posture change from *standing* → *seated* could possibly have changed

the peripheral perfusion in one of two ways:

- a) *Toe pressure decreased*: as the feet went from vertical to horizontal, reducing arterial load volume.
- b) *Toe pressure increased*: with reduction in venous volume, the VAR mechanism deactivated, with dilation of the arteries and increasing toe pressure.

Because of the standard approach for all 92 participants in the assessment of ischaemia, with 10 minutes resting time, it is unlikely that the haemodynamic mechanisms affected the TBI and Medicap to such an extent to change their ischaemia classification. It can therefore be argued that the study retains its internal validity. However, without accounting for the variation in posture compared to standard TBI protocol, and the extent to which it could have affected arterial flow in the foot, it must be accepted that this presents a methodological limitation, and threatens its external validity.

A main feature of this research was to present findings that would be relevant to a usual podiatry clinic. In such settings, it is not always possible for patients with leg ulcers, pain, orthopnea, shortness of breath or heart complications to lie supine as recommended by the TBI protocols. For most patients, the legs are usually in dependency or at least outstretched horizontally, hence assessment in this posture is more pragmatic and representative of both the clinical and patient realms. This also presents potential for further research to define ischaemia thresholds that are relevant to a routine clinical environment.

7.5.4 Summary of Medicap and TBI in assessment of ischaemia.

In summary, the study found a total of 20 suspected ischaemia cases, with 10 each from the TBI (macroischaemia) and the Medicap (microischaemia). These results suggest that neither method (Medicap or TBI) on its own provides a complete picture of ischaemic status, and in this group of participants the two methods were not comparable. With regards to early detection, it suggests that rather than competing, the Medicap and TBI could instead be complementary assessment methods. This is also consistent with current opinion, where macro (quantity of supply) and micro (quality of supply) ischaemia assessment methods are seen as complementing each other.

Chapter 8 EXPERIMENTAL STUDY 8: COMBINED RESULTS

The findings from Chapters 6 and 7 are further analysed jointly in this Chapter as experimental study 8, whose position within the thesis context is shown in Figure 8.1.

Figure 8.1: Showing Experimental study 8 within the thesis context.



This chapter summarises the results from the neuropathy (Chapter 6) and ischaemia (Chapter 7) experimental studies, an overview of which is given in Figure 8.2:

Figure 8.2: Showing a summary of the primary outcome measures

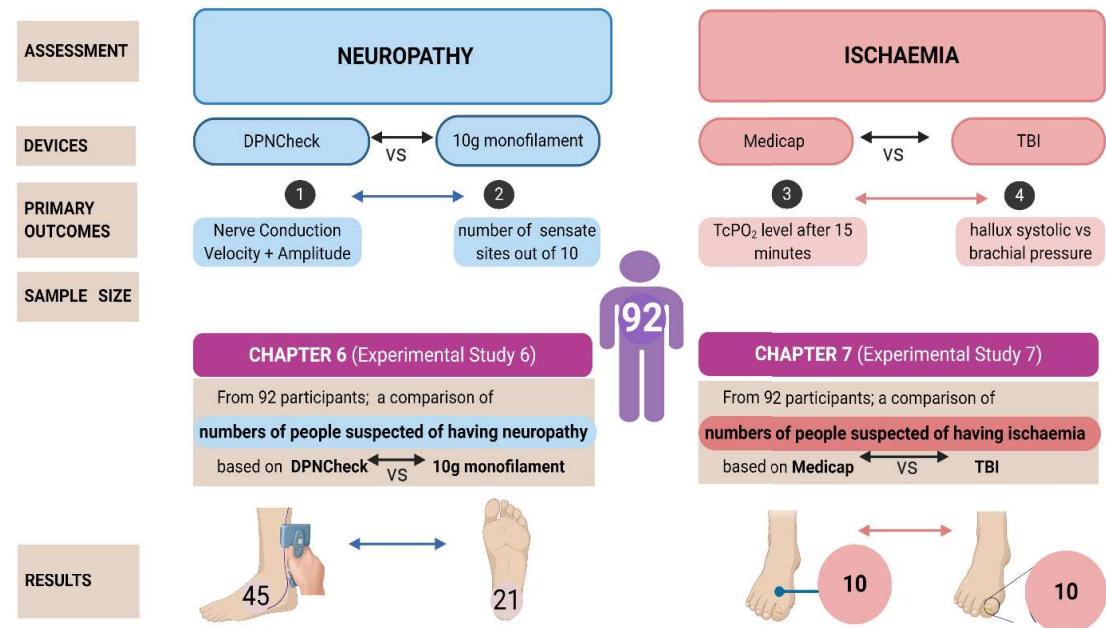


Image: Author's own. Created with Biorender.com

8.1 Study participants

The clinical characteristics of the 92 participants enrolled onto the study are shown in table 8.1.1

Table 8.1.1: Showing the clinical characteristics of the study participants

Age (years)	56
<i>median (IQR)</i>	(50 - 61.8)
Total Participants	92
Gender	
<i>Male</i>	63%
<i>Female</i>	37%
Test Centre	
<i>Southampton</i>	60.9%
<i>Manchester</i>	39.1%
Diabetes Duration (months)	75
<i>median (IQR)</i>	(10.5 -185)
HbA1c (mmol/mol)	60
<i>median (IQR)</i>	(53 -81.8)
BMI (kg/m²)	30.8
<i>median (IQR)</i>	(27.7 – 37.4)
Smoking History	
<i>Never Smoked</i>	57.6%
<i>Current</i>	16.3%
<i>Quit</i>	26.1%
Diabetes Medication	
<i>Diet Only</i>	15.2%
<i>Metformin</i>	23.9%
<i>Other (Sulfonylureas/Gliptins)</i>	3.3%
<i>Insulin</i>	4.3%
<i>Multiple</i>	53.3%
Other Medication	
<i>Antihypertensive</i>	65.2%
<i>Anticoagulant</i>	2.2%
<i>Antiplatelet</i>	23.9%
<i>Statins</i>	69.6%
<i>Anti-COPD</i>	19.6%
Previous Ulceration	12%
Previous Amputation	4.3%

8.2 Summary of the Primary Outcomes

8.2.1 Neuropathy.

The results from Chapter 6 show a significant difference in the numbers of people suspected of having neuropathy using the DPNCheck® (45), compared to using the 10g monofilament (21). The results show that there is sufficient evidence to reject the null hypothesis, and it will therefore be concluded that there is a significant difference in the number of people diagnosed with neuropathy. The DPNCheck® is more effective at the assessment of diabetes neuropathy; and the 10g monofilament will be deemed to lack adequate validity to the assessment of diabetes foot neuropathy. The null hypothesis is rejected, and the alternative hypothesis is adopted.

8.2.2 Ischaemia.

The results from Chapter 7 show no significant difference in the numbers of people diagnosed with ischaemia using the Medicap (10), and those diagnosed based on the TBI (10). The null hypothesis is therefore accepted. Of interest is the finding that the Medicap and the TBI did not agree on any diagnosed cases of ischaemia, indicating further differences in micro and macro ischaemia.

8.3 Exploratory Analyses

8.3.1 Distribution of data

All data was analysed by the Kolmogorov-Smirnov Test, with normality assumed if $p > 0.05$. Only the Medicap data ($TcPO_2$) conformed to a gaussian distribution. After \log_{10} transformation, TBI data also became normally distributed. All other outcome measures (10g monofilament, nerve conduction velocity and amplitude) had skewed data. With most variables maintaining skewed distributions, therefore non-parametric approaches to data analysis were employed.

8.3.2 Exploratory Correlations:

As potential confounders, it was important to explore the effects of ankle circumference, foot temperature and age on the main outcome measures, beginning with summary correlations from amongst the main outcome measures themselves:

a) Summary correlations.

Table 8.3.1: Showing a summary of correlations between the main outcome measures

	Neuropathy			Ischaemia
	10g monofilament vs DPNCheck® velocity	10g monofilament vs DPNCheck® Amplitude	DPNCheck® velocity vs DPNCheck® amplitude	
Spearman σ	0.48	0.53	0.69	0.07
Significance	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p = 0.49$

b) The effect of age on the main outcome measures

Table 8.3.2: The effects of age on the main outcome measures

	Effects of age on				
	Neuropathy			Ischaemia	
	10g monofilament	DPNCheck® velocity	DPNCheck® amplitude	TBI	Medicap (TcPO ₂)
Spearman σ	- 0.09	- 0.17	- 0.21	- 0.4	- 0.2
Significance	$p = 0.41$	$p = 0.1$	$p = 0.046$	$p < 0.001$	$p = 0.06$

The results in Table 8.3.2 show that age had no significant effect on 10g monofilament, DPNCheck® velocity or TcPO₂. However it did have a significant, albeit borderline, effect on DPNCheck® amplitude ($\sigma = -0.21$, $p < 0.05$), possibly due to idiopathic age dependant decline in nerve fibre density. Age also had a significant negative effect on TBI ($\sigma = -0.4$, $p < 0.001$), possibly due to reduction in ankle size, and increased frequency of anti-hypertensive medication with age.

c) *The effect of diabetes duration on neuropathy and ischaemia*

Table 8.3.3: The effects of diabetes duration on the main outcome measures

	Effects of diabetes duration on				
	Neuropathy			Ischaemia	
	10g monofilament	DPNCheck® velocity	DPNCheck® amplitude	TBI	Medicap (TcPO ₂)
Spearman σ	- 0.33	- 0.35	- 0.3	- 0.07	-0.33
Significance	<i>p</i> = 0.001	<i>p</i> = 0.001	<i>p</i> = 0.004	<i>p</i> = 0.5	<i>p</i> = 0.001

Longer diabetes duration was associated with reduced 10g monofilament, DPNCheck® and Medicap scores as shown in Table 8.3.3 .

d) *The effect of HbA1c on neuropathy and ischaemia*

Table 8.3.4: The effects of HbA1c on the main outcome measures

	Effects of HbA1c on				
	Neuropathy			Ischaemia	
	10g monofilament	DPNCheck® velocity	DPNCheck® amplitude	TBI	Medicap (TcPO ₂)
Spearman σ	- 0.3	- 0.26	- 0.25	σ = 0.06	σ = -0.01
Significance	<i>p</i> = 0.004	<i>p</i> = 0.012	<i>p</i> = 0.015	<i>p</i> < 0.57	<i>p</i> = 0.9

Higher HbA1c was associated with reduced 10g monofilament and DPNCheck® scores as shown in Table 8.3.4.

e) *The effect of ankle circumference on the main outcome measures*

Table 8.3.5: The effects of ankle circumference on the main outcome measures

	Effects of ankle circumference on				
	Neuropathy			Ischaemia	
	10g monofilament	DPNCheck® velocity	DPNCheck® amplitude	TBI	Medicap (TcPO ₂)
Spearman σ	- 0.14	- 0.1	- 0.11	σ = - 0.4	σ = -0.2
Significance	<i>p</i> = 0.19	<i>p</i> = 0.37	<i>p</i> = 0.29	<i>p</i> = 0.02	<i>p</i> = 0.06

Ankle circumference had no significant associations with nerve conduction , 10g monofilament scores, or $TcPO_2$. It was however associated with reduced TBI. This could be explained by the ankle size being affected by fluid volume around the ankle, which in turn increases would constrict the digital arteries , and increase the foot temperature (Table 8.3.6).

f) The effect of foot temperature on main outcome measures.

Table 8.3.6: The effects of Foot Temperature on main outcome measures

	Effects of Foot Temperature on				
	Neuropathy			Ischaemia	
	10g monofilament	DPNCheck® velocity	DPNCheck® amplitude	TBI	Medicap (TcPO ₂)
Spearman σ	$\sigma = -0.11$	$\sigma = -0.11$	$\sigma = -0.1$	$\sigma = 0.36$	$\sigma = -0.09$
Significance	$p = 0.29$	$p = 0.28$	$p = 0.33$	$p < 0.001$	$p = 0.41$

The results in Table 8.3.6 show that foot temperature had no significant effect on the neuropathy, or on $TcPO_2$. For neuropathy, the DPNCheck® operates at foot temperatures $\geq 23^\circ C$, below which it would indicate an error and shut down. Since participants had the neuroischaemic assessments simultaneously, and all gave DPNCheck® readings, this aspect of the DPNCheck® acted as a de facto temperature control. However, the foot temperature did have a significant effect on the TBI ($\sigma = 0.36$, $p < 0.001$). This could be accounted for by a combination of the TBI being affected by the blood volume around the foot. Increased blood volume tends to increase ankle size (Table 8.3.5), the TBI and foot temperature (Table 8.3.6). In contrast, the Medicap probe heats the skin to a set temperature at the localised site, and achieves stable localised temperature control across all participants, and is relatively unaffected by ankle size and ambient foot temperature.

8.3.3 Exploratory Group comparisons

These were carried out to determine whether there were significant differences in outcomes based on gender or study site.

a) *Gender*

Table 8.3.7: Showing the effects of gender on the main outcome measures

	NEUROPATHY TESTS median (IQR)			ISCHAEMIA TESTS median (IQR)	
	DPNCheck®		10g monofilament	TBI	TcPO ₂
	Velocity	Amplitude			
Male (n=58)	48 (35 - 53)	7 (3-10)	10 (7-10)	0.95 (0.86-1.1)	67.2 (56.8 – 80.1)
Female (n=34)	50 (45 - 54)	5 (3-8)	10 (9-10)	0.91 (0.8 – 1)	67.7 (60.3 – 81.2)

Mann-Whitney U test

1.1 (p=0.29)	-0.56 (p=0.58)	0.89 (p=0.37)	1.01 (p=0.32)	-0.5 (p=0.61)
No significant differences in neuropathy between males and females			No significant difference in ischaemia between males and females	

Gender had no significant effects on the main outcome measures.

b) *Test site*

Table 8.3.8: Showing the effects of study site on the main outcome measures

	NEUROPATHY TESTS Median (IQR)			ISCHAEMIA TESTS Median (IQR)	
	DPNCheck®		10g monofilament	TBI	TcPO ₂
	Velocity	Amplitude			
Southampton n= 56	50 (37 - 54)	6 (3 - 10)	10 (8-10)	0.96 (0.97-1.1)	74.6 (61.7 - 88)
Manchester n=36	46 (38 - 53)	5 (3 -9)	10 (9-10)	0.9 (0.8-1)	61.2 (56.1 -69.8)

Mann-Whitney U test

-0.69 (p=0.49)	-0.12 (p=0.9)	0.28 (p=0.78)	-1.22 (p = 0.22)	-2.97 (p = 0.003)*
No significant differences in neuropathy between Southampton and Manchester			No significant differences in TBI, but *significant differences in TcPO₂ between Southampton and Manchester	

There were no significant differences in the neuropathy status, or the TBI between

Southampton and Manchester. However, there was a significant difference in TcPO₂ between participants from Southampton and Manchester (z score = -2.97; p=0.003), which is possible due to participants in Manchester having a longer duration of diabetes.

c) The effect of smoking on the main outcome measures

Table 8.3.9: Showing the effects of smoking on the main outcome measures

	NEUROPATHY TESTS Median (IQR)			ISCHAEMIA TESTS Median (IQR)	
	DPNCheck®		10g monofilament	TBI	TcPO ₂
	Velocity	Amplitude			
Never Smoked n = 53	47 (37 - 54)	4 (3 - 9)	10 (10-10)	0.9 (0.8-1)	69.6 (57.4 – 84.1)
Quit n = 24	51 (44 - 53)	8 (4 - 14)	10 (8-10)	0.9 (0.8 – 1.1)	63.4 (55.8 – 76.9)
Smoking n = 15	45 (0-52)	4 (0-7)	8 (5-10)	1 (0.9-1.2)	64.9 (61.8 – 74.6)

Kruskall-Wallis test for 3 groups

1.96 (p=0.38)	6 (p=0.05)*	7.16 (p=0.03)*	4.4 (p = 0.11)	8.62	p = 0.44
*Significant differences in neuropathy based on smoking status			No significant differences in ischaemia based on smoking status.		

10g monofilament. The Kruskal-Wallis test indicated there was a statistically significant difference in 10g monofilament scores between the groups based on smoking status, H(2) = 7.16, p= 0.03.

DPNCheck®. The Kruskal-Wallis test indicated there was no statistically significant difference in nerve conduction velocity, between the groups, H(2) = 1.96, p= 0.38; However there was a borderline, but statistically significant difference in nerve conduction amplitude between the groups, H(2) = 6, p= 0.05. This could be attributed to glycaemic control, with the Mann-Whitney U test indicating that participants currently smoking had significantly higher HbA1c (median = 78 mmol/mol) than those who had quit (median = 58 mmol/mol)

TBI: The Kruskal-Wallis test indicated there were no statistically significant differences between the groups, H(2) = 4.4, p= 0.11.

Medicap: The Kruskal-Wallis test indicated there were no statistically significant differences between the groups, H(2) = 1.62, p= 0.44.

Section 8.3 has looked at the potential effects of independent variables of ankle size, foot temperature, age, gender, study site, smoking status, diabetes duration and HbA1c on the main outcome measures. It has shown that gender had no significant effect any outcomes, but the other main outcome measures were significantly affected as summarised in Table 8.3.10.

Table 8.3.10: Showing the effect of independent variables on the main outcome measures

Variable	Significant effect on:
<i>ankle size</i>	TBI
<i>foot temperature</i>	TBI
<i>age</i>	TBI, DPNCheck® Amplitude
<i>gender</i>	none identified
<i>study site</i>	TcPO₂
<i>smoking status</i>	10g monofilament and nerve conduction amplitude
<i>diabetes duration</i>	TcPO₂, 10g monofilament, DPNCheck® Amplitude, DPNCheck® Velocity
<i>HbA1c</i>	10g monofilament, DPNCheck® Amplitude, DPNCheck® Velocity

These independent variables, will be considered alongside other known or potential confounders during regression modelling (Section 8.7)

8.4 Analysis of Secondary Outcomes

8.4.1 Risk Stratification.

The outcomes from the primary analysis (section 8.2) were used in the risk stratification of each participant, based on the combined neurological and ischaemic components as described in the Methods Chapter (Table 4.9.1, page 102). The risk stratification frequencies for each category, based on combined (nerve conduction + TcPO₂) compared to combined (10g monofilament + TBI)

Table 8.4.1: Showing the frequency counts for each category after risk stratification

		Risk Stratification according to DPNCheck® + Medicap			Total
		Low Risk	Increased Risk	High Risk	
Risk Stratification according to NG19	Low Risk	41	20	0	61
	Increased Risk	5	16	5	26
	High Risk	0	3	2	5
Total		46	39	7	92

$\kappa_{\text{weighted}} = 0.42$ (95% CI: 0.28 - 0.57, $p < 0.001$) showing moderate agreement between the two stratification systems.

8.4.1 The role of neuropathy in risk stratification.

From the risk stratification results in Table 8.4.1, emerged the role played by neuropathy in the identification of those “at risk”. It therefore became important to determine the ability of the DPNCheck® to detect those “at risk” on its own, when compared against the combined NICE NG19 recommended methods (10g monofilament + TBI). This follows the secondary objectives outlined in Chapter 4.10.2, and Table 4.10.2 (page 103), the results of which are shown in Table 8.4.2:

a) *DPNCheck® in identifying “at risk” participants on its own*

Table 8.4.2: Showing stratification according to DPNCheck® on its own against TBI+10g monofilament

Risk Stratification according to 10g monofilament + TBI	Risk Stratification according to DPNCheck® alone		Total
	Low Risk	“At Risk”	
Low Risk	46	25	71
“At Risk”	1	20	21
Total	47	45	92

This also showed $\kappa = 0.43$ ($p < 0.001$; 95% CI = 0.25-0.61) with moderate agreement between the two classification systems. The DPNCheck® on its own, identified 45 ‘at risk’ participants, whilst the combined (10g monofilament + TBI) identified 21 ‘at risk’ participants. Therefore, nerve conduction impairment, on its own, was more effective than NICE NG19 recommended methods, at identifying people “at risk”.

b) *DPNCheck® in further assessment of NICE NG19 “low risk” participants.*

For the early identification of neuropathy at assessment, it is of greater clinical importance to investigate the “low risk” group of participants, as this is the group that at some point will transition to become “at risk”. According to Table 8.4.1, NICE NG19

criteria classified 61 participants as 'low risk', but as the 10g monofilament has low sensitivity and high false negative rates at neuropathy assessment (Wang *et al.*, 2017) it was likely that some 'at risk' participants were 'hidden' amongst these. Given the prominent role of neuropathy assessment in risk stratification, and with the DPNCheck® being more effective at the assessment of neuropathy, the DPNCheck® values were used to investigate potential crossover thresholds between from amongst the 61 NICE NG19 'low risk' participants.

It was possible to be guided by interquartile ranges (IQR) of either the conduction velocity or amplitude in subdivision of this 'low risk' category. The IQR for velocity was selected as it showed a broader range (0 – 51 m/s) and the drop in velocity was greater between low-increased risk (51 m/s down to 37.5 m/s; (Figure 8.4.2), in contrast to the relatively narrower range shown by the amplitude (8 – 3 μ V, Figure 8.4.1).

Figure 8.4.1: Showing decreasing conduction amplitude from Low Risk to Increased risk

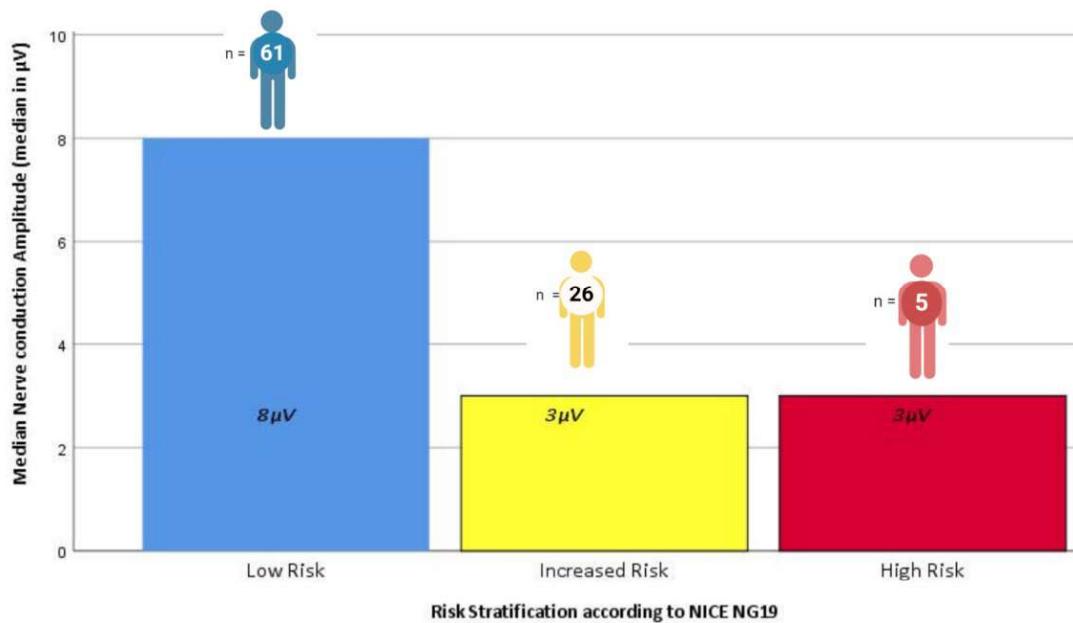
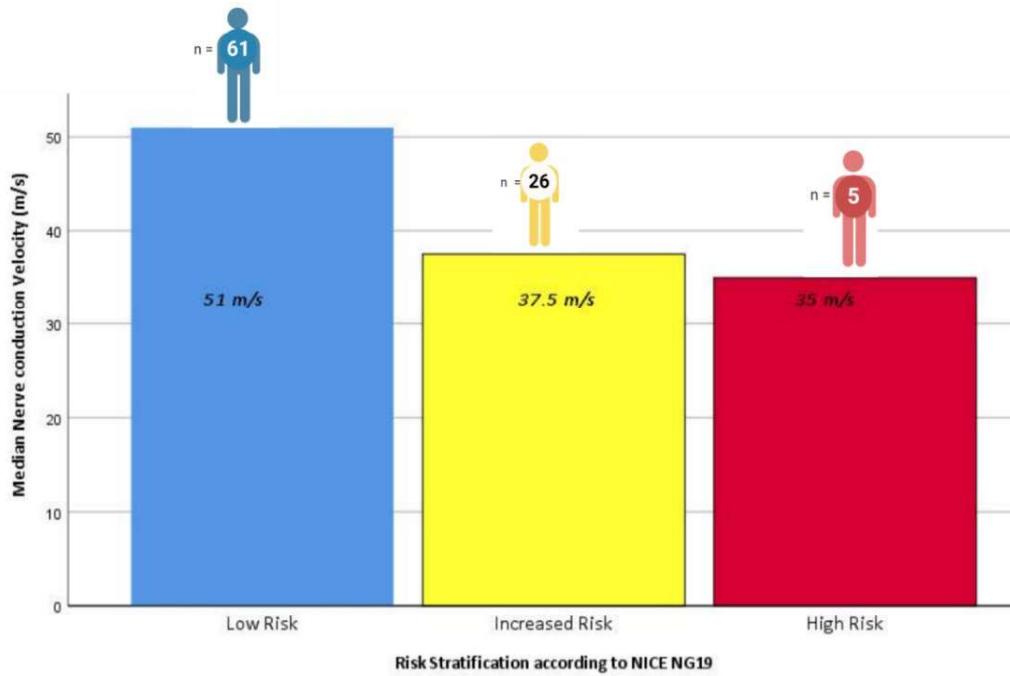


Figure 8.4.2: Showing decreasing conduction velocity with increasing risk status



From the NICE NG19 stratification, there is a significant drop in conduction velocity between groups from 51m/s (low risk) to 37.5m/s (increased risk) which then remains stable at 35 m/s (high risk)(Figure 8.4.2). This is further evidence that a threshold exists through which 'low risk' participants transition to become 'at risk', but a threshold which current NICE NG19 approaches are not sensitive enough to detect. The DPNCheck® could be used to investigate this "low risk"/ "at risk" threshold, having earlier demonstrated its discriminant ability to risk stratify on its own (Table 8.4.2). This was done on the 61 participants identified as "low risk" by the 10g monofilament + TBI, and led to further sub-classification as shown in Figure 8.4.3 :

Figure 8.4.3: Showing sub-analysis of NICE NG19 'low risk' participants by the DPNCheck®

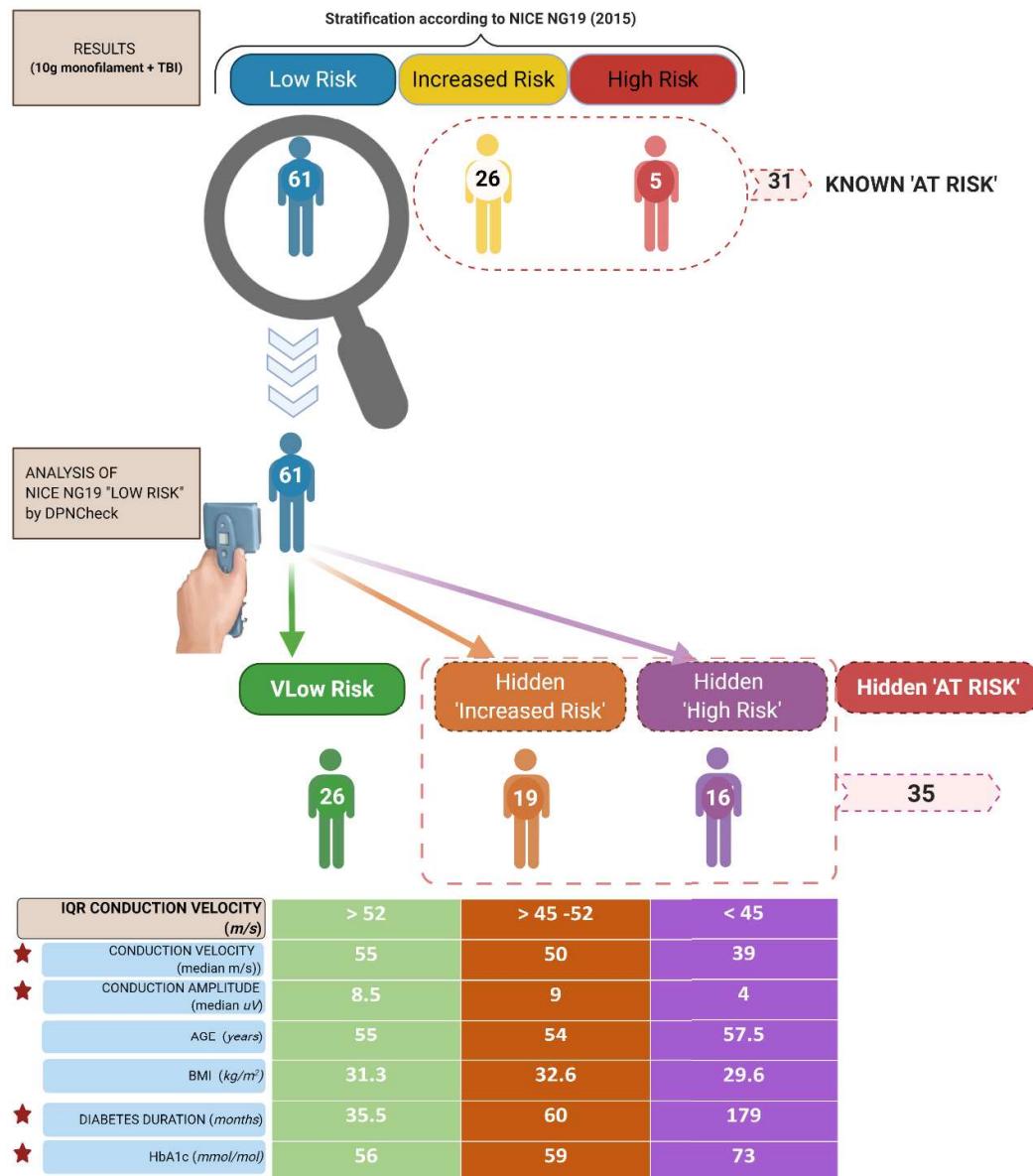


Image: Author's own. Created with Biorender.com

The results suggest a potential 'low risk' – 'at risk' threshold of 52 m/s for velocity.

Analysis of this very low risk (VLow risk) group with 26 participants gave median values for velocity = 55 (IQR 54 – 57) m/s; and for amplitude = 9 (IQR 6-14) μ V. The hidden 'at risk' group, with 35 participants, had median values for velocity = 46 (IQR 39 – 50) m/s, and for amplitude = 7 (IQR 4 – 12) μ V.

As shown in Figure 8.4.3, of the 61 participants determined as 'low risk' by NICE NG19 (2015), the DPNCheck® confirmed 26 as being very low risk (VLow Risk), and 35 as being 'at risk'. These groups also showed significant differences in neuropathy severity (indicated by conduction velocity [Figure 8.4.4]), diabetes duration (Figure 8.4.6) and HbA1c (Figure 8.4.7), with increasing risk status.

Figure 8.4.4. Showing decreasing conduction velocity with increasing risk status after DPNCheck® sub-analysis of 'low risk'

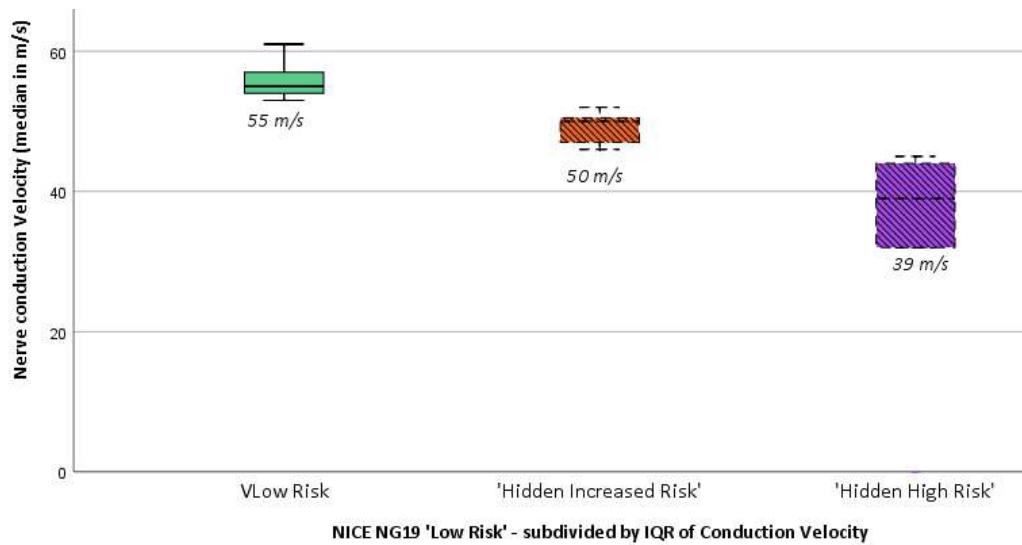
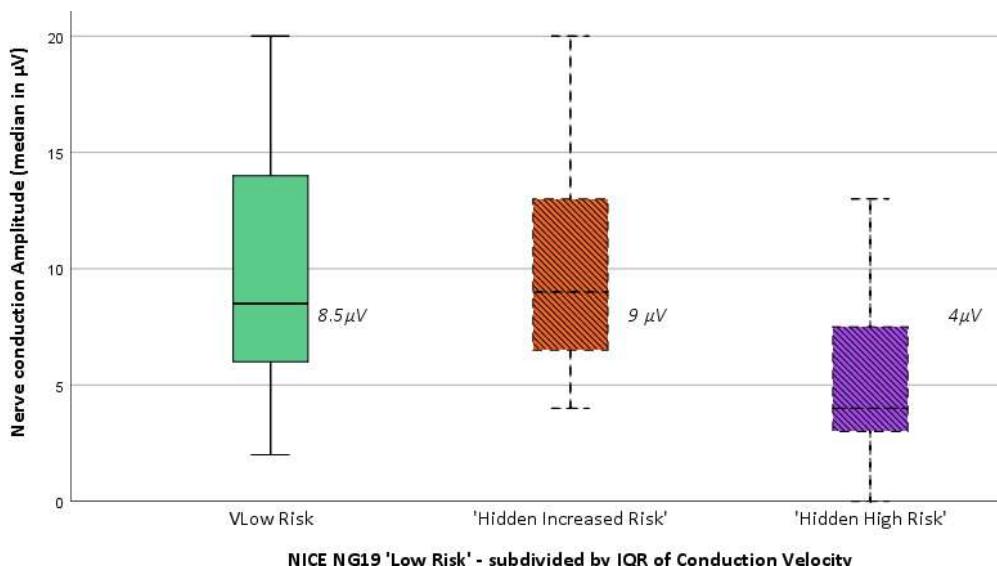


Figure 8.4.5. Showing change in conduction amplitude with risk status after DPNCheck® sub-analysis of 'low risk'



Conduction amplitude could distinguish between the 'hidden at risk' and other groups, but could not distinguish between VLow risk and hidden increased risk (Figure 8.4.5). There were no significant differences in age, gender, BMI or ischaemic status (T_cPO_2 or TBI) between the groups.

Figure 8.4.6: Showing longer diabetes duration with increasing risk status after DPNCheck® sub-analysis

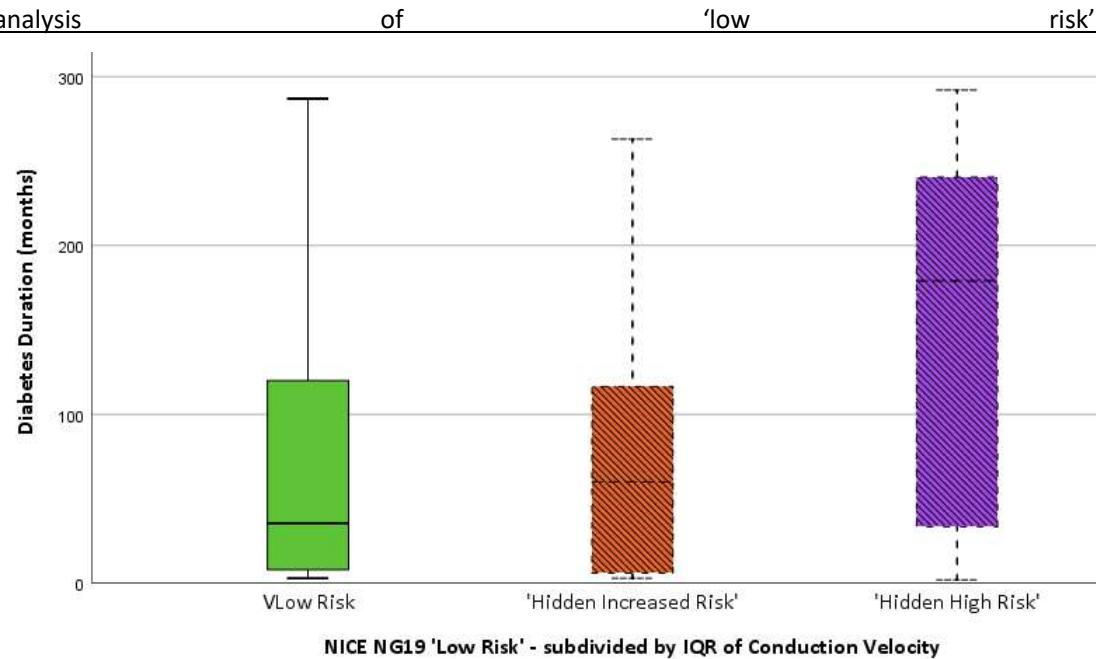
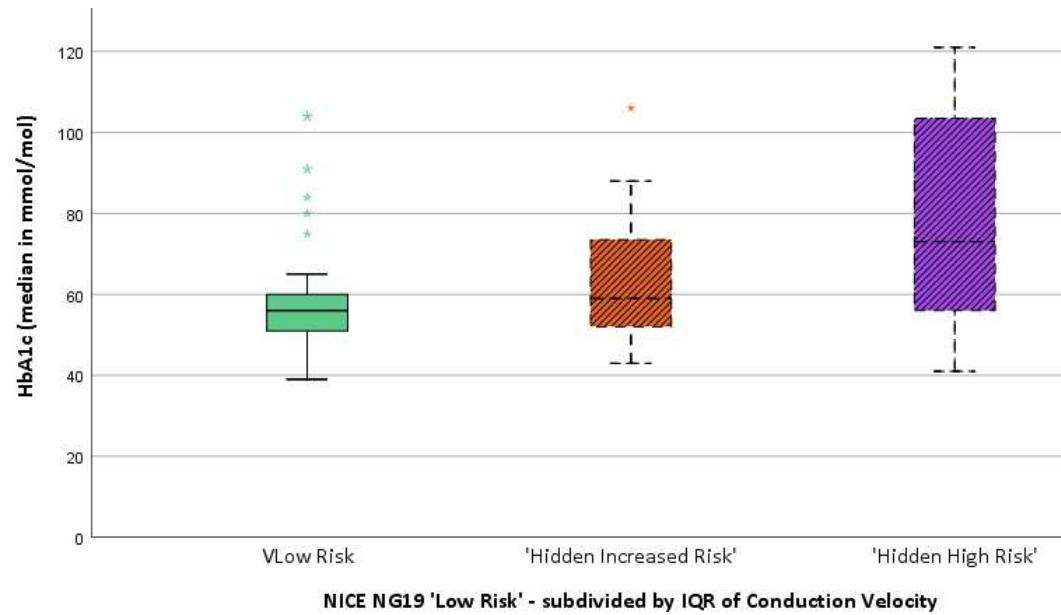


Figure 8.4.7: Showing higher HbA1c with increasing risk status after DPNCheck® sub-analysis of 'low risk'.



In summary, section 8.6.2 has shown that the DPNCheck® was more effective at

identifying those 'at risk' than the recommended NICE NG19 method. The DPNCheck®'s nerve conduction velocity showed a broader range between 'low risk' and 'at risk' groups than its amplitude. The IQR for velocity was therefore used to further stratify and identify potential crossover thresholds for the 61 'low risk' participants earlier identified by the NICE NG19 method. Using the suggested crossover 'at risk' nerve conduction thresholds of 52m/s, the DPNCheck® revealed 35 'at risk' participants (57%) which the NICE NG19 approach was unable to identify, as shown in Figure 8.4.3.

8.4.2 The role of ischaemia in risk stratification.

From the risk stratification results in Table 8.4.1, ischaemia appears to have a limited role during assessment and identification of those 'at risk'. It was however important to determine the ability of the Medicap to detect those "at risk" on its own, when compared against the combined NG19 recommended methods (10g monofilament + TBI). This follows the secondary objectives of Chapter 4.10.3 (page 104) and Table 4.10.3, with the results shown in Table 8.4.3.

Medicap in identifying "at risk" participants on its own

Table 8.4.3: Showing stratification according to Medicap on its own against TBI+10g monofilament

Risk Stratification according to Medicap alone	Risk Stratification according to 10g monofilament + TBI		Total
	Low Risk	"At Risk"	
Low Risk	64	18	82
At Risk	7	3	10
Total	71	21	92

$\kappa_{\text{weighted}} = 0.54$ ($p = 0.57$), indicated moderate agreement between the classification systems, but this did not reach statistical significance. The Medicap, on its own, identified 10 'at risk' participants, whilst the NICE NG19 recommended method (10g monofilament + TBI) identified 21 'at risk' participants. The Medicap on its own was not more effective than NICE NG19 recommended methods, at identifying people "at risk". This adds further support to the suggestion that the identification of 'at risk' participants during assessment largely depends on their neuropathic status. It was important to determine the potential effects of macro and micro-ischaemia, respectively, on neuropathy.

8.4.3 The effect of macroischaemia on neuropathy.

The potential effect of macroischaemia on neuropathy scores follows the objectives of Chapter 4.10.4 (page 104), and are shown in Table 8.4.4.

Table 8.4.4: Showing neuropathy scores based on TBI ischaemia stratification.

	No Ischaemia n=82	Mild n=8	Moderate n=0	Severe n=0	Calcified n=2
Nerve conduction					
Amplitude (μ V)	6 (0-37)	5 (3-8)	-none	none	3.5 (1-3)
Velocity (m/s)	48.5 (0-61)	48.5 (16-37)	-none	none	21.5 (0-43)
10g monofilament	10 (0-10)	10 (0-10)	-none	none	10 (10-10)

The Kruskal-Wallis test indicated there were no statistically significant differences between the groups, $H(2) = 1.84$, $p= 0.4$. Neither nerve conduction nor the 10g monofilament could distinguish between those with and without macroischaemia, or the extent of macroischaemia based on the TBI.

8.4.4 Can neuropathy scores be used to distinguish microischaemia severity?

Table 8.4.5: Showing neuropathy scores based on TcPO₂ ischaemia stratification.

	No Ischaemia n=82	Mild n=8	Moderate n=1	Severe n=1
Nerve conduction				
Amplitude (μ V)	6 (0-37)	7 (0-14)	4	3
Velocity (m/s)	48.5 (0-61)	42.5 (0-57)	53	48
10g monofilament	10 (0-10)	9.5 (4-10)	9	6

The Kruskal-Wallis test indicated there were no statistically significant differences between the groups, $H(3) = 4.52$, $p= 0.21$. Nerve conduction could not be used to distinguish between those with and without microischaemia, or the extent of microischaemia based on TcPO₂.

From the findings in sections 8.4.4 and 8.4.5 neither the DPNCheck® nor the 10g monofilament could be used to distinguish between participants based on ischaemia severity.

8.4.5 The neuropathy values for each category of NICE NG19 stratification

(Low- Increased-High Risk) are shown in Table 8.4.6:

Table 8.4.6: Showing neuropathy scores for NICE NG19 stratification.

	Low Risk (n=61)	Increased Risk (n=26)	High Risk (n=5)
Nerve Conduction (Median (IQR))			
Amplitude (μ V)	7 (0-37)	2 (0-61)	1 (0-3)
Velocity (m/s)	50 (0-61)	2 (0-34)	0 (0-48)
10g monofilament	10 (2-10)	6 (2-10)	4.5 (0-8)

The Kruskal-Wallis test for each neuropathy measure indicated there were statistically significant differences between the groups:

- For the 10g monofilament this showed $H(2) = 67.5$, $p < 0.001$.
- Analysis of nerve conduction amplitude showed $H(2) = 29.9$, $p < 0.001$
- Analysis of nerve conduction velocity showed $H(2) = 24.2$, $p < 0.001$.

8.4.6 Can ischaemia scores be used to distinguish between neuropathy severity.

It was also important to investigate the potential of macro and microischaemia to identify neuropathy groups. Following the objectives of Chapter 4.10.5 (page 104). The Medicap and TBI median values of those identified with nerve conduction impairment were compared and analysed for significance, and shown in Table 8.4.7.

Table 8.4.7: Showing ischaemia scores based on DPNCheck® neuropathy stratification.

	No Neuropathy n=48	Mild n=5	Moderate n=27	Severe n=12
Ischaemia scores (median (IQR))				
TBI	0.94 (0.71-1.24)	0.96 (0.8-1.5)	0.88 (0.6-1.4)	1 (0.77-1.31)
Medicap (mmHg)	65.3 (31.6-147)	54.7 (38.7-57.4)	75.8 (20.2-115)	67.9 (44.9-87.2)

- For the TBI, Kruskal-Wallis analysis showed $H(3) = 6.9$, $p= 0.08$, indicating no significant differences in macroischaemia between the groups.
- For the Medicap, Kruskal-Wallis analysis showed $H(3) = 10.2$, $p= 0.02$, which indicates statistically significant differences in micro ischaemia between the groups. Of particular interest is the change from 65.3 mmHg in those with no neuropathy, to 54.7 mmHg in participants with mild neuropathy. However this compares a much

larger asymptomatic sample (48 participants), against only 5 with mild neuropathy. When comparing $TcPO_2$ differences between those with no neuropathy ($n = 48$, $TcPO_2 = 64.9$ mmHg) against those with neuropathy ($n = 44$, $TcPO_2 = 6.8$ mmHg); Kruskal-Wallis analysis showed no significant differences between the groups $H(1) = 0.08$, $p = 0.78$.

These results contrast those by Eleftheriadou *et al.*, (2019), who found that participants with $TcPO_2$ had a negative and significant correlation to neuropathy severity (Spearman's $\rho = -0.36$, $p < 0.001$ (48 mmHg). However their neuropathy diagnosis was based on the NDS, whose individual components (ankle reflex, vibration perception, 10g monofilament, pin prick, temperature perception) rely on subjective responses, interpretation and vulnerable to operator variability. In addition, with peripheral ischaemia based on the ABI and colour arterial duplex, more of their participants had macroischaemia (42%) than the current study (10.8%). Therefore, the differences in neuropathy diagnosis and in the ischaemic status, makes the studies less comparable, and could explain the observed discrepancies. Findings from this thesis suggest that $TcPO_2$ could not distinguish between participants based on the severity of neuropathy.

8.5 Prediction model for neuropathy and ischaemia outcomes.

An attempt was made to construct prediction models through regression, in order to determine the extent to which the independent variables that showed significant relationships (diabetes duration, HbA1c, age, BMI), could be used to predict the dependant variables (10g monofilament score, DPNCheck® parameters, TBI, Medicap parameters).

8.5.1 Confounding

Potential confounders were identified from the literature search and from independent variables that were considered confounders within the forward selection procedure in multivariate regression modelling.

8.5.2 Collinearity

Collinearity occurs in the presence of highly correlated independent variables that are modelled together, which would increase the variance, and reduce our level of certainty, on the contribution made by any one factor to the outcome variable. Potential collinearity between age, diabetes duration, HbA1c and BMI, ankle circumference and foot temperature was initially suggested from their respective bivariate correlations, as shown in Table 8.5.1:

Table 8.5.1: Showing significant bivariate correlations

		Spearman σ Correlations					
		Age	BMI	Diabetes Duration	HbA1c	Foot Temp.	Ankle Circ.
Age	Correlation			0.25			
	Sig. (2-tailed)			p = 0.02			
BMI	Correlation					0.53	
	Sig. (2-tailed)					p < 0.001	
Diabetes Duration	Correlation	0.25			0.4	-0.25	
	Sig. (2-tailed)	p = 0.02		p < 0.001		p = 0.02	
HbA1c	Correlation			0.4			
	Sig. (2-tailed)			p < 0.001			
Foot Temperature	Correlation					0.26	
	Sig. (2-tailed)					p = 0.01	
Ankle Circumference	Correlation	0.53	-0.25		0.26		
	Sig. (2-tailed)	p < 0.001		p = 0.02		p = 0.01	

To explore these correlations further, the variance inflation factor (VIF), was calculated by auxiliary regression of age, BMI, diabetes duration, HbA1c, foot temperature and ankle circumference, with each taking a turn at being the dependent variable as shown in Table 8.5.2.

Table 8.5.2: Showing collinearity statistics after auxiliary linear regression

a) Dependant Variable = Age			b) Dependant Variable = BMI		
	Collinearity Statistics			Collinearity Statistics	
	Tolerance	VIF		Tolerance	VIF
BMI	0.735	1.360	Diabetes Duration	0.764	1.310
Diabetes Duration	0.835	1.198	HbA1c	0.831	1.203
HbA1c	0.863	1.158	Foot Temperature	0.920	1.086
Foot Temperature	0.921	1.086	Ankle Circumference	0.896	1.116
Ankle Circumference	0.671	1.490	Age	0.895	1.118

c) Dependant Variable = HbA1c			d) Dependant Variable = Diabetes Duration		
	Collinearity Statistics			Collinearity Statistics	
	Tolerance	VIF		Tolerance	VIF
Age	0.908	1.101	HbA1c	0.973	1.027
BMI	0.719	1.391	Foot Temperature	0.920	1.087
DM Duration	0.894	1.119	Ankle Circumference	0.696	1.437
Foot Temperature	0.928	1.077	Age	0.957	1.045
Ankle Circumference	0.676	1.478	BMI	0.720	1.390

e) Dependant Variable = Foot Temperature			f) Dependant Variable = Ankle size		
	Collinearity Statistics			Collinearity Statistics	
	Tolerance	VIF		Tolerance	VIF
Ankle Circumference	0.706	1.416	Age	0.873	1.145
Age	0.874	1.144	BMI	0.959	1.043
BMI	0.718	1.393	DM Duration	0.790	1.266
Diabetes Duration	0.762	1.313	HbA1c	0.837	1.195
HbA1c	0.837	1.195	Foot Temperature	0.968	1.033

Table 8.5.2 shows that the VIF was relatively low, with all $VIF < 1.5$, and suggests that even though they may have some correlations, these factors can be modelled together.

8.5.3 **Neuropathy**

a) Prediction model for 10g monofilament score

i. Significant correlations.

The 10g monofilament had significant correlations with diabetes duration (Spearman $\sigma = -0.33$, $p < 0.001$) and HbA1c (Spearman $\sigma = -0.3$, $p < 0.004$).

ii. Univariate analysis of diabetes duration and 10g monofilament score

Longer diabetes duration predicted lower 10g monofilament neuropathy scores ($\beta = -0.008$, 95% CI = -0.01 - -0.003; $p = 0.003$). R-squared value was 0.092, indicating that diabetes duration explained 9.2% of the variability in 10 g monofilament score.

iii. Univariate analysis of HbA1c and 10g monofilament score

Higher HbA1c values predicted lower 10g monofilament neuropathy scores ($\beta = -0.03$, 95% CI = -0.05 - -0.009; $p = 0.007$). R-squared value was 0.077, indicating that HbA1c explained 7.7% of the variability in 10 g monofilament score.

iv. Univariate analysis of age on 10g monofilament score

Age had no significant effect on 10g monofilament score ($\beta = -0.42$, 95% CI = -0.1 - -0.02; $p = 0.18$)

v. Univariate analysis of gender on 10g monofilament score

Gender had no significant effect on 10g monofilament score ($\beta = 0.63$, 95% CI = -0.4 – 1.7; $p = 0.25$)

vi. Univariate analysis of smoking status on 10g monofilament score

Smoking status had no significant effect on 10g monofilament score, ($\beta = -0.38$, 95% CI = -0.98 – 0.22; $p = 0.21$)

vii. Univariate analysis of BMI on 10g monofilament score

BMI had no significant effect on 10g monofilament score ($\beta = -0.03$, 95% CI = -0.11 – 0.05; $p = 0.48$)

viii. Multivariate analysis on the effect of diabetes duration and HbA1c on 10g monofilament score

Multivariate regression with block selection was conducted to assess the effect of diabetes duration and HbA1c on 10g monofilament scores [block 1], in the presence of known confounders [block 2](age, gender, BMI, smoking status). Within [block 2] for the confounders, an additional forward selection process removed age, gender, BMI, and smoking status as they showed no significant effect on outcome with β -coefficient changing less than 10%. Fully adjusted linear regression showed that; after adjusting for confounders and including HbA1c, diabetes duration predicted a lower (worsening neuropathy) 10g monofilament score (β -0.006, 95% CI = -0.012 - -0.01; p = 0.03). HbA1c had no significant contribution to determining 10g monofilament score (β = -0.022, 95% CI -0.05- 0.002; p = 0.07)

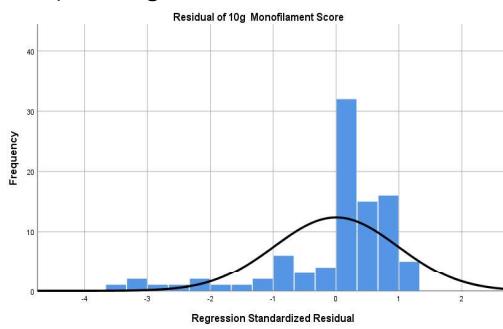
The adjusted R-squared value for the overall model was 0.106, showing that this model could account for 10.6% of 10g monofilament variability.

ix. Regression diagnostics – distribution of residuals

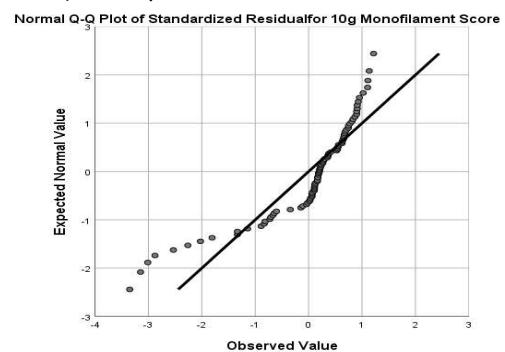
Assumptions underlying the linear regression model were visually checked through the residual distribution (histogram and QQ plot) and variance (scatterplot) as shown in Figure 8.5.1.

Figure 8.5.1: Showing residual distribution and variance for the 10g monofilament

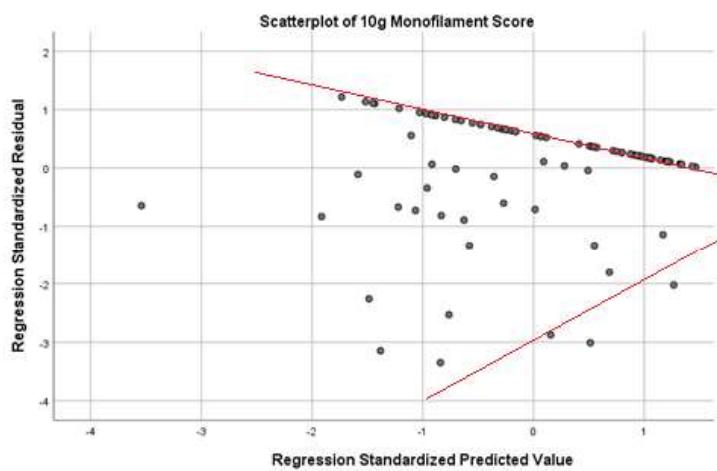
a) Histogram



b) Q-Q plot



c) Scatterplot showing variance of 10g monofilament residuals



The histogram, Figure 8.5.1(a), and Q-Q plot, Figure 8.5.1 (b) suggest skewed residual distribution. This could be expected as 10g monofilament data does not follow a Gaussian distribution, even after data transformation. Given its subjective nature, 10g monofilament scores do not gradually decrease in a uniform manner with progression of neuropathy, as loss of dermatomes can lead to large changes in the scoring, giving rise to skewed data observations. Variance of residuals was assessed using a scatter plot, Figure 8.5.1 (c), which confirmed the presence of heteroscedasticity (variance of the residuals was not constant) with clear funnelling towards the x-axis regression line at higher values. Prediction of neuropathy therefore becomes more consistent the longer the duration of diabetes. In summary, the residuals contain structure not fully explained by this model, and the model itself departs from the assumptions underpinning linear regression, and therefore this 10g monofilament regression model is unsuitable in the prediction of neuropathy.

b) Prediction model for the DPNCheck®

i. Centering of nerve conduction scores

The nerve conduction prediction model presented a challenge because the outcome relies on two dependant variables (nerve conduction velocity and nerve conduction amplitude) that were strongly correlated (Spearman $\sigma = 0.69$, $p < 0.001$), which together give an indication of neuropathy severity. To conduct correlation analysis, there were three options:

- to select and analyse only one of the variables; or
- to analyse both variables separately, or
- to combine the variables through centering with linear weighting.

Before analysing only one variable or each variable separately, consideration was given to the clinical implications of doing this. Since neither nerve conduction velocity nor amplitude in isolation fully capture neuropathy parameters, analysing either one, or both in isolated prediction models could lead to an incomplete picture of variance and risks giving misleading conclusions.

The clinical implications therefore guided the decision to combine the two correlated dependant variables for joint analysis, and to incorporate linear weighting to account for neuropathy severity, and derive a composite score. To represent neuropathy as a concept by combining its velocity and amplitude components required “operationalism” as a statistical approach suggested by Campbell and Fiske (1959). This was achieved through centering the dependant variables (velocity and amplitude) using the respective velocity and amplitude medians in a stepwise procedure as follows:

- Centering the nerve conduction velocity by subtracting the velocity median
- Centering the nerve conduction amplitude by subtracting the amplitude median
- Combining the centred scores by adding the centred median velocity to the centred median amplitude for each participant
- Calculating the mean for the combined centred scores for each participant
- Applying linear weighting to account for neuropathy severity, with healthy scores indicated by higher weighing. This was achieved on a 3, 2, 1, 1, scale where the calculated mean for each participant was multiplied by the weighting factor as shown in Table 8.5.3:

Table 8.5.3 Showing weighting factors used in centering of DPNCheck® velocity and amplitude

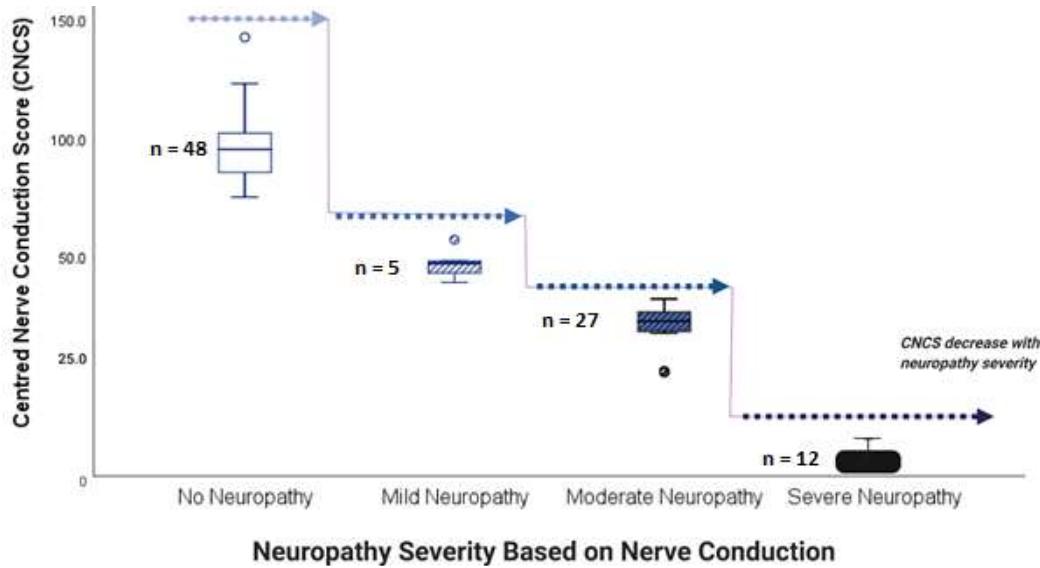
Neuropathy Severity	Weighting factor	Centred Nerve Conduction Score (CNCS)
No Neuropathy	3	<i>Centred Mean x 3</i>
Mild Neuropathy	2	<i>Centred Mean x 2</i>
Moderate Neuropathy	1	<i>Centred Mean x 1</i>
Severe Neuropathy	1	<i>Centred Mean x 1</i>

After weighting the combined nerve velocity and amplitude, this gave rise to the centred nerve conduction score (CNCS). Analysis of how this derived CNCS score reflects across the neuropathy risk categories is shown in Figure 8.5.2.

ii. Effectiveness of centering to derive the Centred Nerve Conduction Score (CNCS): to assess the quality of the operationalism approach

The centering procedure carried out added the two correlated dependant variables (velocity and amplitude), and applied weighting to the mean, to derive the CNCS. The CNCS carries the attributes of the original conduction velocity and amplitude without loss of neuropathy information. This is confirmed by analysing the CNCS spread across the neuropathy categories from the 92 participants in this study (Figure 8.10), and the strength and significance of CNCS correlations with other variables including the velocity and amplitude from which it is derived (Table 8.25). The centering procedure was therefore effective.

Figure 8.5.2: Bloxplot showing CNCS score across the DPNCheck® neuropathy stratification



iii. Significant correlations. Further assessment of the quality of the operationalism approach

The DPNCheck® conduction and amplitude had significant correlations with diabetes duration, HbA1c and age as shown in Table 8.25 . After centering, the CNCS also shows similar correlations with diabetes duration (Spearman $\sigma = -0.32$, $p = 0.002$), HbA1c (Spearman $\sigma = -0.28$, $p = 0.006$) and age (Spearman $\sigma = -0.22$, $p = 0.035$), and strong correlations with velocity (Spearman $\sigma = 0.85$, $p < 0.001$) and amplitude (Spearman $\sigma = 0.94$, $p < 0.001$), indicating that the centering process maintained the integrity of the DPNCheck® scores.

Table 8.5.4: Showing significant correlations with DPNCheck® parameters

		DPNCheck® velocity	DPNCheck® amplitude	CNCS (from combined Velocity + Amplitude)
Diabetes Duration	Spearman σ	-0.35	-0.3	-0.32
	Significance	$p = 0.001$	$p = 0.004$	$p = 0.002$
HbA1c	Spearman σ	-0.26	-0.25	-0.28
	Significance	$p = 0.012$	$p = 0.015$	$p = 0.006$
Age	Spearman σ		-0.21	-0.22
	Significance		$p = 0.046$	$p = 0.035$
CNCS	Spearman σ	0.85	0.94	
	Significance	$p < 0.001$	$p < 0.001$	

iv. Univariate analysis of diabetes duration and CNCS

Longer diabetes duration predicted more severe neuropathy, with lower CNCS ($\beta = -0.16$, 95% CI = -0.24 - -0.07; $p < 0.001$). R-squared value was 0.127, indicating that diabetes duration explained 12.7% of the variability in nerve conduction score.

v. Univariate analysis of HbA1c and CNCS

Higher HbA1c predicted more severe neuropathy, with lower CNCS ($\beta = -0.57$, 95% CI = -0.94 - -0.2; $p = 0.003$). R-squared value was 0.094, indicating that HbA1c explained 9.4% of the variability in nerve conduction score.

vi. Univariate analysis of age on CNCS

Increasing age was predictive of more severe neuropathy, with lower CNCS ($\beta = -1.17$, 95% CI = -2.17 - -0.17; $p = 0.022$). R-squared value was 0.057, indicating that age explained 5.7% of the variability in nerve conduction score.

vii. Univariate analysis of gender on CNCS

Gender had no significant effect on CNCS ($\beta = 0.33$, 95% CI = -17.6 – 18.3; $p = 0.97$).

viii. Univariate analysis of smoking status on CNCS

Smoking status had no significant effect on CNCS ($\beta = 6.2$, 95% CI = -3.8 – 16.2; $p = 0.22$).

ix. Univariate analysis of BMI on CNCS

BMI had no significant effect on CNCS ($\beta = -0.68$, 95% CI = -2.04 – 0.68; $p = 0.32$).

x. Multivariate analysis on the effect of diabetes duration, HbA1c and age on CNCS

Multivariate regression with block selection was conducted to assess the effect of diabetes duration, HbA1c and age on CNCS [block 1], in the presence of known confounders [block 2](gender, BMI, smoking status). Within [block 2] for the confounders, an additional forward selection process removed gender, BMI, and smoking status as they showed no significant contribution to the model, with β -coefficient changing less than 10%. Fully adjusted linear regression showed that, after adjusting for confounders HbA1c, diabetes

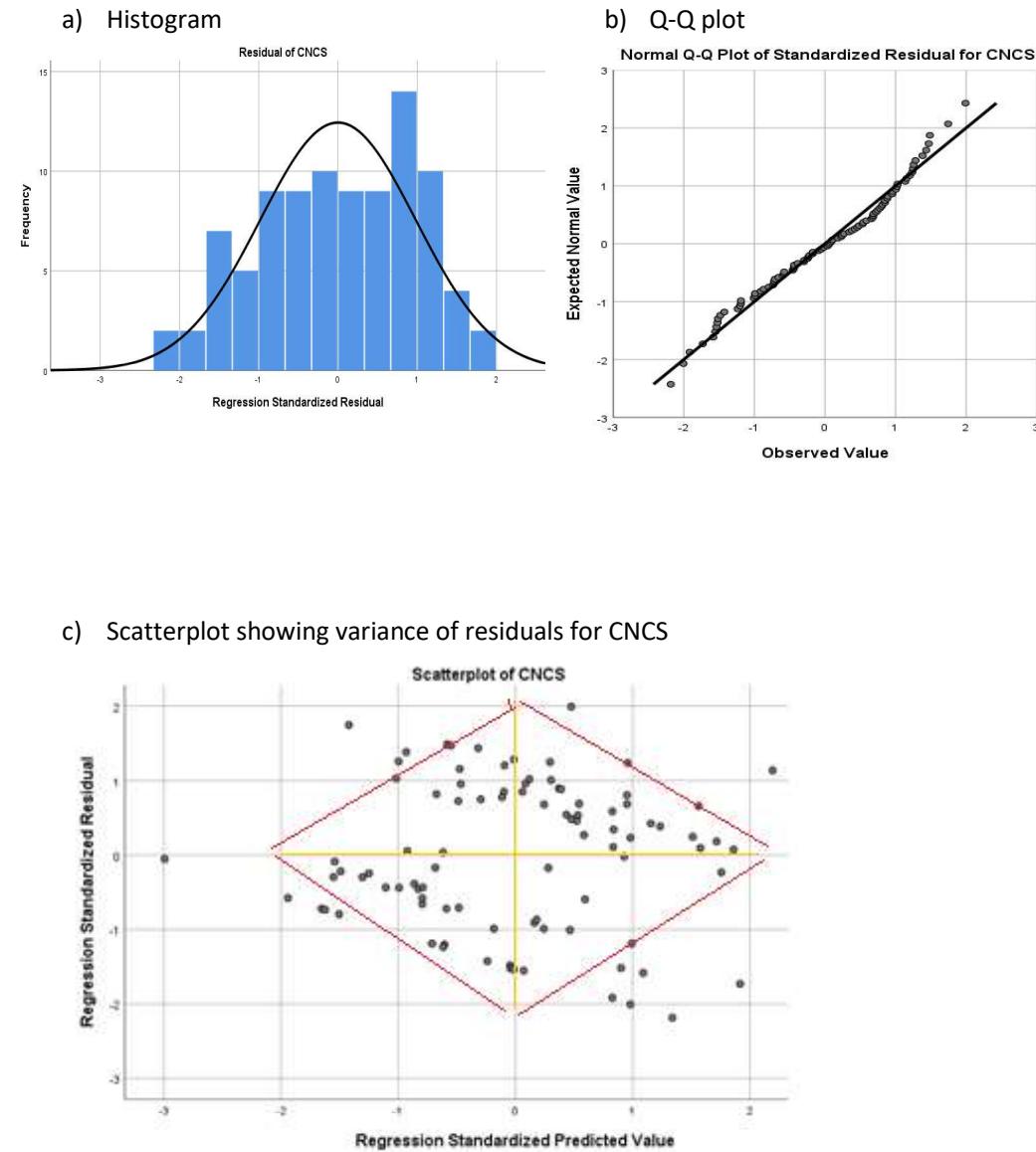
duration and age predicted a lower (worsening neuropathy) CNCS, with $\beta_{\text{Age}} = -1.03$; $\beta_{\text{DiabetesDuration}} = -0.09$; $\beta_{\text{HbA1c}} = -0.47$.

The adjusted R-squared value for the overall model was 0.177, showing that this model could account for 17.7% of nerve conduction variability.

xi. Regression diagnostics – distribution of residuals

Assumptions underlying the linear regression model were checked through the residual distribution (histogram and QQ plot) and variance (scatterplot) as shown in Figure 8.5.3.

Figure 8.5.3: Showing residual distribution and variance for CNCS



The histogram (Figure 8.5.3 (a)) and Q-Q plot (Figure 8.5.3(b)) show that the residuals plots follow a Gaussian distribution. The variance of residuals as seen on the scatter plot (Figure 8.5.3 (c)) further confirmed the presence of homoscedasticity (variance of the residuals was constant) with an approximately even distribution about both the y- and x-axes regression lines, suggesting prediction is therefore consistent throughout the model. The residuals contain structure that is largely explained, thereby supporting the use of the CNCS regression model in the prediction of neuropathy.

8.5.4 Comparison of neuropathy prediction models

Overall, the CNCS, (i.e. nerve conduction) model is a more effective prediction model for neuropathy based on clinical and statistical grounds. The main aim of assessment is to detect risk of neuropathy at an early stage and if this is to be part of an algorithm to predict neuropathy risk, then it needs one that does so consistently. This therefore suits the CNCS model as it maintains its predictive consistency throughout, in contrast to the 10g monofilament model that becomes more consistent only with longer diabetes duration, and therefore less suitable for an early detection model.

8.5.5 Ischaemia

a) Prediction model for the TBI

i. *Significant correlations.*

The TBI had significant correlations with age (Spearman $\sigma = -0.4$, $p < 0.001$), foot temperature (Spearman $\sigma = 0.36$, $p < 0.001$) and ankle size (Spearman $\sigma = 0.24$, $p = 0.02$)

ii. *Univariate analysis of ankle size and TBI*

Bigger ankle size predicted higher TBI ($\beta = 0.015$, 95% CI = 0.001 - 0.029; $p = 0.031$). R-squared value was 0.051, indicating that ankle size explained 5.1% of the variability in TB

iii. Univariate analysis of foot temperature and TBI

Higher temperatures predicted higher TBI ($\beta = 0.018$, 95% CI = 0.004 - 0.033; $p = 0.013$). R-squared value was 0.067, indicating that foot temperature explained 6.7 % of the variability in TBI

iv. Univariate analysis of age and TBI

Increasing age predicted lower TBI ($\beta = -0.007$, 95% CI = -0.01 - 0.003; $p < 0.001$). R-squared value was 0.13, indicating that age explained 13 % of the variability in TBI

v. Univariate analysis of study site and TBI

Whether the TBI was assessed in Manchester or Southampton, had no significant effect on the TBI ($\beta = -0.027$, 95% CI = -0.097 – 0.04; $p = 0.45$)

vi. Univariate analysis of gender on TBI

Gender had no significant effect on the TBI ($\beta = -0.036$, 95% CI = -0.11 – 0.035; $p = 0.32$).

vii. Univariate analysis of smoking status on TBI

Smoking status had no significant effect on the TBI ($\beta = 0.016$, 95% CI = -0.02 – 0.06; $p = 0.42$)

viii. Univariate analysis of diabetes duration on TBI

Diabetes duration had no significant effect on the TBI ($\beta = 0.000$, 95% CI = 0.00 – 0.00; $p = 0.51$)

ix. Univariate analysis of HbA1c on TBI

HbA1c had no significant effect on the TBI ($\beta = 0.001$, 95% CI = -0.001 – 0.002; $p = 0.31$)

x. Univariate analysis of BMI on TBI

Higher BMI predicted lower TBI ($\beta = -0.006$, 95% CI = 0.001 - 0.011; $p = 0.03$). R-squared value was 0.051, indicating that BMI explained 5.1 % of the variability in TBI

xi. Multivariate analysis on the effect of ankle size, foot temperature and age on TBI

Multivariate regression with block selection was conducted to assess the effect of ankle size, and foot temperature [block 1], in the presence of potential confounders variables [block 2] (gender, study site, smoking status, BMI, diabetes duration, HbA1c). Within both [block1] and [block 2], an additional forward selection process was used to analyse and if necessary remove any dependant variable that showed no significant effect (less than 10% in the β -coefficient).

Fully adjusted linear regression showed that after adjusting for confounders, Increasing age predicted a lower TBI , hence increased vulnerability to ischaemia ($\beta = -0.007$, 95% CI = -0.01 - -0.003; $p < 0.001$).

Higher foot temperature predicted a higher TBI score ($\beta = 0.017$, 95% CI = 0.003-0.031; $p = 0.02$)

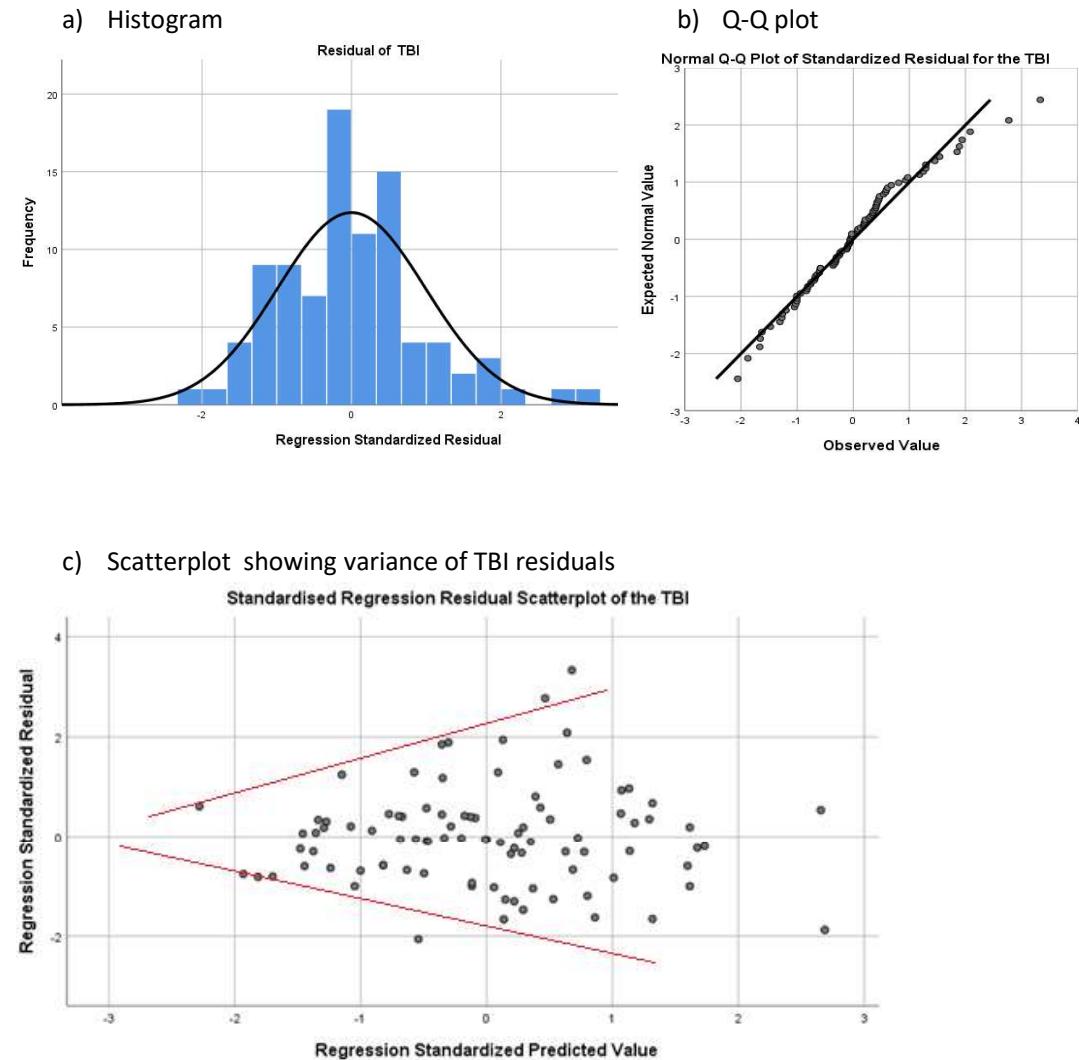
The ability for ankle size to predict the TBI did not reach statistical significance ($\beta = 0.009$, 95% CI = -0.004- 0.022; $p = 0.18$)

The adjusted R-squared value for the overall model after removal of non-significant factors, was 0.194, showing that this model could account for 19.4% of TBI variability. For comparison, an alternative regression procedure forced the model to include all the factors (age, foot temperature, ankle size, diabetes duration, HbA1c, study site, gender, smoking status) regardless of significance of contribution; and this gave an adjusted R-squared value of 18.5%.

Therefore, the selected model for TBI prediction is the one that uses age and foot temperature as predictors of TBI.

xii. Regression diagnostics – distribution of residuals for the TBI regression model

Figure 8.5.4: Showing residual distribution and variance for the TBI



The histogram (Figure 8.5.4 (a)) and Q-Q plot (Figure 8.5.4 (b)) show that the residuals plots follow a Gaussian distribution. However, variance of residuals was assessed using a scatter plot (Figure 8.5.4 (c)) which confirmed the presence of heteroscedasticity (variance of the residuals was not constant) with clear funnelling towards the x-axis regression line at lower values. This suggests that prediction of ischaemia based on the TBI in people with diabetes is therefore more consistent the younger the age, and the lower the foot temperature, of the participant.

In the clinical context, this presents a challenge when building a TBI prediction model for macroschaemia based on age and foot temperature, as the effects of increasing age, and longer duration of diabetes makes prediction less reliable. The significant contributors to the model (age, foot temperature) are those that would otherwise be considered confounders, whilst the diabetes related constructs appear to have little effect. This further suggests that macroschaemia prediction would be more reliable the younger the participant, before the onset of other age related insults such as diabetes make the model less stable. It is important to place these assumptions within the context of the sample from which the model was derived, which was powered to screen for neuropathy rather than ischaemia. This limits the extent to which we can rely on a macro-ischaemia regression model from this population, and indeed leaves the derived model too unstable and therefore unsuitable to predict TBI macro-ischaemia.

b) *Prediction model for the Medicap*

i. Significant correlations.

TcPO₂ had significant correlations with diabetes duration (Spearman $\rho = -0.33$, $p = 0.001$)

ii. Univariate analysis of ankle size and TcPO₂

Ankle size had no significant effect on TcPO₂ ($\beta = 1.36$, 95% CI = -0.27 - 3; $p = 0.1$).

iii. Univariate analysis of foot temperature and TcPO₂

Foot temperature had no significant effect on TcPO₂ ($\beta = -1.17$, 95% CI = -2.9 - 0.56; $p = 0.18$).

iv. Univariate analysis of age and TcPO₂

Increasing age predicted lower TcPO₂ ($\beta = -0.5$, 95% CI = -0.97 - 0.026; $p = 0.04$). R-squared value was 0.047, indicating that age explained 4.7 % of the variability in TcPO₂.

v. Univariate analysis of study site and TcPO₂

The study site predicted TcPO₂, with those being higher in Southampton and lower in Manchester. With Southampton as the reference site ($\beta_{Southampton} = 1$), this gave ($\beta_{Manchester}$

= - 11.64, 95% CI = -19.6 – 3.7; p =0.005). R-squared value was 0.086, indicating that study site explained 8.6% of the variability in TcPO₂.

vi. Univariate analysis of gender on TcPO₂

Gender had no significant effect on TcPO₂ (β = 2.15, 95% CI = -6.2 – 10.5; p =0.51).

vii. Univariate analysis of smoking status on TcPO₂

Smoking status had no significant effect on TcPO₂ (β = 0.16, 95% CI = -8.01 – 1.33; p =0.16).

viii. Univariate analysis of diabetes duration on TcPO₂

Longer diabetes duration predicted lower TcPO₂ (β = - 0.06, 95% CI = -0.1 – 0.019; p =0.004).

R-squared value was 0.088, indicating that diabetes duration explained 4.7 % of the variability in TcPO₂.

ix. Univariate analysis of HbA1c on TcPO₂

HbA1c had no significant effect on TcPO₂ (β = 0.001, 95% CI = -0.18 – 0.18; p =0.99).

x. Univariate analysis of BMI on TcPO₂

BMI had no significant effect on TcPO₂ (β = - 0.21, 95% CI = -0.84 – 0.43; p =0.52).

xi. Multivariate analysis on the effect of ankle size, foot temperature and age on TcPO₂

Multivariate regression with block selection was conducted to determine the effect of diabetes duration, HbA1c, BMI and age [block 1], in the presence of known variables [block 2] (gender, study site, smoking status). Within both [block1] and [block 2], an additional forward selection process was used to analyse and if necessary remove any dependant variable that showed no significant effect (less than 10% in the β -coefficient).

Fully adjusted linear regression showed that after adjusting for confounders,

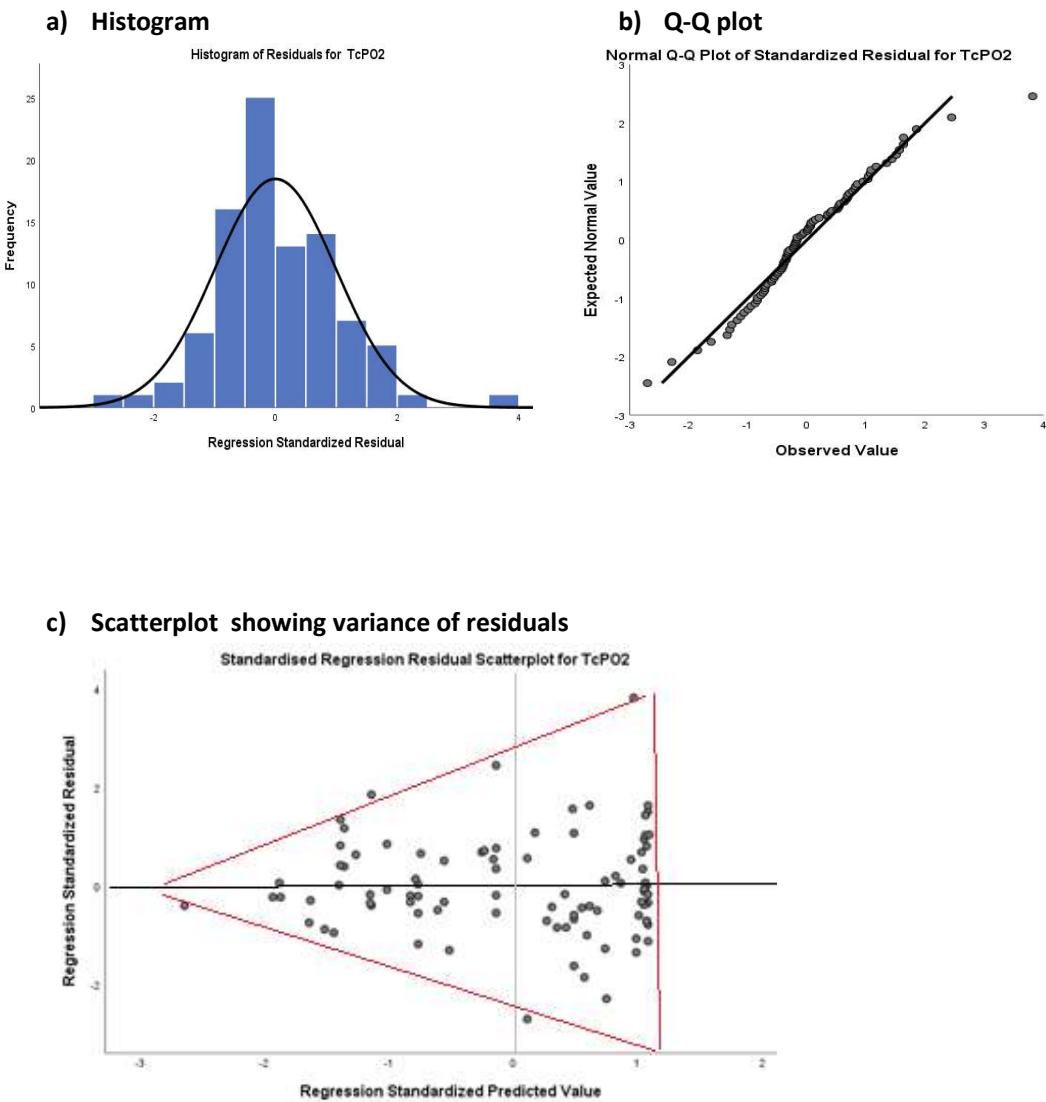
Longer diabetes duration predicted lower TcPO₂ values (β = -0.06, 95% CI = -0.101 – -0.019; p = 0.004).

The contributions of age, HbA1c, BMI, gender and study site did not reach statistical significance. The adjusted R-squared value for the overall model after removal of non-significant factors, was 0.09, showing that diabetes duration alone could account for 9 %

of $TcPO_2$ variability.

xii. Regression diagnostics – distribution of residuals

Figure 8.5.5: Showing residual distribution and variance for $TcPO_2$



The histogram (Figure 8.5.5 (a)) and Q-Q plot (Figure 8.5.5 (b)) show that the residual plots follow a Gaussian distribution. Variance of residuals was assessed using a scatter plot (Figure 8.5.5 (c)) which confirmed the presence of heteroscedasticity (variance of the residuals was not constant) with clear funneling towards the x-axis regression line at lower values, and a buttress effect at higher x-axis values, giving rise to an unbalanced x-axis at higher data points. This model suggests it has greater stability during the early

stages of diabetes in predicting $TcPO_2$ micro-ischaemia, but becomes more unstable with diabetes duration, thereby sacrificing its predictive ability. However in the clinical context, the role of ischaemia is to predict healing capacity, and this role becomes more prominent as diabetes progresses. This suggests the model could be of some use early on, perhaps during initial diabetes diagnosis, but with loss of its predictive ability with diabetes progression, the model becomes of little use. This is consistent with the findings of Biotteau (2009), discussed in Chapter 3.4, who suggested an early window before the manifestation of advanced peripheral ischaemia; during which $TcPO_2$ could be valuable in predicting DFU healing potential.

This again must be placed within the context that the model was derived from a sample powered for neuropathy rather than ischaemia. With this, and from the residual distribution suggesting that with progression of diabetes the model becomes increasingly unstable, it is a model ill-suited to predict $TcPO_2$ micro-ischaemia.

8.5.6 Comparison of ischaemia prediction models

Both the TBI macro-ischaemia, and the $TcPO_2$ micro-ischaemia prediction models appear to become more unstable with time (age for TBI; diabetes duration for $TcPO_2$), and neither appear suitable. However, from an ischaemia perspective, both models are drawn from a possibly underpowered sample, from which it is not possible to build more effective prediction models, nor draw definitive conclusions on the clinical implications.

8.5.7 Summary of regression modelling

From the regression modelling for neuropathy (Section 8.7.3), the model derived for the 10g monofilament was not suitable in predicting neuropathy, but the derived CNCS produced a suitable model. From the regression modelling for ischaemia (section 8.5.5 (b)), neither the TBI, nor the Medicap derived suitable models to predict ischaemia.

8.6 Chapter 8: Summary of main findings

This chapter outlined the results from the neuropathy (Chapter 6) and ischaemia (Chapter 7) experimental investigations, and suggests that the mainstay of risk stratification at assessment was the detection and classification of sensory neuropathy. All the 'at risk' participants from this, and their risk status, are fully captured by combining nerve conduction (DPNCheck®) in addition to both TcPO₂ and TBI.

It also compared the effectiveness of the instruments used in neuropathy assessment and found that despite sharing moderate agreement, the DPNCheck® was the more effective at the assessment of sensory neuropathy. The DPNCheck® was more effective on its own at identifying participants 'at risk' than the combined 10g monofilament and TBI. In addition, the DPNCheck® further identified neuropathy from amongst the 10g monofilament 'low risk' group without apparent neuropathy, thereby uncovering a 'hidden at risk' group, not detectable by the 10g monofilament. From the DPNCheck® nerve conduction amplitude and velocity, was derived the Centred Nerve Conduction Score (CNCS) as a novel construct. The CNCS was progressed through regression modelling, and from which emerged a possible model suitable to predict sensory neuropathy.

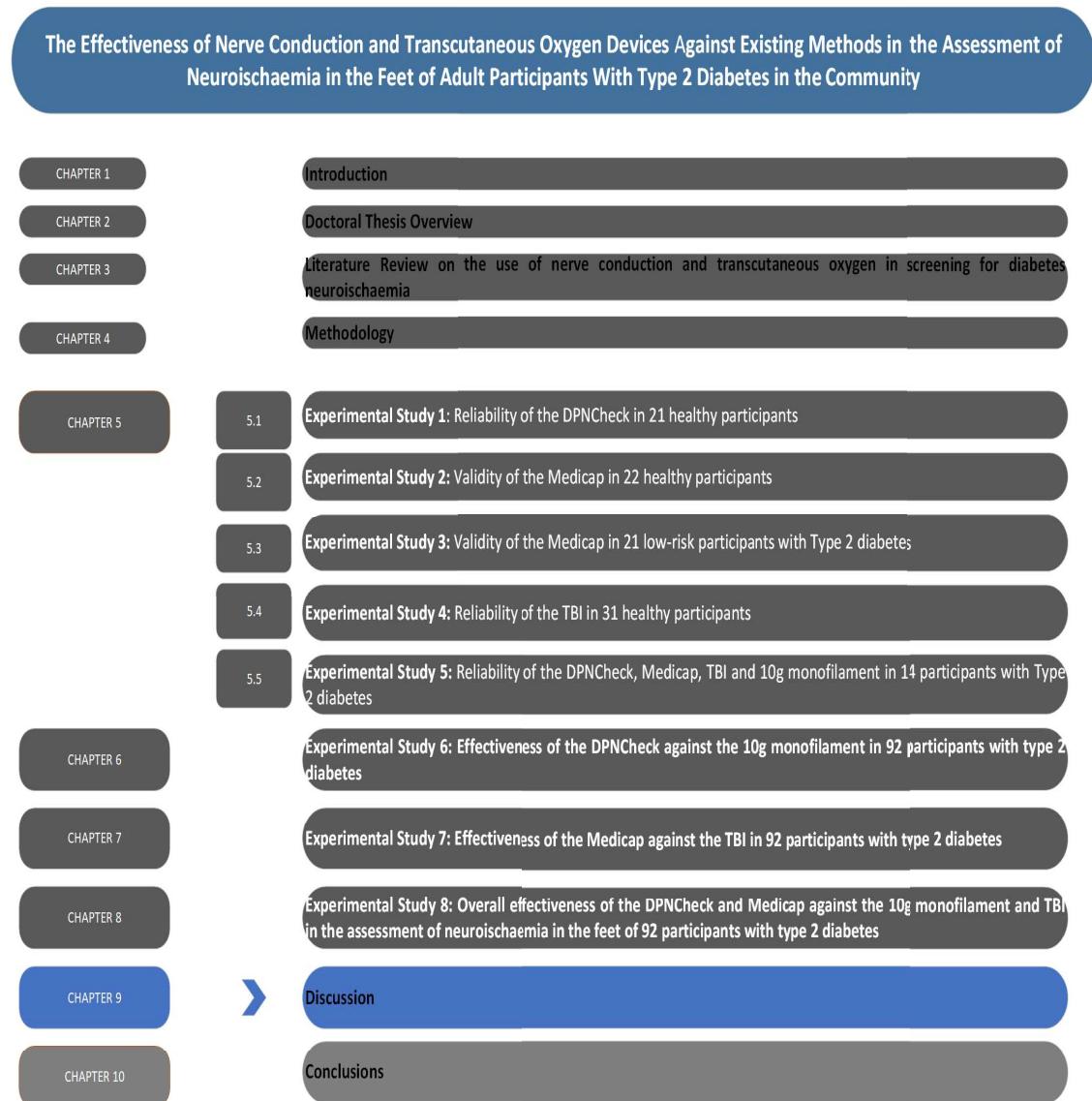
This chapter also compared the effectiveness of the TBI and the Medicap in ischaemia assessment, and found they shared poor agreement, and they did not identify ischaemia in the same participants. Neither instrument was suitable in the construct of an ischaemia prediction model, but this must be considered in the context of the study being powered to screen for neuropathy. The implications for practice from these findings, and possible ways for the novel CNCS, are taken forward into the discussion in Chapter 9.

Chapter 9 DISCUSSION

9.1 Introduction

In the preceding chapters, a literature review identified potential for the use of portable nerve conduction (DPNCheck®) and TcPO₂ (Medicap) in the assessment of neuroischaemia in the feet of people with type 2 diabetes. Within the context of this thesis, this chapter sits as shown in Figure 9.1.

Figure 9.1: Showing the main discussion, within the overall thesis context.



To answer the primary research questions, these devices were individually compared against their corresponding NICE NG19 (2015) recommended counterparts:

9.1.1 **In Chapter 6:** the DPNCheck® was more effective at the assessment of sensory neuropathy than the 10g monofilament. The null hypothesis is therefore rejected with acceptance of the alternative hypothesis.

9.1.2 **In Chapter 7:** the Medicap was not more effective at the assessment of ischaemia than the TBI, and therefore the null hypothesis holds.

Results from these investigations were summarised in Chapter 8, which sought to understand confounding variables and the extent to which they affected any associations, as well as the potential to unify the DPNCheck® scores.

This chapter crystallises the above findings, and takes the significance of the DPNCheck® findings in Chapter 6 as a platform to expose a potential blind spot of the NICE NG19 (2015) guidelines, before discussing the implications for clinical practice. The main conclusions of this chapter are that the DPNCheck® identifies neuropathy from amongst the NICE NG19 'low risk' category, thereby it broadens the clinical realm in neuropathy assessment. This detection of previously subclinical sensory neuropathy is a key finding, which can be used to inform a person with diabetes of their condition at an earlier stage, to self-manage and prevent later complications.

9.2 Primary research questions:

In general, the combined approach of the DPNCheck® and Medicap was more effective at the assessment of neuroischaemia than the NICE NG19 recommended method, which combines the 10g monofilament and TBI. Taking the neuropathy and ischaemia components separately, it is clear that this was due to the detection of subclinical neuropathy by the DPNCheck® over the 10g monofilament, with the Medicap not being more effective than the TBI in identifying ischaemia. The assessment ability of the DPNCheck® was more effective at identifying 'at risk' participants than the combined 10g monofilament and TBI.

Therefore, what this doctoral thesis has shown is that neuropathy assessment by the DPNCheck® alone could be a more prominent contributor in the identification of those 'at risk', and of risk stratification, than the NICE NG19 recommended approaches.

9.3 Advancing on the use of the DPNCheck® and Medicap in the assessment of diabetes neuroischaemia.

For this investigation, all the 'at risk' participants were identified by assessing the physiological parameters outlined in Table 9.3.1., notably without contribution from the only subjective tool: the 10g monofilament.

Table 9.3.1: Showing physiological parameters assessed in neuropathy and ischaemia

	Ontological Category		<i>proposed combined score (quality + quantity)</i>
	QUALITY	QUANTITY	
NEUROPATHY	velocity	amplitude	CNCS ?
ISCHAEMIA	TcPO ₂ <i>microischaemia</i>	TBI <i>macroischaemia</i>	<i>combined ischaemia score?</i>

The table also shows the potential of a composite quality and quantity measurement of this investigation, and carries on the discussion began in the preceding chapters.

9.3.1 Neuropathy.

Neuropathy assessment by the DPNCheck® depends on electrophysiological parameters of nerve fibre quality (indicated by the velocity); and nerve fibre quantity (indicated by the amplitude); as shown in Figure 9.3.1. As discussed in Chapter 3.3, each parameter's diagnostic threshold was determined through ROC curves (Lee *et al* 2014), against neuropathy reference standards (NDS; Toronto) (Chatzikosma *et al* 2016; Binns-Hall *et al* 2018) and fixed nerve conduction (Kural *et al* 2019), which altogether contributed towards establishing the DPNCheck®'s criterion validity in diagnosing sensory neuropathy.

It has also been found to have strong and significant correlations with small fibre neuropathy (Sharma *et al* 2015) as discussed in Chapter 3.3.2. The DPNCheck® had high test-retest reliability for velocity and amplitude (ICC (3,1) = 0.96 ((95% CI = 0.87-0.99)). This is despite the limitations of the reliability investigations of Experimental Study 5, but the reliability findings of the DPNCheck® (Table 5.5.2) can be accepted as they agree with earlier investigations (Lee *et al* 2014; Shibata *et al* 2019), as discussed in Chapter 5.5.7 (d). The DPNCheck® was more effective at neuropathy assessment than subjective methods, which corroborates previous investigations, (Vogt *et al* 2017), and can also be used in low resource settings (Polouse *et al* 2015; Vogt *et al* 2017). This therefore shows that the DPNCheck® is valid and reliable, and this thesis has shown that it was more effective than the 10g monofilament at the assessment of neuropathy in podiatry clinics amongst adults with type 2 diabetes.

Despite this, in providing two scores, it presents a somewhat fragmented picture of the same phenomenon (neuropathy). Therefore this thesis goes on to propose combining the quality and quantity sensory nerve components (velocity and amplitude) of the DPNCheck®, into a composite score (the CNCS from Chapter 8) to help simplify its interpretation, clinical adoption and in further investigating the extent to which it can predict ulceration risk.

9.3.2 Ischaemia.

The Medicap measures TcPO₂ to screen for ischaemia using a different underlying detection process (photochemical) to the established electrochemical probes. In Chapters 5.2 and 5.3 the Medicap demonstrated criterion validity against the TCM400 reference device, across healthy and 'low risk' participants with type 2 diabetes.

Experimental studies 2 and 3 also showed that two locations on the dorsal aspects of the foot (between the 1st - 2nd; and 4th - 5th metatarsal heads) can be used to obtain reliable TcPO₂ measurements. The Medicap however showed consistent TcPO₂ overestimation by 24.8 mmHg, which had to be accounted for when determining its assessment threshold of 50mmHg for subsequent investigations. The Medicap had moderate intrarater reliability (ICC (3,1) = 0.66 (95% CI = 0.24 – 0.87)), however the limitations of Experimental study 5, including the extended retest interval must be borne in mind. The Medicap's TcPO₂ was

negatively and significantly affected by longer diabetes duration (Table 8.3.3), and could distinguish between participants with and without neuropathy (Chapter 8.4.6) which is consistent with the investigation by Eleftheriadou *et al* (2019). The Medicap was however unable to distinguish participants based on neuropathy severity, but this could be attributed to large frequency differences between the neuropathy stratifications (Table 8.4.7). Ultimately, the Medicap did not prove more effective at the assessment of ischaemia than the TBI.

The TBI and the Medicap adopt different approaches in measuring components that represent arterial supply quality ($TcPO_2$) and quantity (TBI). Both are important to determine healing potential, and previous work has shown that macro and microcirculatory assessments are not mutually exclusive, but rather complementary (Rajagopalan *et al* 2017). In Experimental study 7, this thesis found that with either approach finding 10 separate participants, it required both to determine the total number of people suspected of having ischaemia (20 participants). With the two methods not being comparable, this suggests that considering them in isolation also presents a fragmented picture of ischaemia for this profile of participants, as shown in Figure 9.3.1. Therefore, combining $TcPO_2$ and TBI assessments could potentially be applied to give a broader view of the quality and quantity, respectively, of the arterial supply to the foot. If combined, the $TcPO_2$ and TBI could then provide a unified measure of ischaemia, which again could assist in clinical adoption and provide a more complete picture in predicting healing capacity, albeit at a cost of greater time burden for patients. Whilst combining the two assessments could potentially advance the assessment of ischaemia, consideration must also be given towards the diagnostic thresholds that underpin these approaches, and the methodological limitations of this study (Chapter 7.5.3; Chapter 9.5.2).

9.3.3 Potential advances in the assessment of neuroischaemia in people with diabetes.

In addition to providing a more complete picture, unifying neuropathy and ischaemia's individual components reduces complexity at assessment. As the DPNCheck® assesses nerve quality and quantity individually, combining these appears to be a natural

progression in neuropathy assessment, which could also be an avenue to explore for ischaemia assessment. Throughout this thesis, no literature was identified that discusses the concept of combining the quality and quantity components of the neuropathy and ischaemia assessments. Therefore the CNCS for neuropathy (Table 8.5.3, Figure 8.5.2) and for both neuropathy and ischaemia as outlined in Table 9.3.1.; could be novel concepts. However there are some major differences with practical implications to consider. For neuropathy assessment using the DPNCheck®, both nerve quality and quantity are determined simultaneously and within 30 seconds on the same device. In contrast, the quality component of ischaemia assessment ($TcPO_2$) takes at least 15 minutes, in addition to the TBI which, despite the evidence, is itself infrequently used in clinical practice. In addition, despite the ABI and TBI being recommended for ischaemia assessment for the past several years, they are yet to be widely adopted in podiatry assessment clinics. These factors could inhibit clinical adoption of $TcPO_2$ for assessment purposes in the first instance, when the TBI itself is not often used, long before consideration is even given to exploring a unified $TcPO_2 + TBI$ picture of ischaemia.

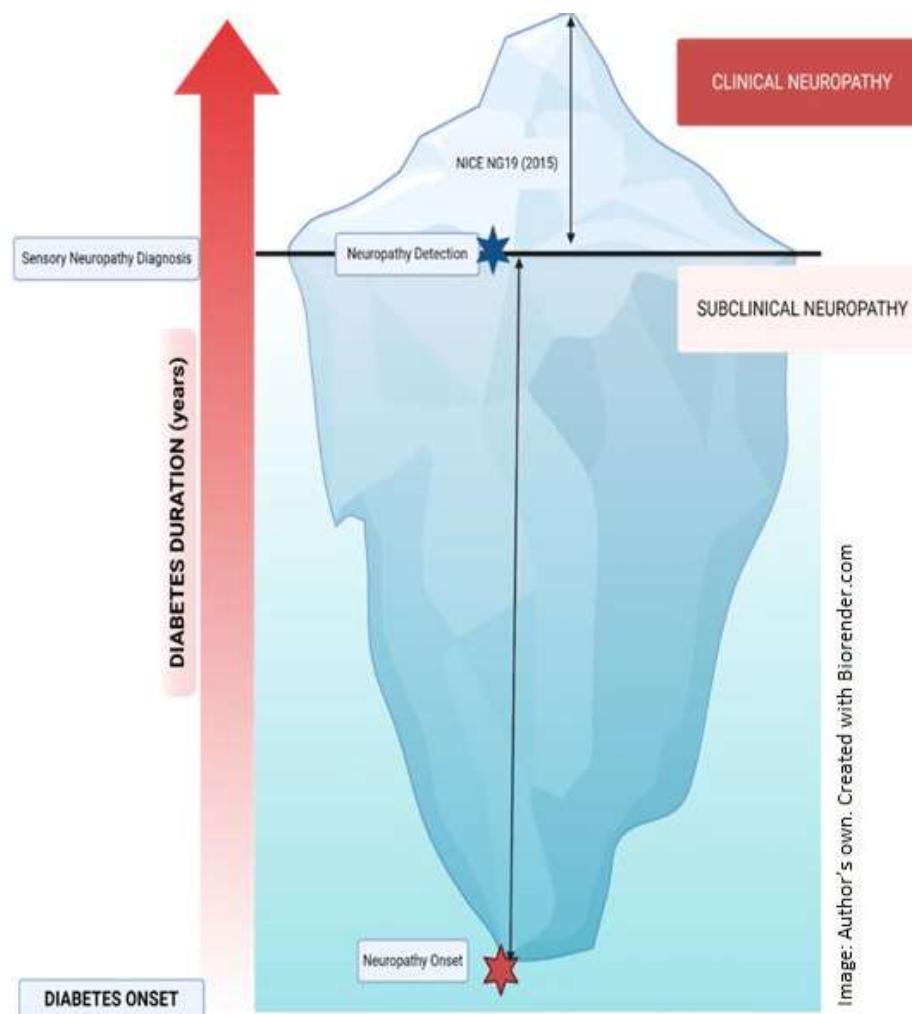
The outlook is more promising for neuropathy assessment, where a single device provides both scores within a short timeframe, and the step change in clinical practice to combining the quality and quantity components (velocity + amplitude = CNCS) seems surmountable.

9.4 What this adds to the field.

As diabetes advances there is a race to prevent complications, which relies on the timely detection of the changes that occur due to glycaemic damage. As discussed in Chapter 1, earlier diagnosis of sensory neuropathy is challenged by a reliance on subjective assessments that can only reliably detect it several years after manifestation. Yet it is these approaches that are still used to define the 'clinical realm', with other earlier symptoms such as numbness and tingling, caused by nerve demyelination and reduction in fibre density, termed 'subclinical' as they are difficult to detect and quantify in clinic. It has been apparent that the 10g monofilament lags so far behind diabetes (Figure 9.4.3) it becomes poorly effective at the assessment of neuropathy to allow time for interventions that arrest deterioration. In Chapter 8 of this doctoral thesis, the DPNCheck® takes a

closer look at the 'low risk' category as defined by NICE NG19, and finds that this includes participants that are in fact 'at-risk', but not able to be detected by the 10g monofilament. What this doctoral thesis has shown, therefore, is the extent to which the neuropathy assessment component of NICE NG19 is limited, and demonstrates that these assessment guidelines carry a potential blind spot, where subclinical neuropathy is that which cannot be detected at the chairside – usually by the 10g monofilament, results in potential 'at risk' participants being classified as 'low risk'. The current status of neuropathy assessment can be summarised by Figure 9.4.1, which visualises current neuropathy assessment as an "iceberg phenomenon". NICE NG19 (2015) guidelines allow the perception of neuropathy which is restricted by the tools available, which only becomes detectable after the 10g monofilament 'catches up' several years after neuropathy onset, as visualised in Figure 9.4.1:

Figure 9.4.1: Showing the current status of Neuropathy Assessment following NICE NG19 (2015)



In Figure 9.4.1, the DPNCheck®, through nerve conduction, brings this previously subclinical component into the clinical realm - making it possible to screen for neuropathy more effectively than current guidelines, as shown in Figures 9.4.2 and 9.4.3. Following this, Figure 9.4.2 shows that with the DPNCheck®, more of this subclinical neuropathy now becomes visible, in effect expanding the clinical realm and allowing for the assessment of neuropathy more effectively than current approaches, as also shown in Figure 9.4.3.

Figure 9.4.2: Showing what nerve conduction (DPNCheck®) adds to the field of neuropathy assessment against NICE NG19 (2015)

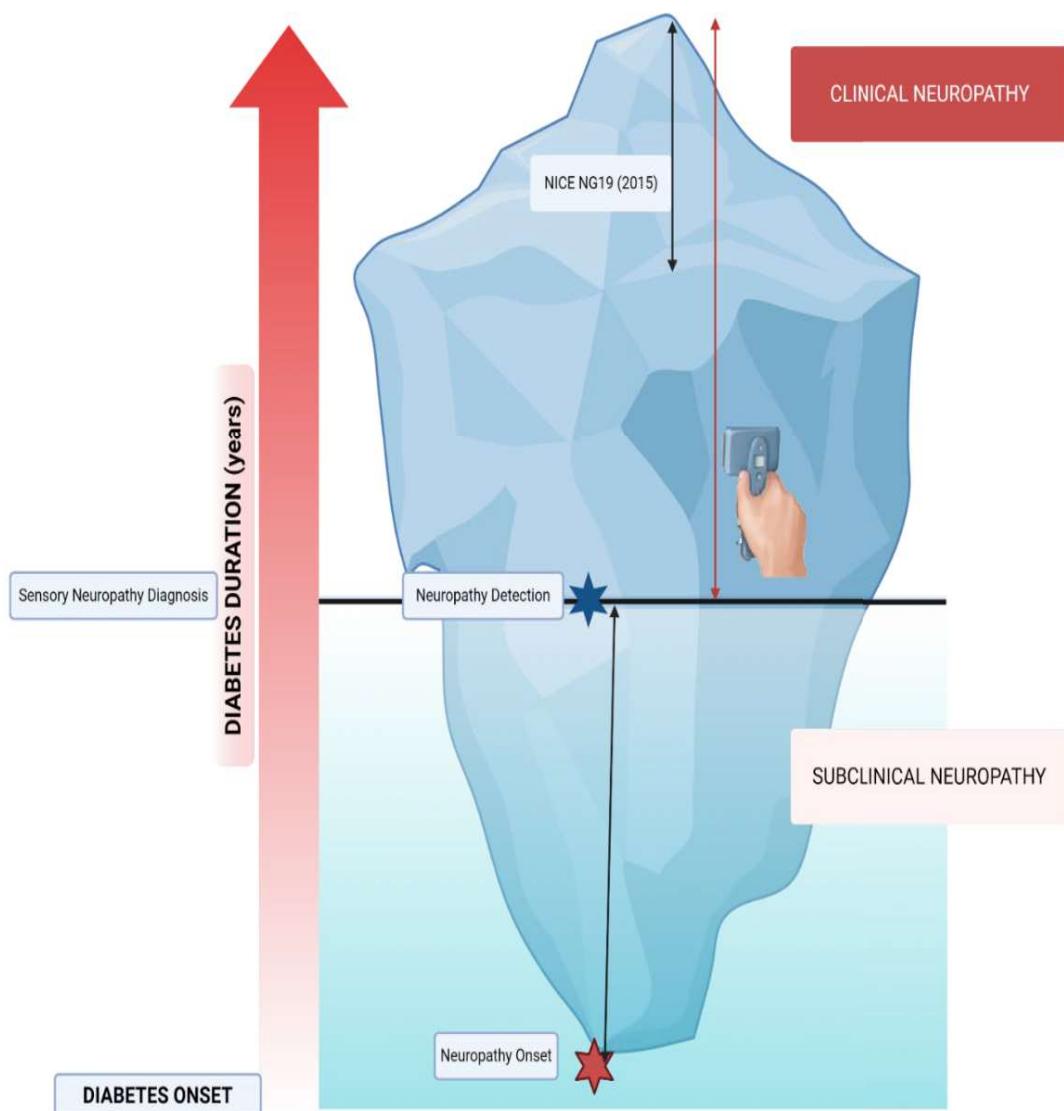
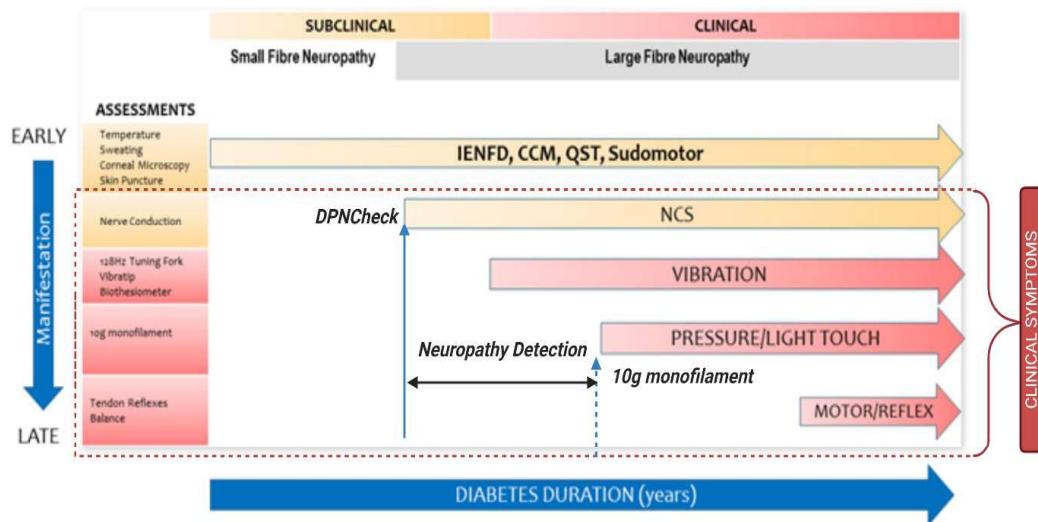


Image: Author's own. Created with Biorender.com

Figure 9.4.3. Showing what the DPNCheck® adds to the field



Therefore more effective and earlier intervention can be made before other neuropathy symptoms become manifest, and this earlier diagnosis can justify implementing measures to delay or prevent the onset of deleterious events.

9.5 Implications for clinical practice

9.5.1 Potential for the DPNCheck® as screening and assessment device

The ability of the DPNCheck® to detect subclinical neuropathy, opens the potential for its use as both an assessment and screening device, as shown in figure 9.5.1. Following the results from Chapter 6, the more effective detection of neuropathy by the DPNCheck® could justify its use in specific target groups such as those with high BMI, with prediabetes and those newly diagnosed with diabetes. As discussed earlier in Chapter 1.7 (pages 55-57) it would effect earlier treatment through evidence based measures such as patient engagement and education (Bailey et al., 2005; Tuomilehto and Schwarz, 2016), early medication use (Aroda et al., 2017), weight control through exercise and diet (Gerhard-Herman et al., 2017), where it has been shown that timely interventions in these aspects (Chatterjee, Khunti and Davies, 2017) can arrest deterioration, ulceration, amputation and mortality (Cefalu et al., 2016; Barry et al., 2017; Dy, Bennett and Sharma, 2017).

Figure 9.5.1: Showing potential clinical implications for DPNCheck® in detecting subclinical neuropathy.

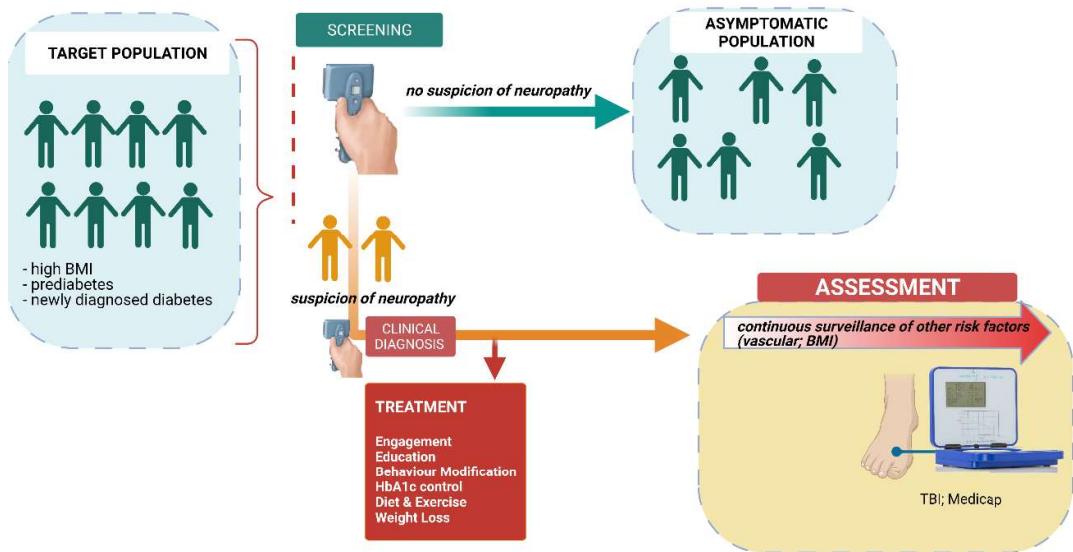


Image: Author's own. Created with Biorender.com

In addition, neuropathy progression on DPNCheck® parameters could become a marker of disease management and advancement, and can potentially be useful ahead of ischaemia detection which is itself a later stage symptom. The DPNCheck® can therefore be used in the early assessment of the target groups in newly diagnosed diabetes, and in those that are at high risk of developing diabetes such those who have a high BMI or in prediabetes, who also carry further cardiovascular risks.

The combination of the DPNCheck®'s ability to detect subclinical neuropathy, and with sensory neuropathy manifesting ahead of ischaemia detection, raises the possibility of nerve conduction supplanting ischaemia detection particularly at the early assessment phase. Advancing on the discussion from chapter 1.5.2 (pages 50-51) where it was suggested that the pathogenic mechanisms of microangiopathy and subclinical neuropathy could be interlinked; in addition to neuropathy being associated with worse macrovascular outcomes (mortality due to ischaemic heart disease); it raises the possibility of the DPNCheck® being a useful proxy for micro and macro ischaemic changes. It also suggests a longitudinal clinical trial of continuous neuroischaemic monitoring to detect which DPNCheck® values correspond to early micro and macro ischaemic manifestations and where these questions could be addressed. At that stage it will be worth considering whether there will be sufficient basis to establish a diabetes

sensory neuropathy screening programme which aims to prevent ulcerations and premature deaths – considering the effectiveness of diabetes retinopathy screening which aims to prevent blindness.

9.5.2 Potential for a standardised assessment approach

NICE guidelines first emerged in 1999, with stated aims to standardise care and end the rationing of treatment by postcode across the UK, thereby reducing variation and improving standards. With reference to diabetes foot assessment, NICE NG19 (2015) aims to prevent and guide the management of diabetes foot problems, and it promotes the importance of early identification of those “at risk” of developing foot problems. This doctoral thesis suggests a potential use of the DPNCheck® in the assessment of neuropathy, as it was found to be more effective at assessing sensory neuropathy than current NICE NG19 (2015) guidelines. The guidelines themselves do not have a standardised approach, and are open to differences in interpretation and implementation, often to the exclusion of ethnic minorities and those in areas of deprivation. This implies that current guidelines are ineffective at standardising the assessment of early neuropathy in its subclinical form, and has led to the continued variation in assessment and treatment approaches. Therefore there are potentially significant numbers of people with diabetes subjected to current assessment protocols based on NICE NG19 (2015), that are in fact ‘at risk’ rather than ‘low risk’. This would imply that despite being a hidden ‘at risk’ group, they would likely be excluded from more intensive management approaches aimed at preventing later complications. With this potential diagnostic blind spot, NICE NG19 may result in the standardised exclusion of those people who have subclinical neuropathy, often from vulnerable groups, who will likely go undetected until they develop the diabetes complications that NICE NG19 (2015, revised 2019) aims to prevent.

With the standardised approach to assessment, findings from this doctoral thesis could potentially mean more inclusion of this previously hidden “at risk” group, and reducing the discrepancies and variation of assessment provision, in underrepresented populations such as ethnic minorities and those in areas of social deprivation. There remain concerns that exerting this on an overburdened health service tasked with reducing costs could

mean a raising of the access criteria and limit provision only to the 'high risk' or ulcerated groups. The main impact of detecting subclinical neuropathy as argued in this doctoral thesis therefore could be, rather than force health services to include these additional previously 'hidden' patients— instead for the patient to be better informed of their true condition (subclinical neuropathy) and at an earlier stage. Earlier detection of subclinical neuropathy would allow susceptible groups to be supported in self managing their diabetes, and broaden the window for behaviour change and other strategies to modify the risk factors to ulceration, amputation and cardiovascular mortality.

9.6 Strengths and Limitations

9.6.1 Strengths

To my knowledge, this doctoral thesis was the first to investigate the combined use of TcPO₂ and portable nerve conduction in the assessment of neuroischaemia in people with type 2 diabetes across all non-ulcerated risk strata, and compare these findings against NICE NG19 recommended approaches. An additional novel aspect of this thesis is the experimental setting being within a 'usual care' clinical site, rather than in a laboratory setting. This enabled consideration of the translation of the important findings relative to nerve conduction more directly to patient care. The cross-sectional nature of the study allowed the direct comparison of the corresponding devices at the same time, and being conducted in podiatry clinical settings across Southampton and Manchester make it more pragmatic, give it some external validity and make the findings more generalisable.

9.6.2 Limitations

The study has several limitations, which are mainly outlined at the ends of each individual sections in Chapters 5, 6 and 7. They are outlined here briefly, beginning with those that affected the study as a whole.

- a) Design:* the cross sectional nature of the study implies that causality cannot be inferred, as all variables were taken as a snapshot in time.
- b) Participants.* The study did not have even distribution across all risk stratifications.

However the main objective was to determine the effectiveness of assessment which aims to detect early symptoms, and is therefore more relevant to the 'low risk' group. It is also possible that some participant groups were underrepresented, which limits the extent these results are applicable to those populations.

- c) *Non responder bias.* In excess of 400 contacts were made by the principal investigator in attempting to recruit for the final study, but the number of positive responses was limited to about 120, of which 93 actually attended. Due to time and resource constraints, it was not possible to follow up the non responders. These were more likely to have work commitments, with fewer clinical appointments and were possibly younger and healthier than those who attended. Alternatively, their healthy status could have deteriorated to such an extent that they withdrew. In either case, if the health status was significantly different to those who attended, this would have affected the prevalence of neuropathy and ischaemia, and these non responders are a possible source of bias in this study.
- d) *HbA1c.* Some HbA1c results were taken up to 6 months previously, and were unlikely therefore to reflect current glycaemic control during assessment. Therefore not all parameters were accurate at the same point in time, and this limitation must be borne in mind when drawing assumptions on the effects of HbA1c on the observations from this cross-sectional study.
- e) *The sample size* was calculated based on the suggested prevalence for diabetes neuropathy, but this potentially left the study underpowered for investigating ischaemia differences between TcPO₂ and TBI in this cohort. Powering the study based on ischaemia prevalence would have required about 300 participants, which was impractical.
- f) *Unilateral leg assessments.* An overall limitation for the main investigations (Chapters 6 and 7) was the unilateral nature of the assessments – focusing on the right foot. This was done for pragmatic reasons. However for completeness, and particularly for ischaemia, bilateral investigations would have extended the study's clinical relevance.
- g) *Linear regression.* During predictive modelling, assumptions were made on linear regression, yet the variables could have non-linear relationships. This could mean that the resulting model could potentially give biased predictions and have

heteroscedastic errors.

- h) *Effects of posture:* the effects of posture on ischaemia readings remain unclear, as participants did not lie supine. This is discussed in depth in Chapter 7.5.3.
- i) *Reliability investigations* (Chapter 5.5) were limited to 14, despite intending to recruit 30. In addition the recall time (4 months) was extended, whereby the health status of the participants could have changed, and therefore not allow for the accurate determination of intra-rater reliability.

9.7 Recommendations for future research

9.7.1 Risk Algorithm:

It will be useful to investigate the potential to develop a risk algorithm, to more accurately predict a person's 'risk status' over the long term, based on DPNCheck® and Medicap values for 10 year outcomes regarding ulceration, amputation and death.

9.7.2 Role of ischaemia in risk stratification.

With nerve conduction being so effective at detecting those 'at risk', even against combined 10g monofilament + TBI, it raises the question whether it is worth the assessment of ischaemia at all in this cohort when nerve conduction is available.

9.7.3 Effects of posture on TBI and TcPO₂

There is a pressing need to establish reference values that are relevant to clinical – rather than research- settings. This is highlighted by the divergent literature on how posture affects the TBI and TcPO₂, and the challenges faced by this investigation.

9.7.4 Threshold values for the TBI

There is no agreement on the actual TBI values that are linked to clinical outcomes, so more investigations are necessary in this area.

9.7.5 Threshold values for the Medicap

As a novel device, the Medicap was validated against the TCM400, but it does need to have its own threshold values and further investigations into the extent to which these could predict the risks of amputation and death.

9.7.6 Unified score for nerve conduction: CNCS

The DPNCheck® still carries complexity in having separate amplitude and velocity scores. It would simplify its use, and help with clinical adoption, if it was further developed to show a single unified score for neuropathy, and compared against long term clinical outcomes.

9.7.7 Unified score for ischaemia

Ischaemia assessment is even more fragmented than that for neuropathy. The complexity derives from different devices with relatively long protocols, and with microischaemia yet to be adopted as standard practice within the UK. It would simplify its use, and help with clinical adoption, if microischaemia and macroischaemia were further investigated for a potential single unified score for ischaemia, and compared against long term clinical outcomes such as ulceration, healing, amputation, and death.

9.7.8 Longitudinal study design:

All these recommendations call for a longitudinal study. This would help to investigate the effects of DPNCheck® and Medicap (even TBI) values on long term outcomes such as ulceration, healing, amputation and death, in people with diabetes, as they progress through the risk strata. Such data is relevant to clinical outcomes.

Chapter 10 CONCLUSIONS

This Chapter provides a conclusion to the thesis overall, as shown in Figure 10.1

Figure 10.1: Showing final conclusions within the context of the overall thesis.



There is increasing focus on dealing with diabetes complications, which continue to face high prevalence, delayed detection and treatment variations. Instead of adding research on the known downstream complications, the overall aims of this doctoral thesis were driven by a need to refocus attention to the early clinical assessment of known risk factors, so as to provide evidence in support of efforts to prevent complications in the

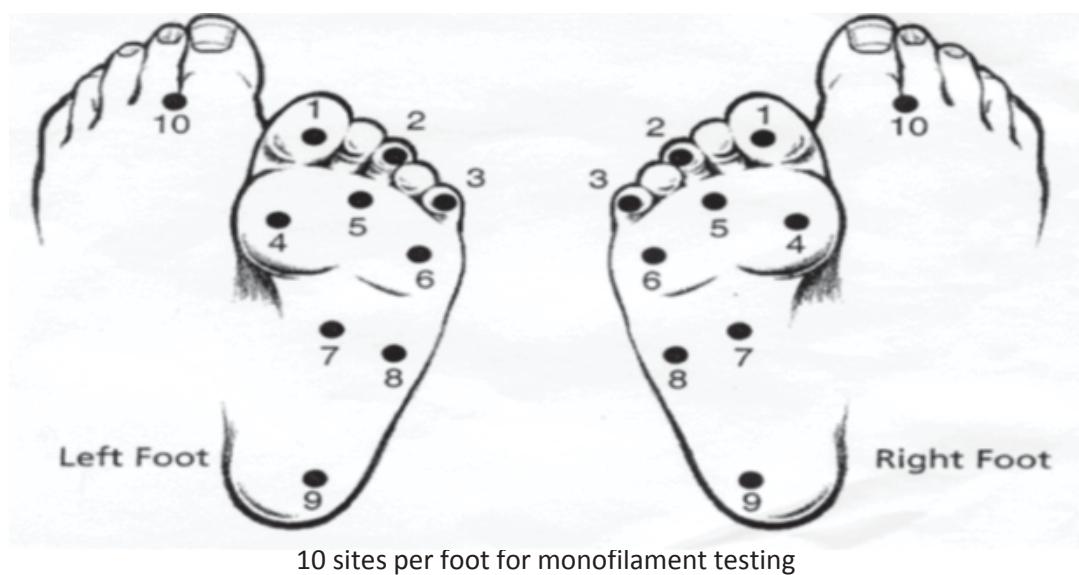
first instance. This doctoral thesis investigated the effectiveness of emerging technologies in the assessment of neuropathy and ischaemia, and compared their performance against NICE NG19 recommended methods. The DPNCheck® has some previous investigations that established its validity and reliability, and it was found to be more effective at the assessment of neuropathy. For the Medicap, it was necessary to first establish its validity, before comparing its performance against the TBI, where it did not prove more effective at the assessment of ischaemia. It was therefore the DPNCheck® that demonstrated best assessment performance, and had the most significant contribution towards identifying participants 'at risk'.

Overall, this doctoral thesis has provided evidence, and some future direction, towards the standardisation of, and reducing disparities in, assessment of diabetes neuroischaemia using these novel devices.

Protocol for the Use of the 10g monofilament in the screening of the diabetic foot

Adapted from: 2014 by Community Podiatry (Northern Devon NHS Trust)

- Sensory examination should be done in a relaxed setting. First apply the monofilament on the patient's inner wrist so the patient knows what to expect.
- The patient must not be able to see if and where the examiner applies the monofilament. The 10 sites to be tested on both feet are shown in the figure below
-



- Apply the monofilament perpendicular to the skin surface as shown below:



Apply sufficient force to cause the filament to bend or buckle for 1-1.5 seconds.

- Do not slide the filament across the skin or make repetitive contact at the test site.
- Ask the patient to respond with a 'yes' every time pressure is detected.
- For the purposes of annual review:
 - normal sensation = detecting eight or more monofilaments
 - abnormal sensation = detecting seven or fewer.

References:

1. Measuring the accuracy of different ways to identify the 'at-risk' foot in routine clinical practice, G P Leese et al 2011.
2. Foot problems in diabetes, pp18-23, NHS Scotland 2008.

NC-stat® | **DPNCheck™**

User Manual



402248003341



DPN-Check User Manual version 1.

IRAS ID: 170265

Date: 30th Aug 2017

NEUROMetrix®

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CHAPTER ONE: INTRODUCTION

1.1 Indications For Use

The NeuroMetrix NC-stat®|DPNCheck™ is intended to measure neuromuscular signals that are useful in diagnosing and evaluating systemic and entrapment neuropathies.

1.2 Contraindications

None.

1.3 Warnings, Precautions & Safety Considerations

- Federal law restricts this device to sale or use by or on the order of a health care provider appropriately licensed by the law in the state in which they practice
- For safe and effective operation of the device, please read and understand the User Manual thoroughly
- Use the device only as described in this manual
- Failure to follow the Warnings listed below may cause injury to the patient or operator
- Possible hazard of fire or explosion. Use care when operating this device close to oxygen sources, flammable gases, and chemicals
- Patients with implanted electronic devices should not be subjected to electrical stimulation unless specialist medical opinion has first been obtained
- Avoid accidental contact with connected but unapplied conductive components, including electrodes
- Do not place any part of the device over broken skin, lesions, or wounds

1.4 Overview

The NC-stat DPNCheck device measures the sural nerve conduction velocity and sensory nerve action potential (SNAP) amplitude. The device includes the following elements:

- **Power/Test Button** – allows users to turn the device on and initiate a test.
- **LCD Display** – area where test results and error messages are displayed.
- **LED Light** – status indicator.
- **Battery Compartment** – holds 3V Lithium battery that powers device.
- **Biosensor Port** – where the biosensor is connected to the device.
- **Infrared Thermometer** – reads the patient's skin surface temperature.
- **Stimulating Probes** – non-invasively deliver electrical stimulation to the sural nerve.
- **Biosensor** – a single patient-use biosensor is needed to conduct each test.
- **USB Port** – for communication with a PC.



CHAPTER TWO: SETUP

2.1 Package Contents

Prior to use, the package should be inspected to ensure that all of the following components are included and undamaged.

STANDARD COMPONENTS:

- NC-stat DPNCheck device
- 3V Lithium Battery
- USB Cable

2.2 Reporting Damage

If any of the components appear to be damaged, or if the NC-stat DPNCheck device fails to operate as described in this manual, contact NeuroMetrix immediately. Within the USA, customers should contact NeuroMetrix Customer Service:

Phone: (888) 786-7287

Fax: (781) 663-3820

E-mail: customerservice@neurometrix.com

International customers should contact the nearest authorized NeuroMetrix representative. If the shipping container is damaged, customers should also notify the shipping carrier.

2.3 Battery Installation

The NC-stat DPNCheck device uses a standard 3V Lithium Ion Battery (Type CR123A).

1. Remove the battery cover on the backside of the device.
2. Insert the battery. Check the battery symbol inside the device to ensure proper orientation of positive and negative contacts.
3. Replace the cover.

2.4 Registration

In order to activate your warranty, receive software updates, and use various optional reporting and data management services, you must register your device with NeuroMetrix. Call NeuroMetrix Customer Service (888) 786-7287 to register the device's serial number. The serial number is an 8 digit number (e.g., 11110001) found inside the battery compartment.

CHAPTER THREE: OPERATING INSTRUCTIONS

This chapter explains the basic operation of the NC-stat DPNCheck device.

3.1 Power On

To power on the device, press the grey button under the LCD Display Screen. The green light will blink once to indicate power on and  indicates that the device is ready for use.

3.2 Power Off

The device will power off automatically after 10 minutes of inactivity. Note: Your last test is saved on the device until a new test is performed.

3.3 Battery Lifetime

The NC-stat DPNCheck is powered by a 3V Lithium Ion Battery. A solid amber light will indicate that the battery is low and should be replaced as soon as you complete the test in progress. A solid red light accompanied by  indicates that the battery must be replaced before any further testing. See section 2.3 for battery installation.

3.4 Test Procedure

Proper patient positioning, skin preparation, and device placement are essential to accurately administer the test. The section below will demonstrate proper techniques.



Step 1: Lay the patient on an exam table and prepare the testing area with a Preparation Pad.

Tip: Both the outer ankle bone (lateral malleolus) and Achilles tendon should be easily accessible as shown at left. Please reference the User Manual for alternative patient positions.

The test area should be vigorously scrubbed with the Preparation Pad provided.



Step 2: Power on the device. The display will show  and the light will turn amber  or red  when the battery needs to be replaced.



Step 3: Fully insert the biosensor into the port. The light will turn green  once the biosensor has been properly inserted. Align to foam. The display will show  to set the leg to be tested.

Tip: Align the biosensor with the foam on all sides; "REMOVE BACKING" label side faces up.



Step 4: Set the leg to be tested. The device display screen will blink with the leg selected (l = left; r = right). To switch the leg, hold the button down for 1-2 seconds and the selection will change to the opposite leg.

Tip: Whenever possible, test the same leg in all patients.

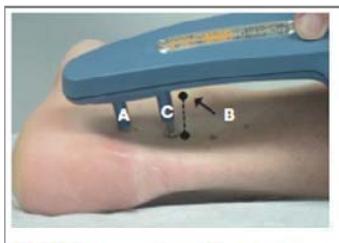


Step 5: Apply a small amount of conductive gel to each probe. The head of the probe should be covered with gel.

Tip: Remove excess gel that may lead to gel smearing between the two probes.



Step 6: Remove the backing from the biosensor.

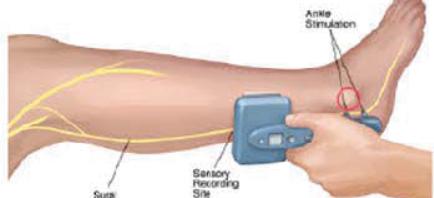


Step 7: Locate the patient's outer ankle bone to align the long probe just behind it.

Tip: The anode (short probe, **A**) and cathode (long probe, **C**) should be aligned to the outer ankle bone, **B**. The cathode should be adjacent to the middle (central prominence) of the ankle bone. The nerve is stimulated only under the cathode.



Step 8: Align the device on the lower calf by pushing down firmly on the foam. The device should point towards the back side of the knee with the **inner edge of the biosensor placed next to the midline** (Achilles tendon). Ensure that the device is aligned to but does not cross over the midline as shown by the dashed line in the image above.



Tip: The probes should be placed behind but not over the outer ankle bone.



Tip: Check for good contact on both sides of the foam.



Step 9: Press the button to start the test. The light will blink with each stimulation. Limb selected will be displayed.

Tip: During test, maintain:
 a.) Firm pressure on **probes**
 b.) Firm pressure on **biosensor**
 c.) **Steady** positioning



Step 10: Maintain constant force throughout the test. The test time may vary per patient, but normally lasts for 10-15 seconds. The results will display once completed.

Patient Positioning

The preferred position is for the patient to lie on their side on an exam table with the leg to be tested on top (Figure 1). If you cannot see both the outer ankle bone and the calf midline (Achilles tendon), adjust patient position to their appropriate side. The patient should be in a comfortable position that allows for relaxation of the leg and foot. It is important that the patient remains relaxed during the test.

Alternative positions may include: side with left leg extended (Figure 2); prone with feet hanging off the exam table (Figure 3); and chair with one leg resting on a chair (Figure 4). The patient should bend their knee and place half of their calf on to the seat in order for the leg to be properly rested and grasp the back of the chair for stability. It is recommended that a sturdy chair with no wheels and a padded seat be used for patient comfort. Note: Users should only use a chair when an exam table is not available.

Figure 1: Alternative position; side



Figure 2: Alternative position; side



Figure 3: Alternative position; prone**Figure 4: Chair; leg up**

3.5 Test Results

When the test is complete, the device display will toggle between the sural nerve conduction amplitude in microvolts (μ V) and the conduction velocity in meters per second (m/s). In cases where the patient has low amplitude (between 2-4 μ V) and the CV cannot reliably be reported, only the amplitude will display on the device. Amplitude result is indicated by a decimal point at the upper right corner of the screen.

Display Example	Result	Actions
40	Conduction Velocity – meters/second	Record and interpret result.
4.	Amplitude – microvolts*	Record and interpret result.
0.	Undetectable Response; no Conduction Velocity displayed	Record and interpret result.
Pn Pr Sn Lb Ec QC Hd	Test Unsuccessful	Note displayed code and refer to Troubleshooting on back.

Recalling Results on Device

If the device powers down after a test, the results of that test can be recalled. To recall the results press and hold the button for 3 seconds and you will see the results appear on the display. Results will display for 10 seconds and then the device will power off. This mode can only be accessed when the device is powered off. If you have powered on the device and need to recall the last result, wait 3 minutes for the device to power down and then follow the instructions above for recalling results.

3.6 Recommended Testing Protocol

This protocol is intended only as a guide. It is the responsibility of the provider to determine the clinical necessity of nerve conduction testing.

Testing a single leg is usually clinically sufficient.

- Whenever possible, the same leg should be tested first in all patients.

If the first test does not provide a result or to confirm the result, the test should be repeated.

- Pressing the test button again is usually all that is required (see Appendix F).

The test will provide a nerve conduction result the first time in most patients.

Tip: In certain circumstances it may be beneficial to confirm the results. Examples include:

- Confirm CV if amplitude is $\leq 4 \mu\text{V}$
- Confirm undetectable response
- Confirm result inconsistent with clinical findings
- If the leg setting on the device was incorrect, then the test should be repeated

If the repeat test does not provide a result or for further confirmation of the results the opposite leg should be tested.

- The same biosensor may be used on both legs.

Note: The NC-stat DPNCheck device should only be used with NeuroMetrix single patient use biosensors. Repeat use of the same biosensor on multiple patients will disable the device as indicated by the “Ub” error code. Disabled devices must be returned to NeuroMetrix for a factory reset. Users will be required to pay a service fee and all shipping and handling charges.

CHAPTER FOUR: SAFETY, WARRANTY SERVICE, CARE, AND SERVICE

4.1 Safety Notes

Do not immerse any portion of the NC-stat DPNCheck device in water or other fluids. Avoid spilling fluids on the Device or accessories. Spilling fluids may damage the device and/or present a fire or shock hazard.

Possible hazard of fire or explosion. Use care when operating this device close to oxygen sources, flammable gases, and chemicals.

Failure to follow the Cautions listed below may change the performance of the equipment, or cause damage to the equipment.

Radio frequency (RF) interference from devices such as cellular phones and two-way radios may cause improper operation of the NC-stat DPNCheck device if used in close proximity.

Accessory equipment connected to the USB port must be certified according to the respective IEC standards (e.g. IEC60950 for data processing equipment and IEC60601-1 for medical equipment). Most computers manufactured by major suppliers meet the IEC60950 standard. If in doubt, consult your local Information Technology support.

4.2 Maintenance and Cleaning

Other than changing the battery, there are no user serviceable parts inside the NC-stat DPNCheck device. Refer to the warranty and service information included in this manual.

The NC-stat DPNCheck device has been manufactured to the highest quality standards. To ensure continued trouble-free operation, avoid exposing the components to excessive shock, vibration, or moisture.

Cleaning the device and any components:

- Remove the battery and close the battery compartment and any other external connections before cleaning the Device or any of the components.
- Use a soft damp cloth or sponge to clean the exterior of the unit.
- Do not use abrasive cleaners or strong solvents to clean the device.

Disinfecting the NC-stat DPNCheck device:

- If the NC-stat DPNCheck device becomes contaminated by body fluids, it should be cleaned using a hospital grade disinfectant and a disposable, soft cloth or paper towel, per standard hospital or office protocol.

4.3 Use of and Disposal of Batteries

The battery is a 3.0V Lithium Battery type CR123A. Dispose of used Lithium battery in accordance with national, regional, and local regulations.

4.4 Storage of Biosensors

NC-stat DPNCheck biosensors are single-use, non-sterile devices. They should be stored lying flat at room temperature in a dry location. Storage temperature should not fall below -22° F (-30° C) or exceed 140° F (60° C). The package should only be opened immediately prior to use. The biosensors should not be used after the expiration date shown on the package.

4.5 NeuroMetrix, Inc. Limited One Year Warranty

NeuroMetrix, Inc. manufactures its hardware products from new components in accordance with industry standard practices. NeuroMetrix warrants the NC-stat DPNCheck device to be free from defects in materials and workmanship. The warranty term is one year beginning on the date of invoice, as described in the following text.

Damage due to shipping the products is covered under this warranty. Otherwise, this warranty does not cover damage due to external causes, including accident, abuse, misuse, problems with electrical power, servicing not authorized by NeuroMetrix, Inc., usage not in accordance with product instructions, failure to perform required preventive maintenance, and problems caused by use of parts and components not supplied by NeuroMetrix, Inc.

This warranty does not cover any items that are in one or more of the following categories: software, external devices (except as specifically noted) or accessories or parts added to a NeuroMetrix device through authorized NeuroMetrix service centers.

NeuroMetrix, Inc., will repair or replace products covered under this limited warranty that are returned to NeuroMetrix's facility or an authorized NeuroMetrix representative. To request warranty service, you must call the NeuroMetrix Customer Service at (888) 786-7287 or call an authorized technical support representative within the warranty period. NeuroMetrix will issue a Return Material Authorization (RMA) Number. The product must be shipped to NeuroMetrix in the original or equivalent packaging, with prepaid shipping charges, and insured against loss or damage during shipment. NeuroMetrix will ship the repaired or replacement units to the originator (freight prepaid) to addresses within the US or Canada. Shipments to other locations will be made freight collect.

All parts removed from repaired products will become the property of NeuroMetrix, Inc. If NeuroMetrix repairs or replaces a product, the original warranty is not extended.

NEUROMETRIX, INC. MAKES NO EXPRESS WARRANTIES OR CONDITIONS BEYOND THOSE STATED IN THIS WARRANTY STATEMENT. NEUROMETRIX DISCLAIMS ALL OTHER WARRANTIES AND CONDITIONS, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES AND CONDITIONS OR MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. SOME STATES (OR JURISDICTIONS) DO NOT ALLOW LIMITATIONS ON IMPLIED WARRANTIES OR CONDITIONS, SO THIS LIMITATION MAY NOT APPLY TO YOU.

NEUROMETRIX'S RESPONSIBILITY FOR MALFUNCTIONS AND DEFECTS IN HARDWARE IS LIMITED TO REPAIR AND REPLACEMENT AS SET FORTH IN THIS WARRANTY STATEMENT. THESE WARRANTIES GIVE YOU SPECIFIC LEGAL RIGHTS IN ADDITION TO OTHER RIGHTS WHICH VARY FROM STATE TO STATE.

NEUROMETRIX INC. DOES NOT ACCEPT LIABILITY BEYOND THE REMEDIES SET FORTH IN THIS WARRANTY STATEMENT OR LIABILITY FOR INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING WITHOUT LIMITATION ANY LIABILITY FOR PRODUCTS NOT BEING AVAILABLE FOR USE OR FOR LOST DATA OR SOFTWARE.

These provisions apply to NeuroMetrix's limited one-year warranty only.

4.6 Service

Should the NC-stat DPNCheck device require service, contact NeuroMetrix Customer Service at (888) 786-7287. When you call NeuroMetrix to request service, please be prepared to provide the following information:

- Serial number
- Description of the problem

Do not return any component of the NC-stat DPNCheck device without first obtaining a Return Material Authorization (RMA) Number from Customer Service. Be sure that this number is clearly visible on the exterior of the return package. If a NC-stat DPNCheck device component must be shipped to a service center, pack it in the original shipping container or in packaging which provides enough protection to prevent damage during shipment.

4.7 FDA Notification

The NC-stat DPNCheck device is manufactured in compliance with the U.S. Federal Quality System Regulation (21 CFR Part 820). As a health care provider, you may have responsibilities under the Safe Medical Devices Act (SMDA) for reporting to NeuroMetrix, and possibly the FDA, the occurrence of certain events. (FDA reportable events are detailed in 21 CFR Part 803.)

In accordance with our Quality System, NeuroMetrix should be notified of any device failures or malfunctions. Issues encountered should be reported to NeuroMetrix Customer Service. Outside of the United States, problems should be reported to the nearest NC-stat DPNCheck device distributor. This information will help ensure that NeuroMetrix continues to provide products and services of the highest possible quality.

SPECIFICATIONS

Dimensions

Device Size	5.5 cm x 19.0 cm x 11.6 cm
Weight	160 g

Environmental - Shipping and Storage

Temperature	-20 °C to 50 °C
Humidity	10% to 90%, non-condensing
Altitude	55 kPa to 100 kPa
Operating	10 °C to 30°C

Hardware

Channels	2
CMRR (typical)	≥ 100 dB
Gain	x977
Noise (typical)	< 2 µV rms
Frequency Response	(-3 dB) 2 Hz – 2 kHz
Sampling Frequency	10 kHz
ADC Resolution	16 bits (effective)
Stimulator Type Constant Current	Monophasic
Stimulator Max Voltage (typical)	420 V
Stimulator Max Current	100 mA hardware, software limited to 70 mA
Stimulator Pulse Width	100 µs
Stimulation Frequency	1 Hz (maximum)
Skin Temperature Measurement	Non-contact, infrared
Battery	3.0 V Lithium Primary (CR123A)
LCD Display	2 digit, 7-segment
Water Resistance	IEC 529 IPX0 not protected from ingress of liquids
Classification Type	BF Applied Part, IEC 60601-1

Neurophysiology

Nerve	Sural sensory, orthodromic
Methodology	Preconfigured electrode array
Stimulation Site	Behind lateral malleolus
Stimulation Configuration	Bipolar (2 cm separation)
Recording Site	9.22 cm proximal to stimulation
Recording Configuration	Bipolar (2 cm separation)
Conduction Velocity (CV)	Onset of negative deflection (m/s)
Response Amplitude	Peak to peak (µV)
Temperature Compensation Method	Linear, 1.0 m/s per degree, maximum correction 5 m/s
Reference Temperature	28 °C

SYMBOLS



Attention/User Manual/device labeling



Type BF Applied Part



0123

Mark identifying compliance with council directive 93/42/EEC

Identification mark of the Notified Body, TUV SÜD

responsible for evaluation of the CE Technical File.



WEEE (Waste Electronic and Electrical Equipment) symbol in accordance with council directive 2002/96/EC

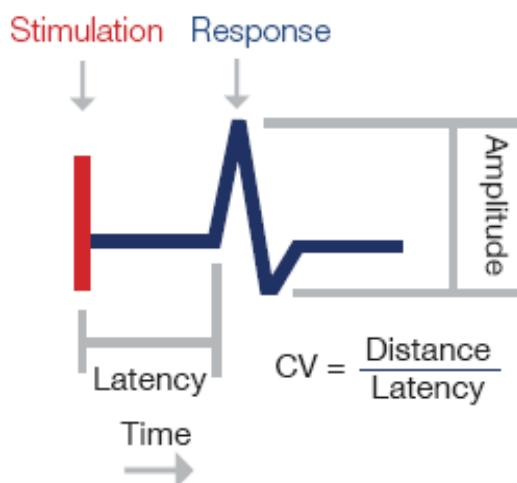
MN

Abbreviation for model number

SENSORY NERVE CONDUCTION PRINCIPLES & NERVE CONDUCTION TERMINOLOGY

Sensory Nerve Conduction Principles

Sensory nerve conduction measures function of large myelinated axons – light touch, proprioception, vibration, and pressure sensation



	CV	Amplitude
Axon Loss		↓
Axonal Atrophy	↓	↓
Demyelination	↓	

Nerve Conduction Terminology

Amplitude – size of nerve response (microvolts, μ V)

Conduction Velocity (CV) – speed of nerve response propagation (meters per second, m/s)

Latency – time between nerve stimulation and detection of response

Distance – propagation distance between site of nerve stimulation and response detection (9.22 cm)

Response – bioelectrical nerve response, typically $<50 \mu$ V

Stimulation – electrical stimulation of nerve, typically 20 – 60 millamps for 100 microseconds

Undetectable – nerve response amplitude is below the threshold of electronic detection, displayed as amplitude 0 μ V

USB CONNECTION

Uploading Data

The most recent test results may be uploaded to your PC using a USB cable. A mini-USB port is located on the side of the device. The device can only retain data from a single test. Users must upload the data after each test for report generation. Note: If the device powers off before performing an upload, the data is still saved on the device and may be uploaded.

1. Power on the device.
2. Open the USB port located on the side of the device.
3. Ensure that the Communicator application is open on the PC.
4. Connect the USB cable to the device and PC.
5. After connecting the device to the PC with the USB cable, the device LCD screen will display PC.
Note: If the red light on the device appears during this step, the data could not be transferred.
See Appendix F for Troubleshooting.

TEMPERATURE COMPENSATION

Nerve conduction measurements may be sensitive to the temperature around the nerve, which in superficially located nerves (e.g., sural), may be different than body temperature. Nerve temperature is usually approximated by the skin surface temperature overlying the nerve.

The NC-stat DPNCheck device compensates for the effect of temperature on sural nerve conduction velocity using a linear temperature compensation factor of 1 m/s per $^{\circ}\text{C}$ with a reference temperature of $28\text{ }^{\circ}\text{C}$. The effect of temperature on sural nerve conduction amplitude is small and therefore compensation is not applied for this parameter. The temperature is measured by an infrared thermometer, located at the base of the handle behind the stimulating probes.

If the temperature is below $23\text{ }^{\circ}\text{C}$, then the patient is too cold to reliably measure nerve conduction and the test will stop with  displayed on the LCD screen.

TROUBLESHOOTING

Display	Light	Description	Possible Causes	Solution
<i>Lb</i>		Data quality issue	• Incorrect limb setting on device.	1. Ensure that the limb setting on the device is correct. 2. If incorrect, re-select the limb on the device by pressing the button down for 1-2 seconds until correct limb is selected (l = left; r = right). 3. Retest.
<i>Pn</i>		Data quality issue	• Adequate signal could not be recorded.	1. Confirm placement and retest.
<i>Pr</i>		Stimulation issue	• Insufficient gel on probes. • Poor contact of probes with skin. • Inadequate skin preparation in probe contact area. • Probe movement during test. • Gel smeared between the probes.	1. Re-do skin preparation and device placement. • Clean probes and re-apply gel. • Vigorously scrub the ankle area. • Reposition the device on the patient with firm pressure to both probes and on biosensor. 2. Retest with constant force to limit device movement during test.
<i>Sn</i>		Biosensor disconnected during test	• Biosensor disconnected during test.	1. Re-insert biosensor with tail traces facing outward. • <u>Entire biosensor tail</u> must be inserted. 2. If problem persists, replace biosensor.
<i>Sn</i>		Data quality issue	• Biosensor backing not removed. • Incomplete biosensor contact. • Skin in biosensor contact area inadequately prepared.	1. Remove biosensor backing and retest. • Check for good contact on <u>both sides</u> of the foam. 2. If problem persists, re-prepare skin and replace with new biosensor. 3. Retest.
<i>Ec</i>		Data quality issue	• Signal contamination due to patient movement or excessive muscle contraction.	1. Confirm that the patient is relaxing leg muscles. 2. Reposition patient if necessary. 3. Retest.
<i>Ec</i>		Data quality issue	• Biosensor backing not removed.	1. Remove biosensor backing and retest.
<i>OC</i>		Patient ankle cold	• Temperature detector field of view obstructed. • Patient's ankle temperature <23°C.	1. Ensure that tester's hand does not obstruct temperature detector. 2. Warm patient's lower leg by: • putting a sock on and elevating the leg. - If unsuccessful: ◦ instruct the patient to put on their shoes and socks then walk around for 1-2 minutes if able. OR ◦ wrap the patient's lower leg and ankle with a blanket or heating pad. OR ◦ briskly rub the patient's lower ankle. (Note: Although it is not an ideal approach, this technique can be used if the tester is in a hurry.) 3. Retest.
<i>Lo</i>		Low battery	• Battery is low.	1. Replace battery.
<i>Hd</i>		Device hardware issue	• Device hardware issue.	1. Contact Customer Service.
<i>Ub</i>		Excessive biosensor reuse detected. Device is disabled	• Excessive biosensor reuse detected. • Excessive repeat testing.	1. Contact Customer Service.

MANUFACTURER'S DECLARATIONS OF CONFORMITY

(in accordance with ISO/IEC 17050-1 and ZLG 3.9 A 4)

MANUFACTURER

NeuroMetrix, Inc
62 Fourth Avenue
Waltham, MA 02451 USA

Object of the declaration: NC-stat DPNCheck

Catalog Number: NC-030, NC-DP1, NC-DP2

Under the sole responsibility of NeuroMetrix, Inc., the object(s) of the declaration described above is in conformity with the requirements of the following documents:

Medical Device Directive 93/42/EEC:
Annex II – NC-030
Annex VII – NC-DP1, NC-DP2

European Authorized Representative:

EMERGO Europe
Molenstraat 15
2513 BH, The Hague
The Netherlands

Notified Body:
(Annex II Products Only)
TÜV SÜD Product Service GmbH
Notified Body Number 0123
Zertifizierstelle
Ridlerstasse 65
80339 München
Germany

Date of First CE Marking: September 1, 2011 (NC-030, NC-DP1), September 11, 2012 (NC-DP2)

Signed for and on behalf of NeuroMetrix, Inc.

Rainer Maas
Director of QA/RA/Compliance
Waltham, MA 02451 USA

ELECTROMAGNETIC COMPATIBILITY DECLARATION

<p>NC-stat DPNCheck is intended for use in the electromagnetic environment specified below. The user should ensure that it is used in such an environment.</p>		
Emissions test	Compliance	Electromagnetic environment – guidance
RF emissions; CISPR 11	Group 1	NC-stat DPNCheck uses RF energy only for its internal function. Its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions; CISPR 11	Class B	NC-stat DPNCheck is suitable for use in all establishments, including domestic establishments and those directly connected to the public low voltage power supply network that supplies buildings used for domestic purposes.
Electrostatic Discharge Immunity (ESD); IEC 61000-4-2	±6kV contact; ±8kV air	Floors should be wood, concrete or ceramic tile.
Radiated RF; IEC 61000-4-3	3 V/m; 80 MHz to 2.5 GHz	3 V/m compliance level
Magnetic Fields; IEC61000-4-8	3 A/m	3 A/m compliance level



DPN-Check Normative Values; version 1. Date: 30th Aug 2017
IRAS ID: 170265

NC-stat® DPNCheck™ Normative Data: Collection, Analysis and Recommended Normal Limits

Introduction

A normal limit is a value below (or above) which a diagnostic test result is deemed abnormal. Nerve conduction normal limits depend on measurement variables including instrument specifications, electrode placement, and temperature compensation.¹ Best practices dictate use of normal limits developed from data obtained with identical methods to those used in clinical practice.¹

A study meeting recommended quality standards¹⁻³ was conducted to develop normal limit recommendations for clinicians using the NC-stat DPNCheck device. The first objective of this study was to obtain a large data base of sural nerve conduction responses, using the NC-stat DPNCheck device, in a population of normal non-neuropathic subjects. The second objective was to derive normal limits for the sural response amplitude and conduction velocity (CV).

Methods

This was a prospective study of a broad spectrum population. Potential study subjects were recruited, between August and October 2012, from communities in two US states (Massachusetts and Iowa) through advertising, referrals, testing days at technology and light manufacturing companies, and testing days at senior centers. Recruited subjects completed written informed consent and a clinical questionnaire. The questionnaire included demographics (gender, age, height, and weight), a medical history suggestive of peripheral neuropathy risk (e.g., previously diagnosed neuropathy, diabetes, cancer), and the Diabetic Neuropathy Symptom (DNS) score.⁴ The DNS score consists of 4 questions (see Table 1) and is a validated predictor of peripheral neuropathy. Inclusion criteria were age over 18 and no physical impediment to testing the sural nerve bilaterally. Exclusion criteria were any of the following (i) BMI > 35 kg/m², (ii) medical history positive for peripheral neuropathy, diabetes, renal failure, cancer, hypothyroidism, B12 deficiency, or alcoholism, and (iii) DNS score > 0.

Table 1. Diabetic Neuropathy Symptom (DNS) Questionnaire

1. Are you unsteady when you walk?
2. Do you have a burning, aching pain or tenderness at your legs or feet?
3. Do you have prickling sensations in your legs or feet?
4. Do you have places of numbness on your legs or feet?

Each question answered yes or no.

Score is the number of yes answers.

All subjects underwent bilateral sural nerve conduction testing. All nerve conduction tests were performed using the NC-stat DPNCheck device (Software Version 2.0). Two tests were performed on each limb for a total of 4 sural responses per subject. The sural nerve was stimulated, using stainless steel probes, just posterior to the lateral malleolous. The sural response was recorded 92.2 mm proximally at the calf with a pair of electrodes (25 mm length) in a bipolar configuration (20 mm center to center spacing). The nerve was stimulated supramaximally with averaging of 4-7 responses. The amplitude was measured peak to peak. An undetectable sural response was defined as amplitude less than 1.5 μ V and was displayed as 0 μ V. The CV was measured to the onset of the initial negative deflection. If the onset could not be reliably determined then CV was not reported. Skin temperature was monitored by an infra-red digital thermometer with CVs normalized to 28°C using a temperature correction factor of 1 m/s per °C. The NC-stat DPNCheck device displays amplitude and CV as rounded whole numbers (e.g., 6 μ V, 52 m/s) per recommended reporting precision.¹

The study data set was created by taking a single sural response (first test on left limb) from each subject in the study population. Amplitude and CV normal limits were defined as the lower 5th percentile. The use of the 5th percentile is based on the accepted practice of a 5% false-positive rate in statistical testing. This level has been adopted in several published nerve conduction normal

limit studies.^{1,6,7} Because the 5th percentile represents a specificity of 95%, the positive predictive value of an abnormal test will be high in patients with moderate pre-test probability of peripheral neuropathy. For example, in a typical diabetic population the pre-test probability is at least 50%⁸ and therefore the positive predictive value is greater than 90%, even if test sensitivity is relatively low.

The dependence of the normal limits on demographic variables (e.g., subject age, height) was evaluated using quantile regression.³ Using this method, the normal limit is expressed as a linear function of demographic variables:

$$\text{Normal Limit} = K + C_1 V_1 + C_2 V_2 + \dots + C_n V_n$$

where K is a constant, V_i is the i^{th} demographic variable, and C_i is the coefficient for the i^{th} demographic variable. Demographic variables that were statistically significant predictors ($p < 0.05$) of the normal limit were retained. The precision of the resulting normal limits was assessed by calculating both point estimates and 95% confidence intervals (95% CI) for representative demographics using the bootstrap method with 100,000 random samples. A precise normal limit has a narrow confidence interval, indicating the appropriateness of the nerve conduction and statistical methods.⁹

Results

A total of 856 subjects were recruited. Of these, 329 (38.4%) met the exclusion criteria leaving a study population of 527. Study subject characteristics are summarized in Table 2. The mean age was 48.3 years, with 21.8% of the subjects 65 years or older.

The amplitude normal limit was statistically dependent on subject age, decreasing by 0.99 (95% CI, 0.60 – 1.3) μV per decade. Figure 1 shows the relationship between age and amplitude. The green line is the age dependent normal limit. The CV normal limit was statistically dependent on subject age and height, decreasing 1.3 (95% CI, 1.0 – 1.7) m/s per decade and 2.0 (95% CI, 1.4 – 2.6) m/s per 10 cm, respectively. Figure 2 shows the relationship between height and CV. The two green lines

show the height dependent normal limits for subjects 45 (upper line) and 65 (lower line) years of age. Table 3 shows estimates of normal limits and confidence intervals for subjects aged 25, 45, and 65 years and height 172 cm.

Table 2. Study subject characteristics.

Characteristic	Mean (Stdev) or %
Gender (%Female)	51.2
Age (years)	48.3 (18.5)
Height (cm)	167 (11.5)
Weight (kg)	73.1 (16.8)
BMI (m/kg ²)	26.0 (4.09)
Amplitude (μV)	16.9 (8.62)
Conduction Velocity (m/s)*	53.0 (5.17)

*Conduction velocity available for 523 subjects

Table 3. Point estimates and confidence intervals for ages 25, 45 and 65 years.

Parameter	5 th Percentile Normal Limit (95% CI)		
	25 yrs	45 yrs	65 yrs
Amplitude (μV)	9 (8–10)	7 (6–8)	5 (4–6)
CV (m/s)	48 (47–49)	45 (45–46)	43 (42–44)

Two of the 527 (0.38%) study subjects had an undetectable sural response among their 4 tests. On this basis, an undetectable response was estimated to have specificity of over 99.5%. The two subjects had ages 58 and 67 years. Although they did not report any prospective exclusion criteria, one of the subjects had a partial foot amputation.

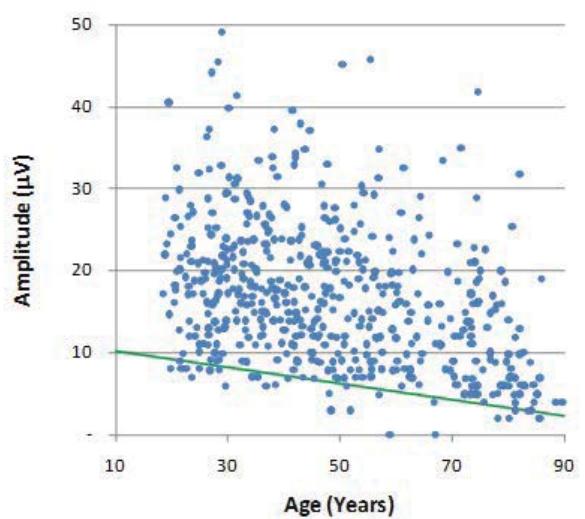


Figure 1. Relationship between subject age and sural nerve amplitude. Green line indicates recommended age dependent normal limit.

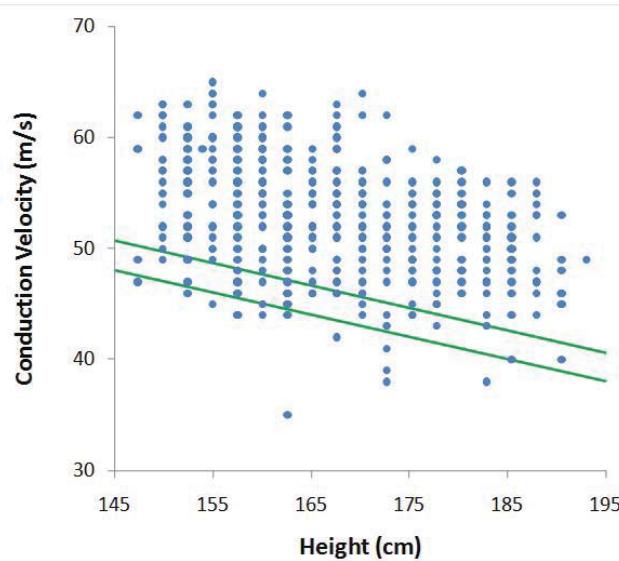


Figure 2. Relationship between subject height and sural nerve CV. Upper and lower green lines indicate recommended height dependent normal limit for subjects 45 and 65 years of age, respectively.

Discussion

The purpose of this study was to develop a large data base of NC-stat DPNCheck data in subjects without evidence of neuropathy and to use the data set to establish statistically robust normal limits. Sural amplitude was found to depend on subject age, declining about 1 μ V for every decade. This clinically significant amplitude reduction represents a 153 fibers/mm² reduction in sural nerve myelinated fiber density.¹⁰ Sural conduction velocity was dependent on both age and height, decreasing by 1.3 m/s for every decade and 2.0 m/s for every 10 cm of height.

The normal limit confidence intervals for both sural amplitude and CV were narrow, at about 1 μ V and 1 m/s respectively. These values support the validity of the nerve conduction and analysis methods used in the present study. These confidence intervals are narrower than prior reports of sural normal limits,^{6,7} reflecting the large sample size. Over 20% of the subjects in the present study were at least 65 years of age. The narrow confidence intervals in this age group and the low rate of undetectable responses suggest the recommended normal limits are reliable in elderly subjects.

Despite studies suggesting that nerve conduction normal limits vary with demographic variables,¹ it remains common practice to use fixed thresholds. The disadvantage of this approach is that diagnostic specificity will vary with the patient's age and potentially other demographic characteristics. The specificity may be very high in younger and short patients, but only modest in elderly and the very tall. For example, at a fixed normal limit of 5 μ V (i.e., amplitudes 4 μ V or less are labeled abnormal), the overall specificity in this study population is 96.6%, which is similar to the target specificity of 95%. However, the specificity varies with age. It is 100% for subjects < 45 years, 98.1% for subjects 45-64 years, and 87.0% for subjects \geq 65 years. By contrast, when using the recommended age dependent normal limits, the specificity is 94.6%, 96.1% and 93.0% for the three age groups.

A number of studies have reported sural normal limits.^{6,7,11-17} The sample size in the present study (N=527) is the largest among prospective studies meeting recommended quality standards for collection and analysis of normative data.^{1,2} Although comparisons of specific normal limit values must account for differences in methodology, relevant conclusions can be drawn from the general findings. In a widely referenced study, Stetson and colleagues¹³ reported sural normal limits in 105 subjects using ordinary linear regression and Gaussian transformation of nerve conduction parameters. They found that sural amplitude was related to gender, age and height and conduction velocity to height. The authors suggested calculation of sural normal limits as 2 standard deviations below the demographic adjusted mean. Although this parametric approach is common,^{1,11,12,17} it makes the generally incorrect assumption that amplitude and conduction velocity variance are independent of demographics.^{3,14} Benatar and colleagues⁷ reported sural normal limits, including the 5th percentile, in 190 subjects using quantile regression. Similar to the present study, they found that sural amplitude was related to age. In contrast to the present and other studies,^{11,13,14} they did not find a statistically and clinically significant relationship between conduction velocity and age or height. Esper and colleagues⁶ evaluated the relationship between the sural amplitude normal limit at the 5th percentile and age in 92 subjects using conventional percentiles¹ and the bootstrap method. They reported a dramatic drop in the normal limit with age, decreasing from 14.0 (95% CI, 10.4–19.0) μ V in subjects < 40 years to 3.2 μ V (95% CI, 2.1–5.6) in subjects \geq 60 years. Although the broad confidence intervals obscured the exact normal limits, the conclusion of a strong dependence of the amplitude normal limit on age was robust.

Recommendations

The values in Table 4 may be entered into the NC-stat DPNCheck Communicator™ software to implement the normal limits described above. These recommendations are provided for information purposes only and do not constitute medical advice. A decision to utilize this information must be made by an appropriately trained medical professional.

Table 4. Recommended Normal Limits.

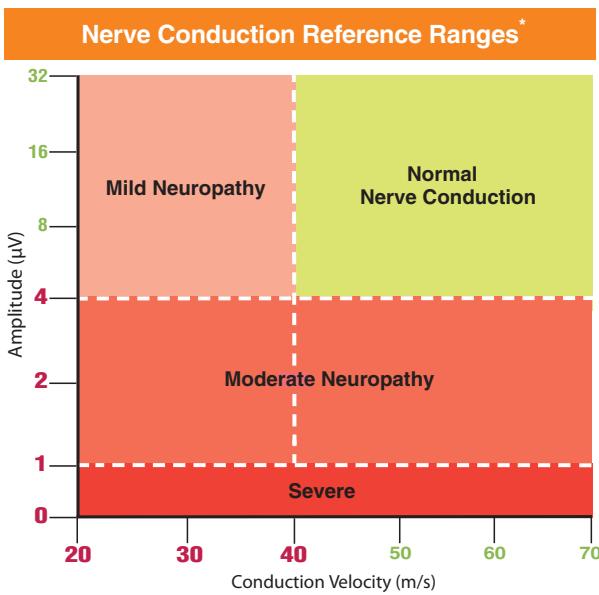
Parameter	Constant	Age Coefficient	Height Coefficient
Amplitude	11.2	-0.099	0
CV	88.5	-0.13	-0.20

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Sural Nerve Conduction Interpretation Guide

*This guide is for informational purposes only.
It does not provide a clinical diagnosis.*



DPN-Check reference Chart Version 1. Date 30th Aug 2017
IRAS ID: 170265

PERFORMING THE TBPI TEST

The TBPI measurement is performed with the patient resting in a supine position. The systolic blood pressure is determined in both arms, and the ankle systolic blood pressure is determined for the right and left posterior tibial (PT) and the dorsalis pedis (DP) arteries. The TBPI for each leg is determined by dividing the toe pressure by the higher of the two brachial readings. The lower TBPI of the two is used for diagnostic purposes.

ADAPTED TBPI PROCEDURE

THIS WAS ADAPTED TO HAVE THE PATIENT SITTING IN A CLINICAL TREATMENT CHAIR.

1. Have the patient lie in a sitting position with legs outstretched. Have the shoes and stockings removed for at least 10 minutes prior to obtaining blood pressure measurements.

2. Apply the blood pressure cuff snugly on the upper arm with the lower edge of the cuff 1 inch above the antecubital fossa. Usually the cuff that is the appropriate size for the patient's arm will also be suitable for the ankle pressure measurement. In the rare instance that upper arm and ankle pressures are markedly different, choose cuff sizes that are appropriate for each site.

3. Apply a 1–2 centimeter ribbon of Doppler gel to the antecubital area. Be sure to use enough gel.

Step 4. Turn the Doppler probe on and place it at the antecubital area at approximately a 60-degree angle to the surface of the skin. Move the probe around until the clearest arterial pulse sounds are heard and keep the probe at that position.

5. Inflate the blood pressure cuff to approx. 20 mm Hg above the numerical reading where the pulse sounds cease.

Step 6. Deflate the cuff at a rate of 2 mm Hg per second until the first arterial pulse sound is heard (Korotkoff sound). When this number is determined, deflate the cuff completely and record this systolic reading. Remove the gel from the patient's skin with a tissue.

Step 7. Repeat the procedure in the other arm and record reading

Step 8. Palpate the area around the medial malleolus to find the posterior tibial (PT) arterial pulse.

Step 9. Place the toe cuff around the base of the great toe. (Use the second toe if the great toe can't be used.)

Step 10. Palpate the pulse signal on the toe's distal pad area. Apply transmission gel to the pulse site.

Step 11. Place the tip of the Doppler probe onto the gel at a 45-degree angle to the skin surface. Direct the probe toward the patient's head to detect the pulse signal.

Step 12. Slowly inflate the toe cuff until the pulse signal is no longer heard (to a maximum of 200 mm Hg). A partial squeeze should adequately inflate the cuff.

Step 13. Slowly deflate the cuff until the pulse signal returns. The point where the pulse signal returns is the toe's systolic pressure.

Step 14. Remove the toe cuff. Use gauze pads to remove leftover gel from the patient's skin and from the Doppler probe. Gently clean the Doppler probe with a damp cloth.

Step 15. Repeat the procedure in the other foot and record reading

Step 16. Use the TBPI worksheet page to calculate the patient's Toe Brachial pressure index.

HELPFUL HINTS

- Follow the instructions specific to the Doppler probe you are using.
- Be sure to use enough gel.
- Use appropriate cuff size, the cuff width should be 20% larger than the limb diameter to compress all of the soft tissue evenly.
- Be sure you're centered on the pulse when you take the reading; if you're off to the side, the reading will be low.
- Ensure the patient has avoided tobacco and caffeine for 30 minutes before the procedure; both can increase blood pressure
- Patients with an TABI value of 0.64 or less are diagnosed as having LEAD (Lower extremity arterial Disease) and considered at increased risk for cardiovascular ischemic events. Prompt investigation and risk-reducing treatments are then warranted.

Toe Pressures/TBI: Selection of Equipment

- **DMX** Doppler with PPG sensor or **ATP** kit
- Toe Cuffs
- Sphyg
- Arm cuffs
- TBI Calculator
- Dopplex® **DR5** for documentation if required



HUNTEIGH

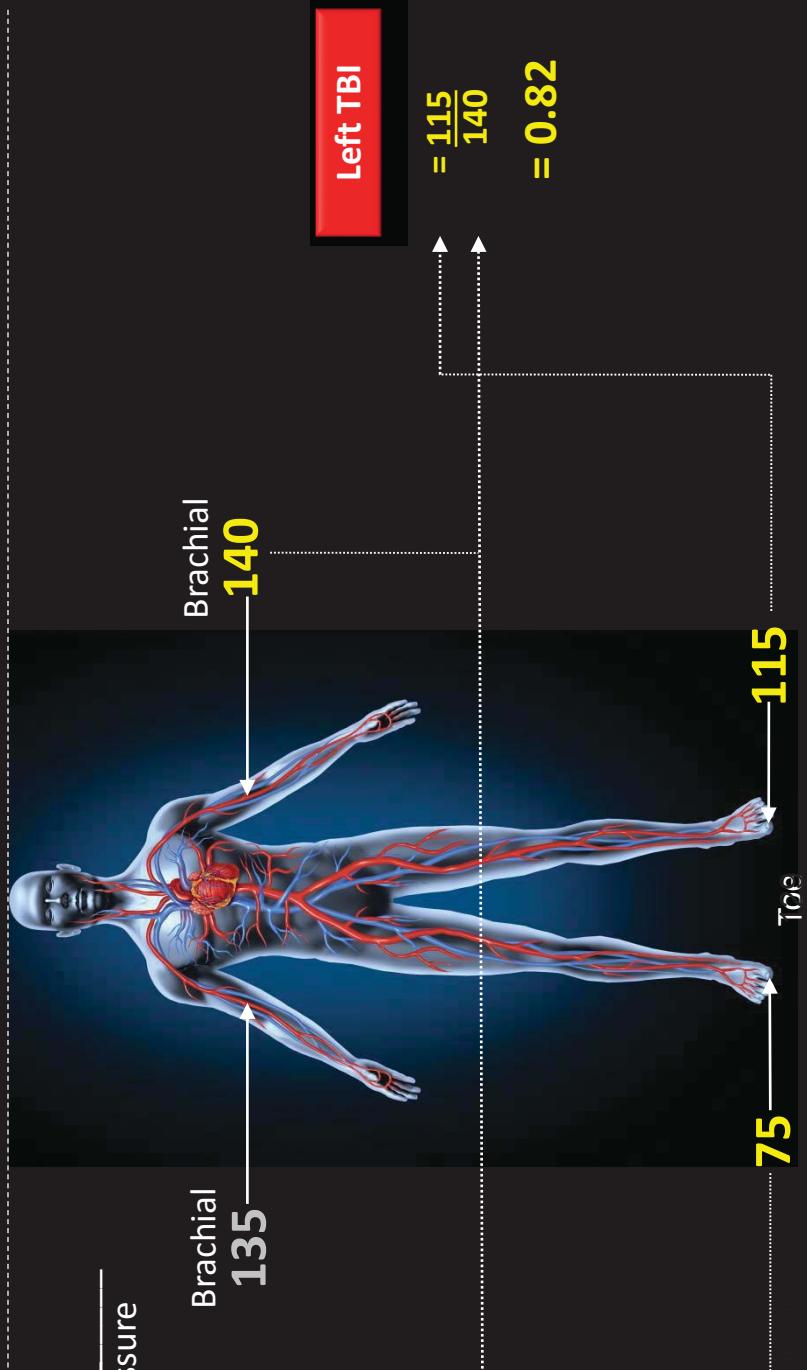


How to Calculate the TBI

TBI calculations

$$\frac{\text{Toe systolic pressure}}{\text{Highest brachial systolic pressure}}$$

HUNTEIGH



Foot Lesion Healing Prognosis

HUNTLIGH

TOE PRESSURE (mmHg)	PERCENTAGE PROBABILITY / TOE SYSTOLIC PRESSURE	DIABETIC	NON DIABETIC PATIENT
20-30	40%		73%
30-55		85%	100%
>55	97%		100%

(Carter, 1993)

If the TBI < 0.64 then PAD is present and compression is not recommended

Recent meta-analysis found that a cut-off value of 30mmHg was associated with 3.25 greater risk of non healing and amputation (Sonter *et al.*, 2014)

		Toe Pressure (mmHg)																																		
		30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190		
Brachial Pressure (mmHg)	230	.13	.15	.17	.20	.22	.24	.26	.28	.30	.33	.35	.37	.39	.41	.43	.46	.48	.50	.52	.54	.57	.59	.61	.63	.65	.67	.70	.72	.74	.76	.78	.80	.83	230	
	225	.13	.16	.18	.20	.22	.24	.27	.29	.31	.33	.36	.38	.40	.42	.44	.47	.49	.51	.53	.56	.58	.60	.62	.64	.67	.69	.71	.73	.76	.78	.80	.82	.84	225	
Brachial Pressure (mmHg)	220	.14	.16	.18	.20	.23	.25	.27	.30	.32	.34	.36	.39	.41	.43	.45	.48	.50	.52	.55	.57	.59	.61	.64	.66	.68	.70	.73	.75	.77	.80	.82	.84	.86	220	
	215	.14	.16	.19	.21	.23	.26	.28	.30	.33	.35	.37	.40	.42	.44	.47	.49	.51	.53	.56	.58	.60	.63	.65	.67	.70	.72	.74	.77	.79	.81	.84	.86	.88	215	
Brachial Pressure (mmHg)	210	.14	.17	.19	.21	.24	.26	.29	.31	.33	.36	.38	.40	.43	.45	.48	.50	.52	.55	.57	.60	.62	.64	.67	.69	.71	.74	.76	.79	.81	.83	.86	.88	.90	210	
	205	.15	.17	.20	.22	.24	.27	.29	.32	.34	.37	.39	.41	.44	.46	.49	.51	.54	.56	.59	.61	.63	.66	.68	.71	.73	.76	.78	.80	.83	.85	.88	.90	.93	.95	205
Brachial Pressure (mmHg)	200	.15	.18	.20	.23	.25	.28	.30	.33	.35	.38	.40	.43	.45	.48	.50	.53	.55	.58	.60	.63	.65	.68	.70	.73	.75	.78	.80	.83	.85	.88	.90	.93	.95	200	
	195	.15	.18	.21	.23	.26	.28	.31	.33	.36	.38	.41	.44	.46	.49	.51	.54	.56	.59	.62	.64	.67	.69	.72	.74	.77	.79	.82	.85	.87	.90	.92	.95	.97	.97	195
Brachial Pressure (mmHg)	190	.16	.18	.21	.24	.26	.29	.32	.34	.37	.39	.42	.45	.47	.50	.53	.55	.58	.61	.63	.66	.68	.71	.74	.76	.79	.82	.84	.87	.89	.92	.95	.97	.100	.101	190
	185	.16	.19	.22	.24	.27	.30	.32	.35	.38	.41	.43	.46	.49	.51	.54	.57	.59	.62	.65	.68	.70	.73	.76	.78	.81	.84	.86	.89	.92	.95	.97	.100	.103	.103	185
Brachial Pressure (mmHg)	180	.17	.19	.22	.25	.28	.31	.33	.36	.39	.42	.44	.47	.50	.53	.56	.58	.61	.64	.67	.69	.72	.75	.78	.81	.83	.86	.89	.92	.94	.97	.100	.105	.106	180	
	175	.17	.20	.23	.26	.29	.31	.34	.37	.40	.43	.46	.49	.51	.54	.57	.60	.63	.66	.69	.71	.74	.77	.80	.83	.86	.89	.91	.94	.97	.100	.103	.106	.109	.112	175
Brachial Pressure (mmHg)	170	.18	.21	.24	.26	.29	.32	.35	.38	.41	.44	.47	.50	.53	.56	.59	.62	.65	.68	.71	.74	.76	.79	.82	.85	.88	.91	.94	.97	.100	.103	.106	.109	.112	170	
	165	.18	.21	.24	.27	.30	.33	.36	.39	.42	.45	.48	.52	.55	.58	.61	.64	.67	.70	.73	.76	.79	.82	.85	.88	.91	.94	.97	.100	.103	.106	.109	.112	.115	165	
Brachial Pressure (mmHg)	160	.19	.22	.25	.28	.31	.34	.38	.41	.44	.47	.50	.53	.56	.59	.63	.66	.69	.72	.75	.78	.81	.84	.88	.91	.94	.97	.100	.103	.106	.109	.113	.116	.119	160	
	155	.19	.23	.26	.29	.32	.35	.39	.42	.45	.48	.52	.55	.58	.61	.65	.68	.71	.74	.77	.81	.84	.87	.90	.94	.97	.100	.103	.106	.110	.113	.117	.120	.123	.127	155
Brachial Pressure (mmHg)	150	.20	.23	.27	.30	.33	.37	.40	.43	.47	.50	.53	.57	.60	.63	.67	.70	.73	.77	.80	.83	.87	.90	.93	.97	.100	.103	.107	.110	.113	.117	.120	.123	.127	150	
	145	.21	.24	.28	.31	.34	.38	.41	.45	.48	.52	.55	.59	.62	.66	.69	.72	.76	.79	.83	.86	.90	.93	.97	.100	.103	.107	.110	.114	.117	.121	.124	.128	.131	145	
Brachial Pressure (mmHg)	140	.21	.25	.29	.32	.36	.39	.43	.46	.50	.54	.57	.61	.64	.68	.71	.75	.79	.82	.86	.89	.93	.96	.100	.104	.107	.111	.114	.118	.121	.125	.129	.132	.136	140	
	135	.22	.26	.30	.33	.37	.41	.44	.48	.52	.56	.59	.63	.67	.70	.74	.78	.81	.85	.89	.93	.96	1.00	.104	.107	.111	.115	.119	.122	.126	.130	.133	.137	.141	135	
Brachial Pressure (mmHg)	130	.23	.27	.31	.35	.38	.42	.46	.50	.54	.58	.62	.65	.69	.73	.77	.81	.85	.88	.92	.96	.100	.104	.108	.112	.116	.120	.124	.128	.131	.135	.138	.142	.146	130	
	125	.24	.28	.32	.36	40	.44	.48	.52	.56	.60	.64	.68	.72	.76	.80	.84	.88	.92	.96	.100	.104	.108	.112	.116	.120	.124	.128	.131	.136	.140	.144	.148	.152	125	
Brachial Pressure (mmHg)	120	.25	.29	.33	.38	.42	.46	.50	.54	.58	.63	.67	.71	.75	.79	.83	.88	.92	.96	.100	.104	.108	.113	.117	.121	.126	.130	.135	.139	.143	.148	.152	.157	.161	.165	120
	115	.26	.30	.35	.39	.43	.48	.52	.57	.61	.65	.70	.74	.78	.83	.87	.91	.95	.100	.104	.109	.113	.117	.121	.126	.130	.135	.140	.145	.151	.157	.161	.165	115		
Brachial Pressure (mmHg)	110	.27	.31	.36	.41	.45	.50	.55	.59	.64	.68	.73	.77	.82	.86	.91	.95	.100	.105	.110	.114	.118	.123	.127	.132	.136	.141	.145	.150	.155	.159	.164	.168	.173	110	
	105	.28	.33	.38	.43	.48	.52	.57	.62	.67	.71	.76	.81	.86	.90	.95	.100	.106	.110	.114	.119	.124	.129	.133	.138	.143	.148	.152	.157	.162	.167	.171	.176	.181	105	
Brachial Pressure (mmHg)	100	.30	.35	.40	.45	.50	.55	.60	.65	.70	.75	.80	.85	.90	.95	.100	.105	.110	.115	.120	.125	.130	.135	.140	.145	.150	.155	.160	.165	.170	.175	.180	.185	.190	100	
	95	.31	.37	.42	.47	.53	.58	.63	.68	.74	.79	.84	.89	.95	.100	.105	.111	.116	.121	.126	.132	.137	.142	.147	.153	.158	.163	.168	.174	.179	.184	.189	.195	.200	95	
Brachial Pressure (mmHg)	90	.33	.39	.44	.50	.56	.61	.67	.72	.78	.83	.89	.94	.100	.106	.111	.117	.122	.128	.133	.139	.144	.150	.156	.161	.167	.172	.178	.183	.189	.194	.202	.206	.211	90	

■ TBPI < 0.64 Abnormal indicating arterial disease

■ TBPI = 0.64 - 0.7 Borderline

TBPI > 0.7 Normal indicating no arterial disease

References: Carter SA. (1993) Role of pressure measurements in: Bernstein FF (ed) *Vascular Diagnosis*. Mosby, 486-512.

Patient must be rested and in supine position or ankles raised to same height as heart.

$$TBPI = \frac{\text{Toe systolic pressure (C)}}{\text{Highest brachial systolic pressure (A or B)}}$$



A Right Brachial



B Left Brachial



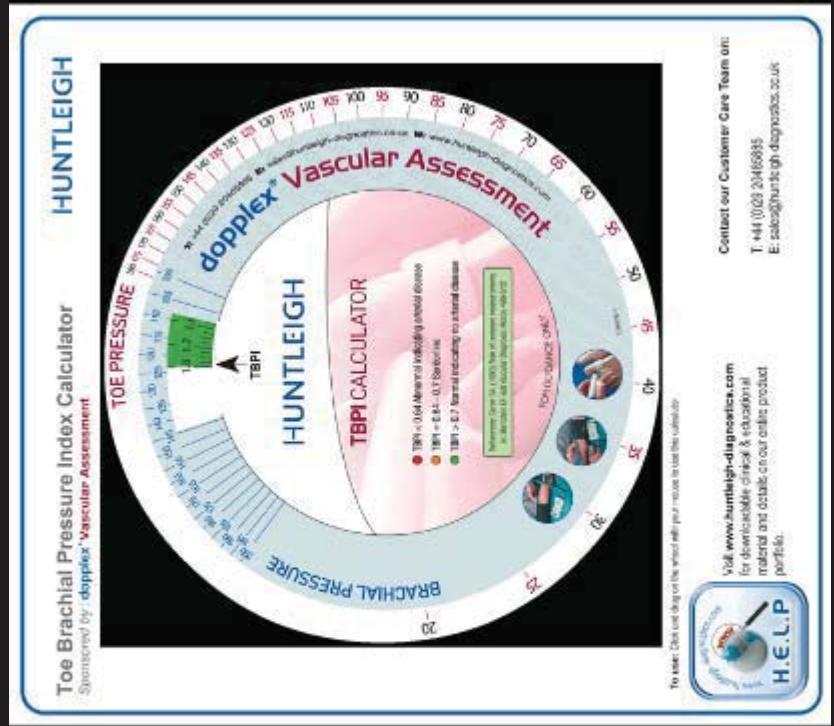
C Hallux

Relationship of systolic pressure to prognosis for healing of skin lesions of the toes or feet		
Absolute Toe pressure (mm Hg)	Probability of healing (%)	
	No diabetes	Diabetes
Below 20	25	29
20 to 30	73	40
30 to 55	100	85
Above 55	100	97

Toe Pressures

$$\frac{\text{Toe systolic pressure}}{\text{Highest brachial systolic pressure}} = \frac{75}{140}$$

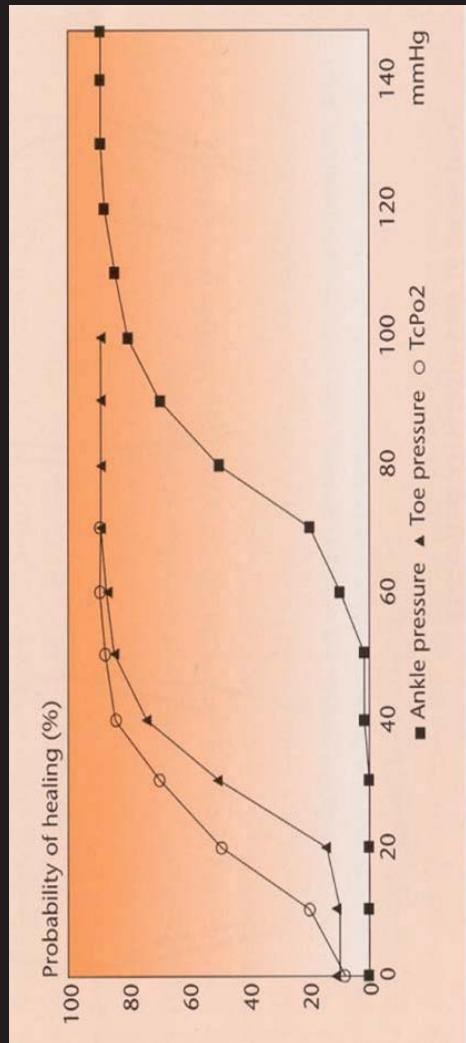
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132

Foot Lesion Healing Prognosis

HUNTLIGH



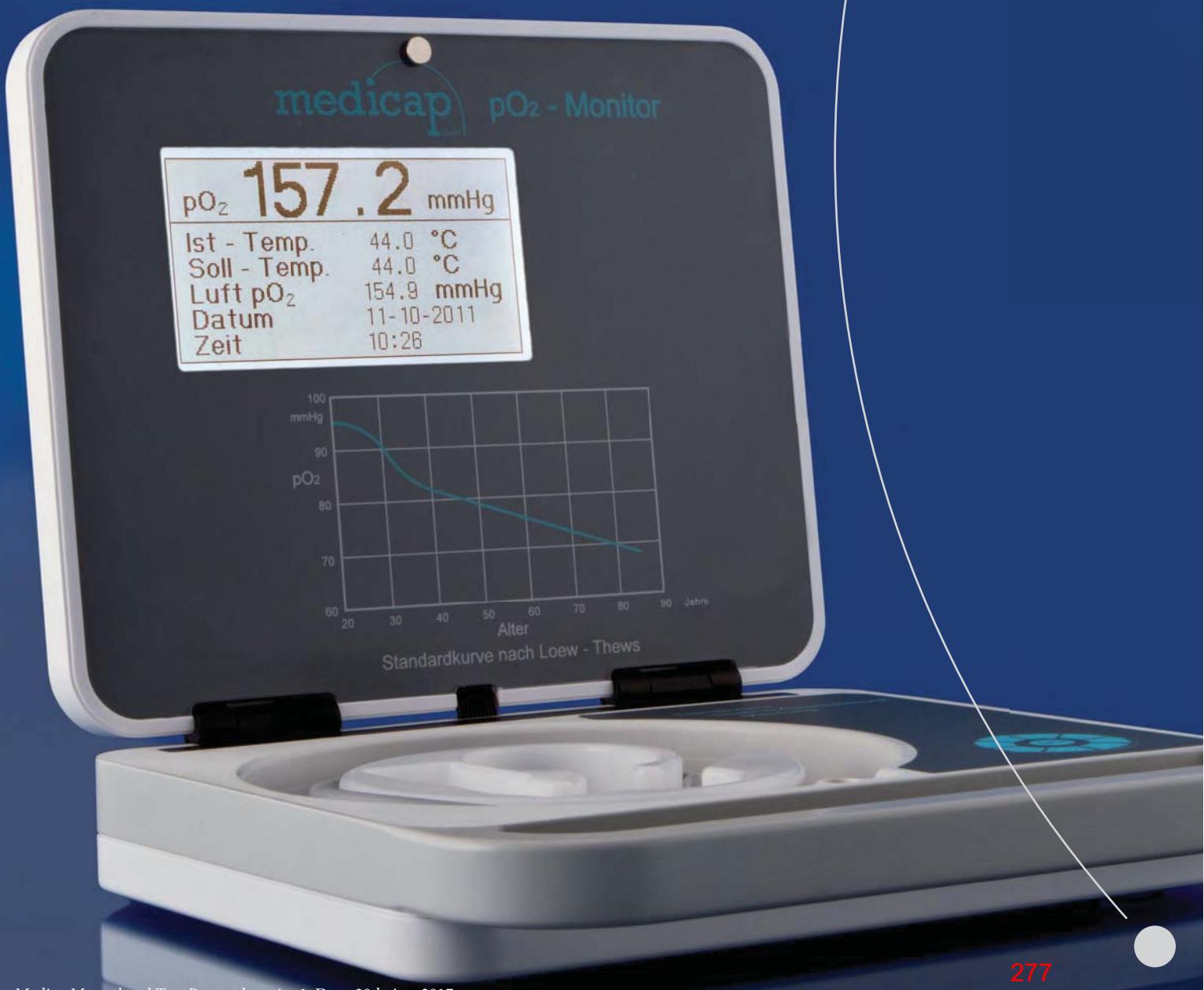
A schematic estimate of the probability of healing of foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure and transcutaneous oxygen pressure (TcPo2) based on selected reports

International Working Group on the Diabetic Foot (International Consensus) 1999



PRÉCISE 8001

*For the quick transcutaneous measurement
of oxygen partial pressure*



PRÉCISE 8001

The compact complete system – safe and precise

A solution

with many advantages – for successful application

FOR EVERYDAY USE

The Précise 8001 allows for quick and precise measurement of tcpO_2 . Due to the 2.5 m long sensor cable – equipped with integrated sensor – an enormous working radius is available. The large LCD display ensures all relevant data is easily read.

INNOVATIVE

The unbeatable advantage of applied sensor technology is that it does not wear. What is particularly user-friendly is the optical oxygen sensor, as it must not be pre-heated for the application.

TIME-SAVING

It couldn't be any easier – the additional cleaning of electrodes is no longer required due to the optical method of measurement. Furthermore, changing of the electrolyte and membrane is not necessary.

CLEVER SENSOR TECHNOLOGY

- Simple and quick measurement preparation
- Lower demand and consumption of measurement media
- No covering of the sensor with membrane
- No fiddly handling of electrolyte fluid
- No pre-heating necessary



FIVE STEPS
Switch on the device.
Easy to use due to the intuitive Touch Control panel.



Start the measurement. The measurement process will continuously update.
After approx. 8 minutes, the oxygen partial pressure can be read and saved.



AREAS OF APPLICATION

- Therapy control
- Efficacy screening
- Wound healing process
- Basic angiological diagnostics
- Confirmation of diagnosis and blood gas monitoring
- Venous insufficiency and ischémia
- Oxygen therapy
- Diabetes and arterial occlusive disease



SOPHISTICATED HARDWARE

- Innovative methods of measurement based on fluorescence
- Graphical representation of measurements on a large display
- Precise measurement, quick and easy
- Automatic adjustment to the atmospheric pressure
- Clean menu navigation and practical operation with Touch Control panel

Ideal and easy to use – the complete fixtures are integrated into the Précise 8001.

Mediap Manual and Test Protocol version 1, Date: 30th Aug 2017
IRAS ID: 170265

The Précise 8001 is no bigger than a laptop – handy and space-saving.

PRÉCISE 8001 Medicap® Test Protocol.

Procedure. (a) System preparation. Prior to arrival of participant, the Medicap, will be switched on, and outputs checked for normal behaviour and to confirm it is free from interference.

(b) Participant positioning. The study will be conducted with the participant sitting on a clinical chair or mattress with their back upright and with their feet and legs straightened (sitting L-shaped). This imitates the position patients would adopt in a usual clinical chair for treatment. The test foot will be rested on cushion if necessary ensuring the participant is comfortable.

(c) Probe positioning. The weight of the probe over bony prominences and large veins will affect the underlying microvasculature, and hence affect the reliability of the readings (Ballard et al. 1995). Therefore probe fixation site is limited to lie between the dorsal 1st and 2nd (Site A) inter-metatarsal spaces; as shown in Figure 2 below. The Medicap will be secured using sticky discs/fixation rings as described by the manufacturers.

Figure 2. Showing probe being dorsally fixated between the 1st and 2nd intermetatarsal space.



All cables will be aligned and anchored with tape.

(d) Readings. Participants will be instructed to sit quietly without talking throughout the study, and readings will be taken for 15 minutes. After this, the probe will be removed/detached along with the fixation ring and any excess contact fluid quickly blotted with paper. All attachments can then be removed and participants asked to sit up slowly and in their own time and will be free to leave.

(e) Time. For the Medicap readings only, the participant measurements are expected to take approximately 15 minutes.

REFERENCE VALUES

$>/= 50$ mm Hg = Normal

> 40 mmHg - 49 mmHg = Mild Ischaemia

>30 mmHg - 40 mmHg = Moderate Ischaemia

< 30 mmHg Severe Ischaemia / Critical Limb Ischaemia

de Meijer et al., (2008)

References.

Ballard, J. L., et al. (1995). "A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems." *J Vasc Surg* 22(4): 485-492.

de Meijer, V. E., et al. (2008). "Reference value of transcutaneous oxygen measurement in diabetic patients compared with nondiabetic patients." *J Vasc Surg* 48(2): 382-388.

Appendix A5 - Ethical Approval for Experimental Study 1

DPNCheck reliability in healthy participants

ERGO II

Ethics and Research Governance Online

29998 - Exploring The Reliability and Validity of the Neurothesiometer in Detecting Vibration Perception in the Feet of Healthy Individuals

Details

Status

Approved

Category

Category 

The end date for this study is currently 30 March 2018

To apply for an extension please click here (</ExtensionReq/ViewCreate?submissionId=29998&showSubmissionLink=False>)

If you are making any other changes to your study please create an amendment using the button below.

Amendment History

 **Original Submission 29998** (Created 03/08/2017)

User Uploaded Documents

Title**Document Type****Original File name**

Current Version

Simba Tanyanyiwa

Subject: FW: Your Ethics Submission (Ethics ID:29998) has been reviewed and approved
Attachments: 4 SCREENING QNNAIRE.PDF; 5 PROTOCOL.PDF; 6 Appendices .pdf; 1 PIS.PDF; 2 CONSENT FORM.PDF; 3 POSTER.PDF

From: ERGO [ergo@soton.ac.uk]
Sent: 19 October 2017 08:31
To: McCormick K.G.
Subject: Your Ethics Submission (Ethics ID:29998) has been reviewed and approved

Submission Number: 29998

Submission Name: Exploring The Reliability and Validity of the Neurothesiometer in Detecting Vibration Perception in the Feet of Healthy Individuals

This email is to let you know your submission was approved by the Ethics Committee.

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment)

Comments

None

[Click here to view your submission](#)

Coordinator: Keith McCormick

ERGO : Ethics and Research Governance Online

<http://www.ergo.soton.ac.uk>

DO NOT REPLY TO THIS EMAIL

APPENDIX A6: Ethical Approval for Medicap Validity against the TCM400 on Healthy and Low Risk Participants

From: [Worsley P.R.](#)
To: [Voegeli D.](#); [Tanyanyiwa S.R.](#)
Subject: FW: Your Ethics Amendment (Ethics ID:17598) has been reviewed and approved
Date: 28 September 2015 11:00:52

FYI

From: ERGO [mailto:ergo@soton.ac.uk]
Sent: 28 September 2015 10:56
To: Worsley P.R.
Subject: Your Ethics Amendment (Ethics ID:17598) has been reviewed and approved

Submission Number 17598:

This email is to confirm that the amendment request to your ethics form (Evaluating the performance of an immersion mattress in terms of tissue viability of participants lying in supine: effects of posture and immersion. (Amendment 1)) has been approved by the Ethics Committee.

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment)

Comments

1. Thank you for your request for approval of an amendment to the study, and for the clarity with which the proposed amendments are presented. I am happy to approve the amendment and wish you every success in the study.

[Click here to view your submission](#)

ERGO : Ethics and Research Governance Online
<http://www.ergo.soton.ac.uk>

DO NOT REPLY TO THIS EMAIL

APPENDIX A7: Ethical Approval for the Reliability of the TBI in healthy Participants

Author: McCormick K.G.

Author email: K.G.McCormick@soton.ac.uk

Subject: FW: Approved by Faculty Ethics Committee - ERGO II 45964.A1

Sent datetime: 12/06/2018 14:43:54

From: ERGOII <ERGOII@soton.ac.uk>

Sent: 06 December 2018 14:35

To: McCormick K.G. <K.G.McCormick@soton.ac.uk>

Subject: Approved by Faculty Ethics Committee - ERGO II 45964.A1

Approved by Faculty Ethics Committee - ERGO II 45964.A1



ERGO II – Ethics and Research Governance Online

<https://www.ergo2.soton.ac.uk>

Submission ID: 45964.A1

Submission Title: A study to investigate the reliability and validity of peripheral neurovascular assessments in healthy individuals (Amendment 1)

Submitter Name: Keith McCormick

Your submission has now been approved by the Faculty Ethics Committee. You can begin your research unless you are still awaiting any other reviews or conditions of your approval.

Comments:

- Approved

[Click here to view the submission](#)

TId: 23011_Email_to_submitter_Approval_from_Faculty_Ethics_committee_cat_B_C_Id: 97479

K.G.McCormick@soton.ac.uk coordinator

Please do not reply to this message as it has been automatically generated by the system. This email address is not monitored.

SERVICE LINE - THE IT SERVICE DESK FOR THE UNIVERSITY OF SOUTHAMPTON

APPENDIX A8: ERGO for Chapters 5.5; 6; 7 and 8 in Type 2 Diabetes

Author: ERGO

Author email: ergo@soton.ac.uk

Subject: Research Governance Feedback on your Ethics Submission (Ethics ID:13474)

Sent datetime: 11/02/2017 14:35:51

Submission Number 13474:

Submission Title Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community:
The Research Governance Office has reviewed and approved your submission

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment) or external ethics review (e.g. NRES). The following comments have been made:

"

I am writing to confirm that the University of Southampton is prepared to act as Research Sponsor for this study under the terms of the Department of Health Research Governance Framework for Health and Social Care (2nd edition 2005). We encourage you to become fully conversant with the terms of the Research Governance Framework by referring to the Department of Health document which can be accessed at:

<http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Public>

If your study has been designated a Clinical Trial of an Investigational Medicinal Product, I would like to take this opportunity to remind you of your responsibilities under Medicines for Human Use Act regulations (2004/2006), The Human Medicines Regulations (2012) and EU Directive 2010/84/EU regarding pharmacovigilance. If your study has been designated a 'Clinical Investigation of a Medical Device' you also need to be aware of the regulations regarding conduct of this work.

Further guidance can be found:

<http://www.mhra.gov.uk/>

The University of Southampton fulfils the role of Research Sponsor in ensuring management, monitoring and reporting arrangements for research. I understand that you will be acting as the Principal Investigator responsible for the daily management for this study, and that you will be providing regular reports on the progress of the study to the Research Governance Office on this basis.

Please also familiarise yourself with the Terms and Conditions of Sponsorship on our website, including reporting requirements of any Adverse Events to the Research Governance Office and the hosting organisation.

If your project involves NHS patients or resources please send us a copy of your NHS REC and Trust approval letters when available. Please also be reminded that you may need a Research Passport to apply for an honorary research contract of employment from the hosting NHS Trust. Both our Terms and Conditions of Sponsorship and information about the Research Passport can be found on our website:

<http://www.soton.ac.uk/corporateservices/rgo>

Failure to comply with our Terms may invalidate your ethics approval and therefore the insurance agreement, affect funding and/or Sponsorship of your study; your study may need to be suspended and disciplinary proceedings may ensue.

Please do not hesitate to contact this office should you require any additional information or support. May I also take this opportunity to wish you every success with your research.

Submission ID : 13474

Submission Name: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community

Date : 02 Nov 2017

Created by : Simbarashe Tanyanyiwa

Coordinator: Simbarashe Tanyanyiwa

ERGO : Ethics and Research Governance Online
<http://www.ergo.soton.ac.uk>

DO NOT REPLY TO THIS EMAIL

In Type 2 Diabetes Participants

- **Chapter 5.5 - all devices reliability**
- **Chapter 6 - DPNCheck effectiveness against 10g MNFt**
- **Chapter 7 - Medicap effectiveness against TBI**
- **Chapter 8: Overall effectiveness of DPNCheck + Medicap against 10gMNF + TBI**

ERGO II

Ethics and Research Governance Online

13474 - Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community

Details

Status

Approved

Category

Category A

The end date for this study is currently 28 February 2019

To apply for an extension please click here (</ExtensionReq/ViewCreate?submissionId=13474&showSubmissionLink=False>)

If you are making any other changes to your study please create an amendment using the button below.

Amendment History

 **Original Submission 13474** (Created 06/01/2015)

User Uploaded Documents

Title**Document Type****Original File name**

Current Version

APPENDIX A9: RESEARCH ETHICS COMMITTEE APPROVAL FOR THE MAIN INVESTIGATIONS



London - Westminster Research Ethics Committee

4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8004

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

01 December 2017

Mr Simbarashe Richard Tanyanyiwa
Innovation and Leadership in Health Sciences
Faculty of Health Sciences
University of Southampton,
University Road
Southampton
SO17 1BJ

Dear Mr Tanyanyiwa,

Study title: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community
REC reference: 17/LO/2033
IRAS project ID: 170265

The Proportionate Review Sub-committee of the London - Westminster Research Ethics Committee reviewed the above application on 21 November 2017.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Favourable opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Please revise page one of the Participant Information Sheet to include the following sentence 'please note that we are unable to reimburse your travel expenses after two visits' This should be included after 'funded by the Wessex Clinical Academic Training Scheme'.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

Informed consent process and the adequacy and completeness of participant information

The Sub-Committee was concerned about the information management for the study given you said the data would be anonymised but also that they wished to compare data between the two visits. The Sub-Committee asked, via email, how this would be managed.

You responded stating there would be linked anonymity as each participant would be allocated a study number. This would allow the data from the two meetings to be compared.

The Sub-Committee was unclear whether the machines would be tested at an additional visit or at a routine visit. If there would be an additional visit, the Sub-Committee wished to know whether travel expenses would be reimbursed or not. The Participant Information Sheet would need to be revised to state whether or not travel expenses would be reimbursed.

You responded that the machines would be tested at an additional visit. Travel expenses would not be reimbursed due to limited funding.

In the Participant Information Sheet section 'Would my taking part in this study be kept confidential?' it stated "images taken by an unlinked digital camera" The Sub-Committee did not know what an unlinked digital camera was and requested an explanation. The explanation would also need to appear in the Participant Information Sheet.

You explained that an unlinked digital camera was a camera that had no other external connectivity apart from an SD card and USB cable for image transfer. An explanation has been given on page

8 of the Participant Information Sheet. Many cameras came as part of mobile phones, and had automated, location, wifi and social media transfer capabilities, which could be difficult to control and therefore carried data protection implications. An unlinked digital camera minimised that risk.

The Committee also requested that the Participant Information Sheet be revised to state that the study was part of a PhD project and to say who was funding the study.

The participant Information Sheet was updated on page 1 to show source of funding and clarify that this is a PhD project.

The Sub-Committee noted that the revised Participant Information Sheet did not say that travel expenses would not be reimbursed and requested this be corrected.

Approved documents

The documents reviewed and approved were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Poster]	1	30 August 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of Southampton Insurance Letter v1]	1	24 July 2017
GP/consultant information sheets or letters [GP Letter]	1	30 August 2017
Instructions for use of medical device [Device Use Instructionsv1]	1	30 August 2017
IRAS Application Form [IRAS_Form_07112017]		07 November 2017
Letter from statistician [Statistician letter]	1	30 August 2017
Letters of invitation to participant [PIS]	1	30 August 2017
Other [supervosr2CVv1]	1	30 August 2017
Other [List of Appendices]	2	20 November 2017
Other [Response to committee's request]		24 November 2017
Participant consent form [Consent Form]	1	30 August 2017
Participant information sheet (PIS)	3	24 November 2017
Referee's report or other scientific critique report [Internal and External Peer Review]	1	30 August 2017
Research protocol or project proposal	2	20 November 2017
Summary CV for Chief Investigator (CI) [SRTshort CV]	1	30 August 2017
Summary CV for supervisor (student research) [Catherine Jane Bowen]	1	30 August 2017
Summary CV for supervisor (student research) [CV Keith G McCormick]		

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research

Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
<http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

17/LO/2033

Please quote this number on all correspondence

Yours sincerely

**PP Mr Robert Goldstein
Chair**

Email: nrescommittee.london-westminster@nhs.net

Enclosures: List of names and professions of members who took part in the review

“After ethical review – guidance for researchers”

Copy to: Ms Diana Galpin, University of Southampton
Ms Catherine Lea, Solent NHS Trust

London - Westminster Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 21 November 2017

Committee Members:

Name	Profession	Present	Notes
Mr Robert Goldstein	Chair - Economist	Yes	Committee Chair
Dr Erika Kennington	Research Funder	Yes	
Mr Michael Puntis	Vice-Chair - ICU Anaesthetist	Yes	

Also in attendance:

Name	Position (or reason for attending)
Ms Laila Sarwar	REC Assistant

Mr Simbarashe Richard Tanyanyiwa
PhD student. University of Southampton and Solent NHS
Trust
Solent NHS Trust, and the University of Southampton
Innovation and Leadership in Health Sciences
Faculty of Health Sciences
University of Southampton, University Road, Southampton
SO17 1BJ

Email: hra.approval@nhs.net

04 December 2017

Dear Mr Tanyanyiwa

Letter of HRA Approval

Study title:	Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community
IRAS project ID:	170265
REC reference:	17/LO/2033
Sponsor	University of Southampton

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.

- Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the [HRA website](#).

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document “*After Ethical Review – guidance for sponsors and investigators*”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the [HRA website](#), and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the [HRA website](#).

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through [IRAS](#).

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the [HRA website](#).

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the [HRA website](#).

Your IRAS project ID is **170265**. Please quote this on all correspondence.

Yours sincerely

Rekha Keshvara
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Diana Galpin, University of Southampton (Sponsor contact)*
Ms Catherine Lea, Solent NHS Trust (R&D contact)

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Contract/Study Agreement template [Model agreement]	1	11 October 2017
Copies of advertisement materials for research participants [Poster]	1	30 August 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [University of Southampton Insurance Letter v1]	1	24 July 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		24 July 2017
GP/consultant information sheets or letters [GP Letter]	1	30 August 2017
HRA Schedule of Events [SoE GP Practice]	1	21 November 2017
HRA Schedule of Events	1	01 December 2017
HRA Statement of Activities	1	04 December 2017
HRA Statement of Activities [SoA GP Practice]	1	21 November 2017
Instructions for use of medical device [Device Use Instructionsv1]	1	30 August 2017
IRAS Application Form [IRAS_Form_07112017]		07 November 2017
Letter from statistician [Statistician letter]	1	30 August 2017
Other [supervosr2CVv1]	1	30 August 2017
Other [List of Appendices]	2	20 November 2017
Other [Response to committee's request]		24 November 2017
Participant consent form [Consent Form]	1	30 August 2017
Participant information sheet (PIS) [PIS]	4	01 December 2017
Referee's report or other scientific critique report [Internal and External Peer Review]	1	30 August 2017
Research protocol or project proposal	2	20 November 2017
Summary CV for Chief Investigator (CI) [SRTshort CV]	1	30 August 2017
Summary CV for supervisor (student research) [CV Keith G McCormick]		
Summary CV for supervisor (student research) [Catherine Jane Bowen]	1	30 August 2017

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, participating NHS organisations, capacity and capability and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Ms Diana Galpin
 Email: rgoinfo@soton.ac.uk
 Tel: 02380595058

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	Modified mNCA will act as the agreement of an NHS organisation to participate. The agreement was modified at the request of the University of Southampton to meet their indemnity and insurance requirements.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	As per the Statement of Activities, there are no funds being provided to the participating sites by the sponsor.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There are two site types:

1. The main research site will carry out all study activities as highlighted in IRAS A18 and A19
2. The single GP surgery will carry out study invitation mail out and poster display

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

The HRA has determined that the main research site **will be expected to formally confirm their capacity and capability to host this research**.

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capability will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The [Assessing, Arranging, and Confirming](#) document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Sites acting as PICs in England **are not expected to formally confirm their capacity and capability to host this research**, because the study activities is limited to sending out study invitation letters and/or poster display.

- The HRA has informed the relevant research management offices that you intend to undertake the research at their organisation. However, you should still support and liaise with these organisations as necessary.
- Following issue of the HRA Approval letter, and subject to the two conditions below, it is expected that these organisations will become participating NHS organisations 35 days after issue of this Letter of HRA Approval (no later than **08/01/2018**):
 - You may not include the NHS organisation if they provide justification to the sponsor

and the HRA as to why the organisation cannot participate

- You may not include the NHS organisation if they request additional time to confirm, until they notify you that the considerations have been satisfactorily completed..
- You may include NHS organisations in this study in advance of the deadline above where the organisation confirms by email to the CI and sponsor that the research may proceed.
- The document “[Collaborative working between sponsors and NHS organisations in England for HRA Approval studies, where no formal confirmation of capacity and capability is expected](#)” provides further information for the sponsor and NHS organisations on working with NHS organisations in England where no formal confirmation of capacity and capability is expectations, and the processes involved in adding new organisations. Further study specific details are provided the *Participating NHS Organisations and Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections of this Appendix.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A Principal Investigator is expected to be in place at the main research sites and a Local Collaborator is expected at the GP surgery.

GCP training is not a generic training expectation, in line with the [HRA/MHRA statement on training expectations](#).

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

The main research site: Use of identifiable patient records held by an NHS organisation to identify potential participants should be undertaken by a member of the direct care team for the patient, so it would not normally be acceptable for this to be done by staff not employed by that organisation. An Honorary Research Contract (or equivalent) would be expected for any external NHS/research staff undertaking all of the other activities for the study once consent from the participant is in place. The pre-engagement checks should include an enhanced DBS check (including a check against the DBS ‘barred list’ for adults), and Occupational Health Clearance.

For PICs: Patient identification and mail out will be carried out by the participants’ direct care team and no other research activity will take place at these participating sites. Therefore, no Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating sites.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in

England to aid study set-up.

- The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.



Arthur J. Gallagher

24th July 2017

TO WHOM IT MAY CONCERN

We, the undersigned Insurance Brokers hereby certify that we have place the following Insurance:

VERIFICATION OF INSURANCE

Unique Market Reference: B1262FI0671217

Type: Clinical Trials Insurance, Professional Indemnity and Medical Malpractice

Insured: University of Southampton and/or University of Southampton Holdings and/or Subsidiary Companies

Period: From: 01st August 2017 To: 31st July 2018 Both days inclusive at Local Standard Time.

Interest: This Policy will indemnify/cover the Insured in respect of their Legal Liabilities arising out of the Insured's activities and as more fully disclosed within the Policy Wording.

Limit of Indemnity: GBP 20,000,000 Any One Claim and GBP 20,000,000 in the Aggregate, including costs and expenses
GBP 10,000,000 Any One Claim and GBP 10,000,000 in the Aggregate, including costs and expenses for Medical Malpractice

Excess: GBP 12,500 Each and Every Claim, including costs and expenses
GBP 5,000 Each and Every Claim, including costs and expenses for Medical Malpractice

Territorial Limits: Worldwide including USA and Canada
Worldwide Excluding USA and Canada for Medical Malpractice

Underwriter: 50.0000% Newline Syndicate 1218
50.0000% NVA Syndicate 2007

This document is for information only and does not make the person or organisation to whom it is issued an additional Insured, nor does it modify in any manner the Contract of Insurance between the Insured and the Insurers. Any amendment, change or extension to such Contract can only be affected by specific endorsement attached thereto.

Should the above mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such manner as to affect this document, no obligation to inform the holder of this document is accepted by the undersigned or by the Insurers. The information provided is correct at the date of signature.

Authorised Signatory
Arthur J Gallagher.



Gallagher

Insurance | Risk Management | Consulting

18th July 2019

TO WHOM IT MAY CONCERN

We, the undersigned Insurance Brokers, hereby certify that the following described insurance:

VERIFICATION OF INSURANCE

Unique Market Reference: B1262 FI0671219

Type: Legal Liability and No Fault Compensation for Human Clinical Trials

Insured: University of Southampton

Period: From: 1st August 2019
To: 31st July 2020 Both days inclusive at Local Standard Time.

Interest: This Policy will indemnify/Cover the insured in respect of their Legal Liabilities arising out of the Insured's activities and as more fully disclosed within the Policy Wording.

Limit of Indemnity: GBP 20,000,000 Any One Claim and GBP 20,000,000 in the Aggregate, including costs and expenses

Excess: GBP 12,500 Each and Every Claim, other than United States of America Jurisdiction where USD 25,000 each and every Claim shall apply

Underwriter: 50.0000% Newline Syndicate 1218
50.0000% Axis Managing Agency Ltd

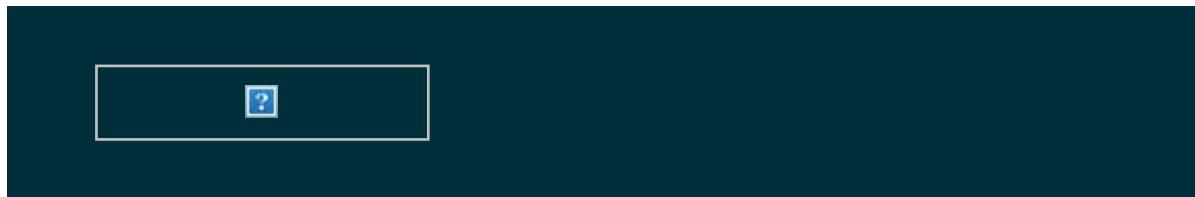
This document is for information only and does not make the person or organisation to whom it is issued an additional Insured, nor does it modify in any manner the Contract of Insurance between the Insured and the Insurers. Any amendment, change or extension to such Contract can only be affected by specific endorsement attached thereto.

Should the above mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such manners as to affect this document, no obligation to inform the holder of this document is accepted by the undersigned or by the Insurers. The information provided is correct at the date of signature.

Authorised Signatory
Arthur J Gallagher

From: ERGOII
To: Tanyanyiwa S.R.
Subject: Study extension request approved - ERGO II 13474
Date: 11 February 2019 13:14:25

Study extension request approved - ERGO II 13474



ERGO II – Ethics and Research Governance Online <https://www.ergo2.soton.ac.uk>

Submission ID: 13474

Submission Title: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community

Submitter Name: Simba Tanyanyiwa

This email is to let you know that the extension request to your research has been approved.

This extension has been approved providing there are no other changes arising from the extension, such as changes to the protocol, sample size or researchers. If there are any additional changes please submit an amendment.

If your study has NHS ethics approvals in place then please ensure the REC are informed as well as all other parties from whom you have received permissions for your study.

If this is a student project, please note that this extension relates to the research itself, but does NOT alter deadlines for submission of your dissertation or thesis. Separate arrangements are in place to request an extension for submission of the dissertation and these can be found in your Handbook or by asking your supervisor.

TId: 23020_Email_to_submitter_confirming_study_extension_request_approval Id: 111035

S.R.Tanyanyiwa@soton.ac.uk coordinator

APPENDIX A13: REC Approval for additional study site: North Manchester General Hospital

Author: nrescommittee.london-westminster@nhs.net

Author email: noreply@harp.org.uk

Subject: IRAS PROJECT ID 170265, REC Reference 17/LO/2033 : Amendment acknowledgement and implementation information

Sent datetime: 07/16/2019 12:21:20

New Site Amendment, Implementation Information

Dear Mr Tanyanyiwa

IRAS Project ID:	170265
Short Study Title:	Objective neurovascular monitoring in feet of Type 2 diabetes patients
Date complete amendment submission received:	19 June 2019
Sponsor Amendment Reference Number:	ERGO 13474 19/06/19
Sponsor Amendment Date:	19 June 2019
Amendment Type:	Non-substantial
For new sites in Northern Ireland and/or Scotland:	Please start to set up your new sites. Sites may not open until NHS management permission is in place.
For new sites in England and/or Wales:	<p><u>For studies which already have HRA and HCRW Approval: This email also constitutes HRA and HCRW Approval for the amendment, and you should not expect anything further.</u> Please start to set up your new sites. Sites may not open until the site has confirmed capacity and capability (where applicable).</p> <p><u>For studies which do not yet have HRA and HCRW Approval: HRA and HCRW Approval for the initial application is pending.</u> You can start the process of setting up the new site but cannot open the study at the site until HRA and HCRW Approval is in place and the site has confirmed capacity and capability (where applicable).</p> <p><u>For studies with HRA Approval adding Welsh NHS organisations for the first time.</u> Please take this email to confirm your original HRA Approval letter is now extended to cover NHS organisations in Wales. You now have HRA and HCRW Approval. Please start to set up your new sites. Sites may not open until the site has confirmed capacity and capability (where applicable).</p>

Thank you for submitting an amendment to add one or more new sites to your project. This amendment relates solely to the addition of **new sites**.

What should I do next?

Please set up the new site(s) as per the guidance found within [IRAS](#). **Please note** that processes change from time to time so please use the most up to date guidance about site set up.

If your study is supported by a research network, please contact the network as early as possible to help support set up of the new site(s).

If you have listed new sites in any other UK nations **we will** forward the information to the national coordinating function(s) for nations where the new site(s) are being added. In Northern Ireland and Scotland, NHS/HSC R&D offices will be informed by the national coordinating function.

Note: you may only implement changes described in the amendment notice.

Who should I contact if I have further questions about this amendment?

If you have any questions about this amendment please contact the relevant national coordinating centre for advice:

- England - hra.amendments@nhs.net
- Northern Ireland - research.gateway@hscni.net
- Scotland - nhsgo.NRSPCC@nhs.net
- Wales - HCRW.amendments@wales.nhs.uk

Additional information on the management of amendments can be found in the [IRAS guidance](#).

User Feedback

We are continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the amendment procedure. If you wish to make your views known please use the feedback form available at: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>.

Please do not hesitate to contact me if you require further information.

Kind regards

Tim Milstead

Health Research Authority

Ground Floor | Skipton House | 80 London Road | London | SE1 6LH

APPENDIX A14: Sponsor Approval for Study Recruitment at North Manchester General Hospital

Author: Dalen L.

Author email: L.Dalen@soton.ac.uk

Subject: RE: IRAS 170265: Confirmation of Capacity and Capability at The Pennine Acute Hospital NHS Trust

Sent datetime: 08/22/2019 16:01:39

Dear Simba

Study References: ERGO Ref 13474/IRAS Ref 170265/R&I Ref P19DIA B05

Study Title: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community

This is to confirm Sponsor approval for commencement of recruitment at The Pennine Acute Hospital NHS Trust.

Following Confirmation of Capacity and Capability from the Research and Innovation Department we issue this “green light” notice and confirm the site activation date as 27th August 2019.

Kind regards

Lindy Dalen, on behalf of the Sponsor Representative.

Dr Lindy Dalen
Research Integrity Officer (Ethics and Clinical Governance)
Research Integrity and Governance Team
University of Southampton
2031, Building 28, Highfield Campus
Southampton SO17 1BJ

Tel: +44 (0) 23 80598848



Our internal [Researcher Portal](#) provides a one stop shop for key information on the research lifecycle.

Research Innovation Services and contacts www.soton.ac.uk/ris

Please note I work part time and will be available Tuesdays and Thursdays.

From: Tanyanyiwa Simbarashe [<mailto:S.R.Tanyanyiwa@salford.ac.uk>]
Sent: 22 August 2019 13:50
To: Rgoinfo <rgoinfo@soton.ac.uk>
Cc: Dalen L. <L.Dalen@soton.ac.uk>; Bartlett T.J. <T.Storey@soton.ac.uk>
Subject: FW: IRAS 170265: Confirmation of Capacity and Capability at The Pennine Acute Hospital NHS Trust
Importance: High

Dear Research Office (Trudi and Lindsay)

As sponsor, could you please forward an email to me as a “green light” for the study to begin, confirming that the study is now open for recruitment.

I will then confirm the site activation date as the 27th August 2019.

This is to fulfil the requirements in the email below.

Thank you for your kind help.

Simba

Research Fellow,
The North Manchester Diabetes Centre and the University of Salford.

Room PO30; School of Health Sciences, Brian Blatchford Building, University of Salford, Salford M6 6PU

From: Daniels Maureen <Maureen.Daniels@srft.nhs.uk>
Sent: 13 August 2019 13:41
To: cuong.dang@pat.nhs.uk; K.G.McCormick@soton.ac.uk
Cc: Tanyanyiwa Simbarashe <S.R.Tanyanyiwa@salford.ac.uk>; deborah.hall@pat.nhs.uk; joanne.shaw@pat.nhs.uk; muhammad.warsi@pat.nhs.uk; ruth.totton@pat.nhs.uk; laura.durrans@pat.nhs.uk; Doyle Katie <Katie.Doyle@srft.nhs.uk>; OLoughlin Victoria <Victoria.OLoughlin@srft.nhs.uk>; Ford Lucy (Research & Innovation) <Lucy.Ford@srft.nhs.uk>; Bray Fiona <Fiona.Bray@srft.nhs.uk>; Abbas Aishah <Aishah.Abbas@srft.nhs.uk>
Subject: IRAS 170265: Confirmation of Capacity and Capability at The Pennine Acute Hospital NHS Trust
Importance: High

Dear Sponsor Representative,

IRAS reference:	170265
R&I reference:	P19DIA B05
Study title:	Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community
Study short title:	Objective neurovascular monitoring in feet of Type 2 diabetes patient
PI:	C Dang
Site:	Pennine - NMGH
NIHR:	Yes
Delivery Reportable to DoH:	Yes
Funding source:	Non-commercial
Date site selected:	9th August 2019
Number of calendar days to recruit 1st participant:	66 calendar days
Target date for first participant recruited:	18th October 2019
Target as confirmed in the Organisation Information Document	35

This email confirms that The Pennine Acute Hospitals NHS Trust has the capacity and capability to deliver the above referenced study. Please find attached our agreed Organisation Information Document as confirmation. Also attached is the HRA approval letter dated 4th December 2017. The documents highlighted on this letter have been reviewed and approved at Pennine.

We agree to start this on a date to be agreed when you as sponsor give the green light to begin. Once agreed, please confirm the site activation date to all in this email.

Dear Sponsor Representative – please send any study amendments to SalfordRDamendments@srft.nhs.uk to ensure prompt review.

Hi Simba – Once you have recruited your first patient, please can RPEAK be updated as soon as possible.

If you wish to discuss further, please do not hesitate to contact me.

Please find pasted below a link to the SOP's at The Pennine Acute Hospitals NHS Trust.

<http://nm-ashanti:86/DMS/Default.aspx?tabid=289&Search=research&Stype=0>

Best wishes

Maureen Daniels

Research & Innovation Support Officer

Research and Innovation Department

Salford Royal NHS Foundation Trust

Northern Care Alliance NHS Group

Comprising the Care Organisations of Salford, Bury & Rochdale, Oldham and North Manchester

Summerfield House, 1st Floor,

544 Eccles New Road,

Salford, Manchester, M5 5AP

tel: 0161 206 7051

email: maureen.daniels@srft.nhs.uk

web: www.NCAresearch.org.uk / <http://www.northerncarealliance.nhs.uk/>

facebook: <https://www.facebook.com/NCAresearchNHS> / <https://www.facebook.com/NorthernCareAllianceNHSGroup/>

twitter: @NCAresearchNHS / https://twitter.com/NCAlliance_NHS



Diabetes Department
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
M8 5RB

University of Southampton
University Road
SO17 1BJ

Date: 10.06.19

REF: NMGHDIAB/research

Dear Professor Catherine Bowen, and Keith McCormick

Please find this letter confirmation of the loan for equipment:

The Vascular Toe Pressure Doppler
The NCStat DPNCheck

I, Simba Tanyanyiwa, confirm that

- The loan of the equipment will be from the 10th of June 2019 until the 23rd of December 2019.
- All equipment will be kept under safe storage and care of the Diabetes Research Department at North Manchester General Hospital, which is covered by the relevant insurance.
- The Principal Investigator, Simba Tanyanyiwa, will be responsible for the safe return of all loaned equipment to the University of Southampton at the end of the loan period.
- The equipment below has electrical certification from EBME as of the 10th of June 2019.
- Certificate Number L4372 (Toe Pressure Doppler from Huntleigh Healthcare)
- Certificate Number L4374 (DPNCheck from Neurometrix)

Yours Sincerely,

S R Tanyanyiwa

Doctoral Research Fellow
University of Salford and North Manchester

Professor Cuong Dang

Diabetic Consultant
Diabetes Centre
North Manchester General Hospital

PI Signature: _____

Date: 10/06/19

Signature: _____

Date: 13/06/2019

Diabetes Department

North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
M8 5RB

University of Southampton
University Road
SO17 1BJ

Date: 10.06.19

REF: NMGHDIAB/research

Dear Professor Geraldine Clough

Please find this letter confirmation of the loan for equipment:

The Precise Medicap 8001

I, Simba Tanyanyiwa, confirm that

- The loan of the equipment will be from the 10th of June 2019 until the 23rd of December 2019.
- All equipment will be kept under safe storage and care of the Diabetes Research Department at North Manchester General Hospital, which is covered by the relevant insurance.
- The Principal Investigator, Simba Tanyanyiwa, will be responsible for the safe return of all loaned equipment to the University of Southampton at the end of the loan period.
- The equipment below has electrical certification from EBME as of the 10th of June 2019.
- Certificate Number L4373 (Precise Medicap from Moor Instruments)

Yours Sincerely,

S R Tanyanyiwa

Doctoral Research Fellow
University of Salford and North Manchester

Professor Cuong Dang

Diabetic Consultant
Diabetes Centre
North Manchester General Hospital

PI Signature: _____

Date: 10 | 6 | 19

Signature: _____

Date: 13 | 6 | 19

APPENDIX A15: Study Statistician Support Letter



Dr Sean Ewings (PhD)
Southampton Statistical Sciences Research Institute
University of Southampton
Highfield SO17 1BJ

Phone: (023) 8059 7638
Email: sean.ewings@soton.ac.uk

16th Aug 2017

Project Title: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community.

To whom it may concern,

I can confirm that I am providing ongoing statistical support on the above named project, for Simbarashe Tanyanyiwa, with the project supervised by Prof. Cathy Bowen and Keith McCormick. In addition, I also confirm that I consider the statistical approaches and analyses to be appropriate for this study and that I support the proposed design methodology.

Yours sincerely,

(signed)

Dr Sean Ewings (PhD)
Medical Statistician and Research Fellow
University of Southampton

STATISTICAL ANALYSIS PLAN

Comparison of Transcutaneous Oxygen and Nerve Conduction Devices Against Existing Methods Screening for Neuroischaemia Status in the Feet of Adult Participants With Type 2 Diabetes in the Community.

A cross-sectional study to determine the effectiveness of nerve conduction and transcutaneous oxygen devices versus the 10g monofilament and toe-brachial index methods in screening for neuro-ischaemia in the feet of people with type 2 diabetes.

IRAS Ref: 170265 / NHS REC Ref: 17/LO/2033

1. INTRODUCTION

1.1. Background and Rationale for the Trial

The full background and rationale for this study is detailed in the study protocol. In summary, the study will assess whether the use of nerve conduction and transcutaneous oxygen (TcPO₂), is more effective at determining the neuro-ischaemic status in the feet of people with type 2 diabetes, when compared to the 10g monofilament and toe-brachial index (TBI). All participants will have their neuro-ischaemic status determined using the four devices as follows:

Neurological Status (nerve conduction; versus 10g monofilament)

Ischaemic Status (transcutaneous oxygen versus TBI)

These will then be used to obtain an overall risk status for each participant

2. TRIAL OBJECTIVES AND OUTCOME MEASURES

The objectives of the study are to assess the clinical effectiveness of using nerve conduction in the diagnosis of neuropathy; and transcutaneous oxygen in diagnosing ischaemia, in a podiatry clinic setting for people with type 2 diabetes. If demonstrated to be effective, the evidence can be used to challenge current recommendations for diagnosing diabetic foot neuroischaemia (NICE clinical guidance NG19) in determining foot risk status and can advance diabetic foot health service delivery models across the United Kingdom.

2.1. Primary Research Questions

- 2.1.1. Is nerve conduction more effective at screening for neuropathy in a podiatry clinic when compared to the 10g monofilament ?
- 2.1.2. Is TcPO₂ more effective at screening for ischaemia in a podiatry clinic when compared to the TBI?

2.2. Primary Research Objective

- 2.2.1. To assess in the feet of patients with type 2 diabetes, whether nerve conduction is more effective at screening for neuropathy compared to the 10g monofilament.
- 2.2.2. To assess in the feet of patients with type 2 diabetes, whether TcPO2 is more effective at screening for ischaemia when compared to the TBI.

2.3. Primary Outcome Measures

The primary outcome measure is the **numbers of people diagnosed with**:

2.3.1. **neuropathy** (nerve conduction vs 10g monofilament); and/or

2.3.2. **ischaemia** (TcPO2 vs TBI);

based on the respective devices scoring systems.

2.4. Secondary Research Questions

- 2.4.1. Is the combined use of (nerve conduction + TcPO2) more effective at identifying people “at risk” (i.e. those with neuropathy and/or ischaemia) than the NICE NG19 recommended methods (10g monofilament + TBI) ?
- 2.4.2. Is the use of nerve conduction alone more effective at identifying people with neuropathy and/or ischaemia than the combined recommended methods (10g monofilament + TBI) ?
In other words: **is the detection of nerve conduction impairment alone, more effective than NICE NG19 recommended methods, at identifying people “at risk”?**
- 2.4.3. Is the use of TcPO2 alone more effective at identifying people with neuropathy and/or ischaemia than the combined recommended methods (10g monofilament + TBI) ?
- 2.4.4. Do people with ischaemia have nerve conduction deficits?
- 2.4.5. Do people with nerve conduction deficits, have ischaemia?
- 2.4.6. What is the effect of ankle circumference on nerve conduction performance?

2.5. Secondary Research Objectives

- 2.5.1. To assess whether the combined use of (nerve conduction + TcPO2) is more effective at identifying people with **neuropathy and/or ischaemia** than the combined NICE NG19 recommended methods (10g monofilament + TBI)
- 2.5.2. To assess whether the detection of neuropathy using nerve conduction alone is more effective at screening for **people with neuropathy and/or ischaemia** than the combined recommended methods (10g monofilament + TBI)
- 2.5.3. To assess whether the detection of ischaemia using TcPO2 alone is more effective at identifying people with **neuropathy and/or ischaemia** than the combined recommended methods (10g monofilament + TBI).
- 2.5.4. To assess whether ischaemia, can distinguish between people with nerve conduction impairment.
- 2.5.5. To assess whether nerve conduction impairment, can distinguish between people with ischaemia
- 2.5.6. To determine the effect of ankle circumference on nerve conduction values.

2.6. Secondary Outcome Measures

- 2.6.1. The number of people identified as having neuropathy and/or ischaemia based on a combined nerve conduction and TcPO₂, compared to those identified as having neuropathy and/or ischaemia based on the 10g monofilament + TBI.
- 2.6.2. The number of people identified as having neuropathy by nerve conduction alone; compared to the number of people identified **with neuropathy and/or ischaemia based on** the combined recommended methods (10g monofilament + TBI)
- 2.6.3. The number of people identified as having ischaemia by TcPO₂ alone; compared to the number of people identified **with neuropathy and/or ischaemia based on** the combined recommended methods (10g monofilament + TBI)
- 2.6.4. The nerve conduction values of the people identified with ischaemia.
- 2.6.5. The TcPO₂ and TBI values of those identified with nerve conduction impairment.
- 2.6.6. Correlate the ankle circumferences to nerve conduction values.
- 2.6.7. **Prediction model (regression analysis) for**
 - (a) **neuropathy and**
 - (b) **ischaemia**

2.7. Primary Analyses of the Primary Outcome

2.7.1. Neuropathy: each assessment (nerve conduction; and 10g monofilament) will initially determine whether or not a participant has sensory neuropathy.

Frequency Counts will be presented for the primary outcome, counting the number of people diagnosed for each category (No Neuropathy or Neuropathy) as follows:

Validity: The truth table will be used to determine validity, based on sensitivity, specificity, and diagnostic accuracy of the 10g monofilament when compared to nerve conduction.

Agreement: Cohen's kappa will estimate the extent of agreement between nerve conduction and the 10g monofilament.

2.7.2. Ischaemia: each assessment (TcPO2; and TBI) will initially determine whether or not a participant has ischaemia.

Frequency Counts will be presented for the primary outcome, counting the number of people diagnosed for each category (No Ischaemia or Ischaemia).

Validity: The above table will be used to determine the sensitivity, specificity, and diagnostic accuracy of TcPO2 when compared to the TBI.

Agreement: Cohen's kappa will estimate the degree of agreement between the two devices,

2.8. Interpretation of primary analysis results

The primary analysis will test the null and alternative hypotheses:

2.9. Secondary analyses of the primary outcomes

2.9.1. Neuropathy: **The severity of neuropathy** will be categorised as mild-moderate or severe, with the frequency counts recorded. The discriminant ability of nerve conduction will be compared to that of the 10g monofilament

- Agreement:** **Weighted kappa** will estimate the degree of agreement between the instruments; taking into account their respective ability to identify participants into the 4 categories.
- Correlations:** **Since data follows a non-normal distribution, Spearman will be used**

2.9.2. Ischaemia: The severity of ischaemia will be categorised as mild-moderate or severe, with the frequency counts recorded. The discriminant ability of TcPO2 will be compared to that of the TBI

- Agreement:** **Weighted kappa** will estimate the degree of agreement between TcPO2 and the TBI taking into account their respective ability to identify participants into the 4 categories.

Observed concordance is smaller than mean-chance concordance so kappa was not calculated by SPSS.

2.10. Exploratory Analysis

2.10.1. Data Transformation. Variable Data will be assessed to determine conformity to a "Gaussian distribution", and any variables that do not will be \log_{10} transformed, and retested again for conformity.

- Kolmogorov-Smirnov Test** since sample > 50 ; **Normality assumed if $p > 0.05$**
- Data \log_{10} transformed, and retested for normality**

2.10.2. Correlations: It will be of interest to determine any associations between potential confounders (e.g. age, HbA1c, gender) on neuropathy and ischaemia values and use these to later adjust during regression analysis. **Since data follows a non-normal distribution, Spearman rho will be used**

2.10.3. Group comparisons to determine the effects of gender and location (Manchester vs Southampton), on main outcome measures will be done.

- a) *Gender:* Any differences in outcome demographics or measures between men and women
- b) *Test site:* Any differences in outcome demographics or measures between Manchester and Southampton

2.11. Analysis of Secondary Outcomes

2.11.1. Risk Stratification: The outcomes from the Primary analysis (6.2) will be used in the risk stratification of each participant, based on the combined neurological and ischaemic components as follows:

	Neurological Function	Vascular Function
LOW RISK		No sensory deficit and no ischaemia
MEDIUM RISK		Either neuropathy or ischaemia , in the absence of other factors
HIGH RISK		Neurological and Vascular deficit Neurological or Vascular deficit in combination with other factors (Previous ulceration ; Previous amputation)

2.11.2. Comparison of risk stratification frequencies for each category, based on combined (nerve conduction + TcPO₂) compared to combined (10g monofilament + TBI) (objective 2.4.1), as shown below:

2.11.3. The ability of nerve conduction to risk stratify on its own, when compared to the combined recommended methods (10g monofilament + TBI). ***Is the detection of nerve conduction impairment alone, more effective than NICE NG19 recommended methods, at identifying people “at risk”?***

3. Statistical Software

The statistical analyses will be undertaken using SPSS v26, supplemented where required by the R statistical packages.



Letter to Participant's General Practitioner

Date: / /

< GP Name / surgery address >

Solent NHS Podiatry Service
Adelaide Health Centre
William Macleod Way
Southampton
SO16 4XE

Tel: 0300 300 2012

Ref: Informing GP of patient's participation in a trial.

NAME.....

D.O.B. date...../month...../ year.....

NHS ID.....

or sticker

Dear Dr < GP Name >

Your patient, named above, whilst receiving podiatry treatment has given their consent and subsequently been enrolled in the following trial:

Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community.

The trial is a cross-sectional study which aims to establish if the use of new neurovascular devices can detect diabetes changes better than current practice in the community. The new devices will monitor the patient's nerve conduction (DPN-Check), and transcutaneous oxygen (Medicap) status to give objective, quantitative measures that will be used to determine their risk status.

All adult patients with Type 2 diabetes, without other systemic causes of



neuropathy or active ulceration are being approached to enter the study. Patients who agree to take part, after full explanation of the trial and provision of a patient information leaflet, are then assessed using current methods to determine their diabetes ulceration risk status as defined by the National Institute of Health and Care Excellence guideline 19; (NICE NG19, 2015). At the same time, they will also be assessed for their sensory (sural) nerve and microvascular (transcutaneous oxygen) function using the new devices, and comparisons made with current guidelines. A separate request may be made to yourself to confirm their most recent HbA1c to determine their glycaemic control at the time of their trial assessment.

Your patient will be asked to attend the Royal South Hants Hospital in Southampton, for an assessment lasting 60 minutes; and they may be requested to attend 3 months later for one follow-up appointment. These visits may be combined with their regular routine follow-up appointments to the patient's convenience, but may also require separate attendance. Your patient has been made aware that they can withdraw at any time without giving a reason, and that no part of this trial, or whether or not they decide to participate or continue participating, will affect the level of care they receive.

If you require any further information about the above trial, please contact myself or the Research and Clinical Audit Office for Solent NHS Trust.

Regards,

S R Tanyanyiwa

Position Principal Investigator

Contact Details: srt1e14@soton.ac.uk

Principal Investigator

S R Tanyanyiwa

srt1e14@soton.ac.uk

02380 597 958

Catherine Lea
Research and Clinical Audit Office,
Western Community Hospital
Room H22, Western Wing
William Macleod Way
Southampton
Hampshire
SO16 4XE
catherine.lea@solent.nhs.uk

Do you have Type 2 Diabetes?

**PARTICIPANTS NEEDED FOR TESTING NEW VASCULAR
AND NEUROLOGICAL SCREENING MACHINES.**

We are looking for adult volunteers with Type 2 Diabetes to take part in a study that uses new machines to test the blood circulation and nerves in the feet.

Project Title: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community.

Background: If you have diabetes, you need to have the nerves and blood circulation in your feet tested every year to see if any changes have happened. There are new machines that hope to improve the way these tests are done, but they have not had a lot of testing. This project is going to test how well these machines work, and compare what they find with what is commonly done at the yearly diabetic checks.

What will be done? You will be asked to attend a Solent NHS podiatry clinic at the Royal South Hants Hospital in Southampton and have diabetes foot checks on the nerves and circulation using the common methods (monofilament and doppler). Then the new machines (DPN-Check and Medicap), will be used to repeat the same tests. You will also be asked about your height, weight, age, and any medications you take.

The study will last up to 1 hour. You will also be asked if you want to return and have the tests repeated 3 months later.

We need adult volunteers

- Between 18 - 65 years of age
- With Type 2 Diabetes
- With no wounds or ulcers
- Without any other causes of nerve or circulation damage apart from diabetes

Contact:

If you would like to volunteer, or need more information: please contact

Simba Tanyanyiwa on email: srt1e14@soton.ac.uk

APPENDIX A20: Participant Information Sheet

Participant Information Sheet

TITLE: Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community.

Researcher: Simbarashe R Tanyanyiwa

Supervisors: Prof Catherine Bowen, Keith McCormick

Ethics Reference: REC 17/LO/2033

You are being invited to take part in a research study which will require you to make two visits. This research study is part of a PhD project, funded by the Wessex Clinical Academic Training Scheme. Please note that we are unable to reimburse your travel expenses after two visits.

Before you decide it is important for you to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with friends and relatives. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you would like to take part, and if you have any questions or need more information to use the contact details on Page 4 below. Thank you for reading this.

What is the purpose of the study?

This study will use the feet of people with type 2 diabetes to test two machines, that will test:

1. the amount of oxygen reaching the skin (Medicap), and
2. how well a nerve is working (DPN-Check);

and compare them against existing methods.

- 1. The amount of oxygen reaching the skin (Medicap):** This study aims to measure the saturation of oxygen in the skin, compared to other methods of measuring circulation.



Transcutaneous oxygen pressure (TcPO₂) involves measuring the amount of oxygen that leaves the small blood vessels inside the foot and passes through to the skin surface, where it is measured by the machine (Medicap). It is a commonly used method that avoids entering or harming the body, and is therefore safer and quicker than other techniques. It is mainly used in assessing conditions with poor circulation, such as wound healing, determining limb amputation level, and skin survival; and it is hoped it can be useful in testing patients with diabetes to see early circulatory changes. In order to widen the small arteries and for the oxygen to flow to the skin more easily, the machine warms the skin up to 44°C, then measures the amount of oxygen arriving at the skin surface over 15 minutes. This will involve you sitting comfortably in a chair or clinic couch for 30 minutes, and the machine attached to the top of your foot as shown below:



2. How well the nerve is working (DPN –Check). This machine works by measuring how quickly the large nerve near the surface of the skin on the outside of the ankle carries messages. It does this by sending a small electric message from one part of the nerve, and measures how long it takes to arrive at another part. It uses this information to measure the health of the nerve, and can pick up early signs of damage. Nerve conduction studies (NCS) are seen as the reference standard in detecting early nerve damage, but until recently other machines that could measure this were more complicated and took a long time to operate. The DPN-Check is a new device that does not damage the skin, is easier to use and gives more useful information on nerve health. It has potential to find signs of nerve damage earlier than existing methods, but it needs more testing in clinics for patients with diabetes, where it can be compared to other methods normally used. We therefore think it can be useful to find and prove its use in clinics that treat diabetes patients, and compare it to existing methods.

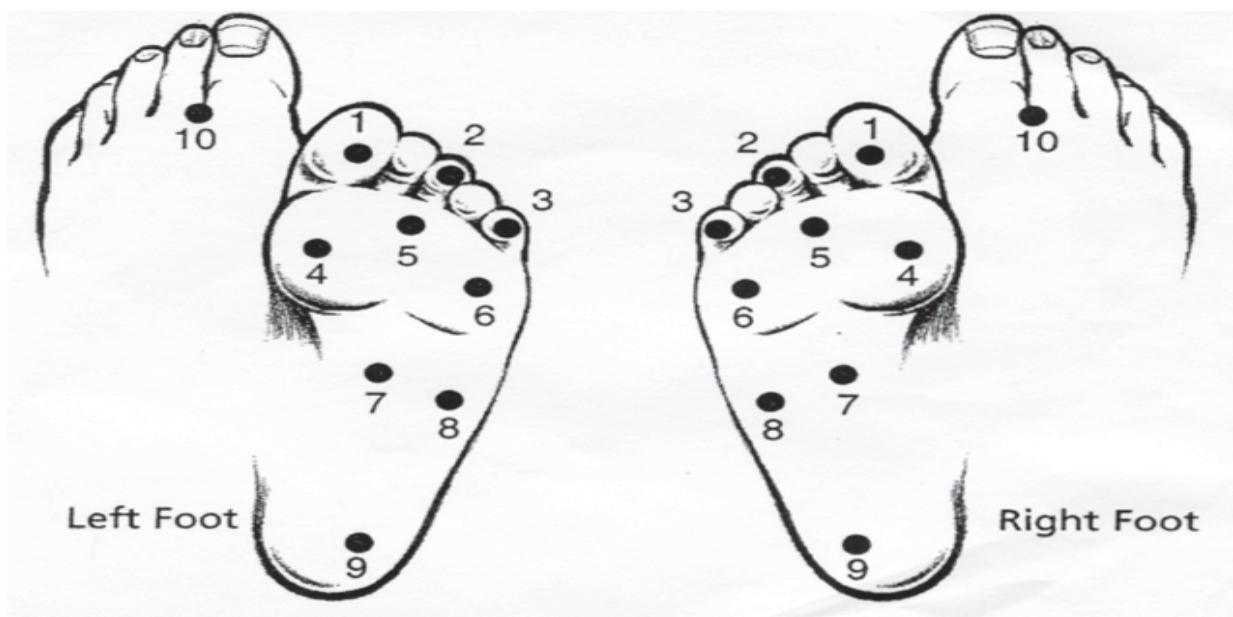


Existing methods

Circulation The pressure of the blood reaching the big toe in your feet will be tested using a Doppler machine as shown below:



Nerve function: a nylon thread will be used to test the feeling in your feet and 10 locations shown below:



What else will you measure?

- **We will also measure:** your ankle size, skin temperature, height and how much you weigh
- **and ask for:** your date of birth, age, if you are male or female; how long you have had diabetes, your if you smoke; your level of diabetes control (HbA1c); any diseases affecting your circulation, liver and kidneys, and any medications you take.

Why have I been chosen?

You have been chosen because you have Type 2 diabetes; and may have responded to a request or to our advertisement, where you can help determine the usefulness of the new machines above when compared to the methods currently used.

Do I have to take part?

It is up to you whether to take part. **Unfortunately, if you have already volunteered for another research project that is still ongoing, then you will not be able to participate in this.** If you do decide to take part, you will be given this information sheet to keep and we will ask for your permission to ask your doctor / GP about your diabetes control levels, and tell them your are taking part in a trial. You will then be asked to sign a consent form. You are free to withdraw from the study at any time and without giving a reason and without affecting your usual treatment.

What will happen to me if I take part?

You will be asked to answer a few questions about yourself. If you meet the criteria of the study and agree to take part you will be enrolled to the study. You will be asked to attend the podiatry clinic at the Royal South Hants Hospital, at least once, and may be asked to return 3 months later for a follow-up for the above tests to be repeated. Each time, the visit will last up to 1 hour.

What happens?

1. During the first visit, you will be asked to sign a form confirming your agreement to take part. Measurements will be taken on your weight, height and ankle size, and you will be asked about your age, any medication you take, how long you have had diabetes, your sugar levels and gender. Recording your information can take up to 15 minutes, and if you think of any questions, you can ask them to the assessor at any time.
2. You will be asked to sit in a clinical chair, which will be adjusted to your comfort. Both your feet will be tested for circulation and nerve health according to usual methods (monofilament and Doppler). This part will take less than 15 minutes.

3. The new machines will then be used to repeat the tests on your nerves and circulation. For your circulation; sticky rings will be fixed to the top of your foot between the big and second toes, and the Medicap machine probe will then be attached to the ring. The Medicap machine will be turned on and your skin will experience a warming sensation, and measurement will begin, and will last no more than 15 minutes. During this time the DPN-Check will test the nerve around the outside of both your ankles, by sending a small electric current.
4. Pictures of your feet and ankles may be taken with the machines attached.
5. *How long will it take?* The total time for all the assessments will be about 45 minutes, but allow for your visit to last up to 1 hour so you are not rushing and to allow for any additional questions you may have. You may be asked to return after 3 months to have the above measurements repeated.

Are there any risks involved?

It is most unlikely that you will suffer any discomfort or adverse effects from this study, although some may experience a mild, painless, short-lasting skin irritation following the skin warming. The nerve conduction device sends a small charge around the ankle, which may result in slight "buzzing" or "tingling" sensation which may make you feel uncomfortable for about 5 - 10 seconds. Both these methods for measuring the amount of skin oxygen and nerve function do not involve entering the body.

Are there any benefits in my taking part?

You would not receive any benefits directly. However, this study will increase our understanding of how a new device compares to another when measuring skin oxygenation. It will also help us to find a way to find changes earlier in the feet of people with diabetes, that may lead to ulcers.

What happens if something goes wrong?

If you have any complaints or concerns during this study you should immediately inform the investigator. In the unlikely event that something goes wrong during the study indemnity insurance has been provided. If you have a concern or a complaint about this study you should contact Trudi Bartlett, Research Governance Officer, at the University of Southampton (Address: Research Integrity & Governance Office, Building 37, Room 4079, University of Southampton, Highfield, Southampton SO17 1BJ. Email: rgoinfo@soton.ac.uk; Tel: 023 8059 5058). If you remain unhappy and wish to complain formally the Research Integrity & Governance Office can provide you with details of the University of Southampton Complaints Procedure.

Would my taking part in this study be kept confidential? Your GP will be informed by letter that you are taking part in this study. All data will be treated in compliance with the Data Protection Act and the University of Southampton policy for the storage of data (<http://library.soton.ac.uk/researchdata/retention>). Results will be recorded on paper, and images taken by an unlinked digital camera. This refers to a camera that has no other external connectivity apart from a storage card and USB cable for image transfer. Your details will be anonymised by a study number and date of birth, and will be transferred to a University of Southampton encrypted computer, and the papers and images then securely destroyed immediately on transfer to the computer. The research data will be stored with the University of Southampton, and your details will be securely stored for up to 10 years from completion of the study, in a secure computer archive. After this period, to enable the secure disposal of electronically held data, the data will be overwritten multiple times and the physical disk destroyed in line with the university of Southampton policy on the destruction of research data (<http://library.soton.ac.uk/researchdata/destruction>).

What will happen to the results of the research? It is hoped that the findings from this study will be published in suitable professional and scientific journals. It will not be possible to identify any individuals from any of the data presented. You will be asked whether you wish to be personally informed of the results of this study at the end.

What happens if I change my mind?

You have the right to withdraw from this study at any time, without giving a reason. This will not affect the level of care you receive or your usual treatment.

Who has reviewed the study?

This study has been reviewed by the Faculty of Health Sciences research ethics committee.

Contacts for further information:

Simbarashe Tanyanyiwa – email: srt1e14@soton.ac.uk

Keith McCormick – email: K.G.McCormick@soton.ac.uk

Prof. Catherine Bowen- email: C.Bowen@soton.ac.uk

You will be given a copy of this information sheet and a signed consent form to keep.

Thank you for taking the time to read this information.

Inclusion Criteria	Justification
Age 18-40	Age can cause spontaneous age related peripheral neuropathy (Tabata et al, 2000). One study found no significant effect of age in participant aged 20-35 (Sterzing, 2009). Participants over 18 so they may give informed consent.
Healthy (See appendix 2)	This study aims to assess the validity and reliability of the neurothesiometer on healthy individuals against nerve conduction.
English speaking	For consent purposes, this study requires a participant to fully understand the study and be able to communicate.
Able to give informed consent	Vulnerable persons including mentally-deficient or severely-injured persons, or persons otherwise demonstrating insufficient capacity to understand or make decisions regarding participation in the study. Judged by the researchers and assessed by the ethics committee (RCN 2011).

Exclusion Criteria	
Exclusion Criteria	Justification
Medical conditions listed in Appendix 1	The medical conditions listed have been shown to affect vibration sensation (NHS Choices, 2015).
Score over 2 on the modified Michigan Neuropathy Screening Instrument (Appendix 4)	An abnormal result on the MNSI indicates reduced sensation and would indicate the participant doesn't have a normal / healthy perception (Moghtaderi et al. 2005). A score of >2 has a 65% sensitivity and 83% specificity for predicting peripheral neuropathy (Moghtaderi et al. 2005).
History of head injuries; and spinal and leg trauma including surgery or amputation in the lower limb	Surgery or amputation to the lower limbs can result in abnormal neurological function e.g. phantom pain or peripheral neuropathy (Shaw et al. 1987; Ehde et al. 2000)

Experimental Study 1: DPNCheck Reliability in Healthy Participants health screening questionnaire

SECTION 1

MNSI (adapted from Moghtaderi et al. (2006))		
Question	Yes	No
Do you ever get numbness in your feet?		
Do you ever have any burning pain in your legs and/or feet?		
Are your feet too sensitive to touch?		
Do you get cramps in your legs and/or feet?		
Do you ever have any prickling feelings in your legs or feet?		
Does it hurt when the bed covers touch your skin?		
When you get into the tub or shower, are you able to tell the hot water from cold water?		
Have you ever had an open sore on your foot?		
Has your doctor ever told you that you have neuropathy?		
Do you feel weak all over most of the time?		
Do your legs hurt when you walk?		
Are you able to sense your feet when you walk?		
Is the skin on your feet so dry it cracks open?		
Have you ever had an amputation?		
Score	/14	

If the participant scores >2/14 they will be excluded from the study.

SECTION 2

Do you or have you ever suffered from any of the following health conditions:		
Medical Condition	Yes	No
Alcohol dependency		
Vitamin B12 deficiency		
Physical damage to the nerves		
Hypothyroidism		
Shingles, Lyme disease, Diphtheria, Botulism or HIV		
Vasculitis		
Chronic Liver Disease; Chronic Kidney Disease		
Monoclonal gammopathy of undetermined significance (MGUS)		

If the participant answers “yes” to any of the above, they will be excluded from the study.

Physical Examination
10g SWM Test

/10

If the participant scores <8/10 they will be excluded from the study.

Foot temperature °C
Dorsum of the foot

If the participant foot temperature is outside of the accepted range (30.6 degrees +/- 2.6 degrees) allow them to acclimatise to the room for 5 minutes. If the foot temperature is still outside of the accepted range the participant will be excluded from the study.

Centre Number:

IRAS ID: 170265

REC Reference:

17/L0/2033

Study Number:

Ethics Reference: ()

Patient Identification Number for this trial:

CONSENT FORM

Title : Comparison of transcutaneous oxygen and nerve conduction devices against existing methods to determine neurovascular status in the feet of adult participants with Type 2 Diabetes in the community

Name of Researcher: Simbarashe Richard Tanyanyiwa

Please initial the box(es) if you agree with the statement (s)

Other Researchers: Keith McCormick; Professor Catherine Bowen

1. I confirm that I have read and understand the information sheet dated **30-Aug-2017** (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. 1

2. I understand that my participation is voluntary and that I am free to withdraw at any time without consequence, without giving any reason, and without my medical care or legal rights being affected. 2

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the above named researchers from **the University of Southampton**, from regulatory authorities or from Solent NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. 3

4. I understand that digital photographs of my feet and ankles will be taken during the study 4

5. I understand that information collected about me during my participation in this study, including any images, will be stored on a University of Southampton encrypted and password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous. 5

6. I understand the study will involve me attending two visits 3 months apart 6

7. I therefore consent to the University of Southampton retaining my personal details on a password protected database. The 'validity' of my consent is conditional upon the University of Southampton complying with the Data Protection Act (1998) and I understand that I can request my details be removed from this database at any time. 7

8. I agree to my GP being informed of my participation in the study. 8

9. I agree to take part in the above study. 9

Name of Participant

Date

Signature

Name of Person taking consent.

Date

Signature

NAME						D.O.B	TRIAL REF/ID
Gender	M		F			Age (yrs)	
Duration of DM	(months)						
Smoking	Y		N				
BMI (kg/m2)	Mass (kg)			BMI			
	Height (m)						
HbA1c (Glycaemic Control)	(%)						
	(mmol/mol)						
MEDICATION	Glycaemic. control	Diet only					
		Metformin					
		Insulin					
		Other					
	Vascular control	Statin therapy					
		Antiplatelet					
		Anticoagulant					
	Other						
FOOT HEALTH							
		Right	Left	Mean			
Ankle circumf. (cm)							
Prev. ulceration							
Prev. Amputation							
				Mean			
NUEROLOGICAL	Monofil score /10						
	Neurothm (V)						
	DPN-Check						
		Amplitude					
Velocity							
Right Left Mean							
VASCULAR	toeABPI						
	TcPO2 (mmHg)						
NEUROPATHY STATUS	MONOFIL	Normal	Neuropathy				
		> 7	Mild 6 -7	Mod 3-5	Severe < 3		
	DPN-Check (see guide)	Normal	Neuropathy				
		Appendix	mild	mod	Severe < 6		
VASCULAR STATUS	toeABPI	Normal >55	Ischaemic				
			mild	mod	severe		
	TcPO2 mmHg	Normal >50	Mild	Moderate	Severe <30		
			40-50	30-39			

Experimental Study		Identified	DNA	Attended	Withdrawn	Reason
1	Reliability of DPNCheck	21	0	21	1 declared exclusion criteria after assessment	
2	Validity Medicap in Healthy	22	0	22	4 faulty equipment	
3	Validity Medicap in Diabetes L-Risk	unsure. About 30	0	21	0	
4	Reliability of TBI in healthy	31	0	31	0	
5	Validity and Reliability of DPNCheck, 10g MNF; TBI, Medicap			part of final study		
6	Effectiveness of DPNCheck	unsure. About 120	about 20	93	1 declined DPNCheck	
7	Effectiveness of Medicap					
Σ =				188	6	
Final				182		

1. PERSONAL INFORMATION

Full name and title:	Simbarashe Richard TANYANYIWA
Employee/Student number:	27423735

2. PRESENT APPOINTMENT

Present post & level:	<ul style="list-style-type: none"> • Doctoral Research Fellow – University of Salford and North Manchester Diabetes Centre • Clinical Doctoral Research Fellow – University of Southampton
Date of appointment to present post:	<ul style="list-style-type: none"> • <i>(January 2019) Doctoral Research Fellow – University of Salford and North Manchester Diabetes Centre</i> • <i>(October 2014 – December 2020) Clinical Doctoral Research Fellow – University of Southampton</i>
Academic Unit/Division:	Faculty of Health Sciences
Faculty:	Health Sciences

3. PREVIOUS SUBSTANTIVE APPOINTMENTS

Appointment	From	To
Podiatry Research Fellow – Solent NHS Trust	Oct 2014	Apr 2018
Research Intern – University of East London	June 2014	Aug 2014

4. QUALIFICATIONS (Educational and Professional)

Date	Title of award	Subject	Class	Awarding body
Dec 2019 (pending)	Doctor of Philosophy (pending)	Health Sciences (Diabetes)		University of Southampton
June 2014	BSc. (Hons)	Podiatric Medicine	1 st	University of East London
June 2007	BSc. (Hons)	Biomedical Science	2.1	Liverpool John Moores University

5. MAJOR HONOURS & DISTINCTIONS

Honour/distinction	Date awarded
Best Clinical Prize: University of East London	June 2014
Best Overall Student: University of East London £250 prize	June 2014
Awarded Solent NHS Trust Clinical Doctoral Research Fellowship.	August 2014.

6. RESEARCH ACTIVITY

a) Summary of current research
Investigating the use of transcutaneous oxygen and nerve conduction to detect neurovascular dysfunction in the feet of people with type 2 diabetes
b) Summary of research in the previous three years
Doctoral Research : Investigating the use of transcutaneous oxygen and nerve conduction to detect neurovascular dysfunction in the feet of people with type 2 diabetes

7. DEVELOPMENT AND TRAINING

Development and training activities undertaken

Over the last three years (including current year) plus any significant activities in previous years.

Dates	Activity
December 2016	Good Clinical Practice Certification

8. MEMBERSHIP OF PROFESSIONAL AND LEARNED SOCIETIES

Health and Care Professions Council Membership – Podiatry CH33540

Signed:	
Date:	28 th July 2019

Check the Register: Details for

Name Simbarashe R Tanyanyiwa

Registration number CH33540

Location Manchester

Status Registered

Period 01/08/2020 to 01/08/2022

Additional Entitlements

- POM-A 
- POM-S 

Frequently asked questions

What do the results mean?

The full details displayed about each registrant are:

- their name;
- their registration status;



Certificate of Completion

Simbarashe Tanyanyiwa

has completed

Introduction to Good Clinical Practice (GCP)

A practical guide to ethical
and scientific quality standards in clinical research

on

05 December 2016

Modules completed:

Introduction to Research and the GCP standards

Preparing to deliver your study

Identifying and recruiting participants: eligibility and informed consent

Ongoing study delivery and data collection

Safety Reporting

Study closure

This course is worth 6 CPD credits



1. PERSONAL INFORMATION

Full name and title:	Keith Graeme McCormick
Staff ID:	1 1846175

2. PRESENT APPOINTMENT

Present post & level:	Lecturer in Podiatry - Level 5 (0.8 WTE) Director of Internationalisation (Health Sciences) (0.2 WTE) Podiatry Placement Lead (Podiatry) Podiatry Admissions Tutor (Podiatry)
Date of appointment to present post:	1 st May 2019 (Director) 1 st August 2006 (Lecturer)
Academic Unit/Division:	Allied Health Professions (AHP) School of Health Sciences
Faculty:	Faculty of Environmental and Life Sciences

3. PREVIOUS SUBSTANTIVE APPOINTMENTS

Appointment	From	To
Lecturer in Podiatry – Health Sciences	2013	2019
Podiatry Admissions Tutor	2018	2019
Podiatry Placement Lead	2015	2019
Clinical Research Fellow – Faculty of Medicine	2010	2013
AHP Placement Lead	2008	2010
Podiatry Placement Lead	2006	2010
Lecturer in Podiatry – Health Sciences	2006	2010
Lead Clinical Specialist Podiatrist – Diabetes, NHS Greater Glasgow and Clyde	2002	2006
Senior II Podiatrist, Forth Valley Primary Care NHS Trust	1997	2002

4. **QUALIFICATIONS (Educational and Professional)**

Date	Title of award	Subject	Class	Awarding body
2012	PCAP	Post Graduate Certificate in Academic Practice	Awarded	University of Southampton
2008	Prescription only medicines certificate	Access and supply of medicines	Awarded	Health Care Professions Council (HCPC) annotation
2003	Certificate	Diabetes Care	Awarded	University of Warwick
2002	MSc	Podiatry	Awarded	Queen Margaret University College
2000	Certificate in Professional Studies	Sports Podiatry	Awarded	Manchester Metropolitan University
1997	BSc(Hons)	Podiatry	2:1	Queen Margaret University College

5. **MAJOR HONOURS & DISTINCTIONS**

Honour/distinction	Date awarded
Appointed as Regional Advisor for the Faculty of Podiatric Medicine. Royal College of Physicians and Surgeons of Glasgow RCPS(Glasg).	August 2019
Nominee (as a member of the Podiatry team) for the vice Chancellors Award - Collegiately.	2019
Southampton University Student Union (SUSU) Academic Awards – Best Pastoral Support.	2019
Research Supervisor for two undergraduate final year project students: Winner of Best Poster – Research Category. Inter and Intra-rater reliability of the Toe-Brachial Pressure Index (TBPI) in healthy individuals. Tissue Viability Society Conference 1-2 nd June 2019.	2019
Research Supervisor for 4 undergraduate final year students: Winner of the Isle of Wight NHS Trust Clinical Audit Prize. Implementation of a foot protection insole for the management of recurrent foot ulcers in people who have diabetes: a service evaluation. This was the first year the competition was open to non-medics.	2019
Examiner for the Inaugural Membership exams in Podiatric Medicine RCPS(Glasg) Queen Elizabeth Hospital.	November 2017
Appointed as an Examiner at the Royal College of Physicians and Surgeons of Glasgow	2017
Inaugural Fellow of Faculty of Podiatric Medicine at the Royal College of Physicians and Surgeons of Glasgow. FFPM RCPS(Glasg) 2012. Membership of the Examinations Committee 2012 – present.	2012
Attainment of Fellow from Higher Education Academy	2012

Inaugural "Jewel in the Crown" presentation prize for the best abstract submitted - College of Podiatrists Annual Conference. Harrogate 2011. "Peripheral neurological and microvascular function is associated with cardiovascular risk in individuals with non-alcoholic fatty liver disease (NAFLD)".	November 2011
Interviewed for ITN television (Meridian) news coverage highlighting the potential importance of the NAFLD trial for patients with diabetes. Report and coverage of the study in the local newspaper (Southampton ECHO).	December 2010
Attainment of Fellowship of the College of Podiatry London (Podiatric Medicine).	2010
Awarded one of two Diabetes UK AHP Research Fellowships.	May 2010
Invited speaker. "The Development of Podiatry and its role in the modern healthcare, the UK experience". Karolinska Institute Stockholm Sweden.	December 2008
Presentation Prize: Overall winner in the Diabetic Foot category of the "Wounds UK" awards 2008 for presentation entitled "An Evaluation of the First Four Years of a Multidisciplinary Diabetic Foot Ulcer Service" £1000 prize.	June 2008
Member of a dermatology wound healing delegation from Oxford University to Yunnan province in China to share best practice for wound healing in Kunming City Hospitals and rural leprosy villages.	Feb 2006

6. TEACHING ACTIVITY

(a) Teaching responsibilities for this and the last academic year

Year: 2018-2019	Sheet 1 of 3
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Programme/Module (and code)	HLTH6092 Management of Adult Diabetes in Primary and Secondary Care	PODY3013 Research Methods 2	PHYSIO3034 Research Methods 2	PODY2028 Administration and Supply Pharmacology
Degree title (and code)	All School of Health Sciences MSc Programmes + MSc Diabetes Best Practice Medicine +CPD	BSc(Hons) Podiatry Taught with Physiotherapy	BSc(Hons) Physiotherapy Taught with Podiatry	BSc(Hons) Podiatry
Students UG/PG:	PG	UG	UG	UG
Year of study:	Varies (Part time /Full time) level 7	Year 3 (level 6)	Year 3 (level 6)	Year 2 (level 4)
Numbers:	13	27	28	10

Contact hours overall:	30	33	33	52
My contribution:	14.5 Hours	18.5 Hours	18.5 (Hours)	21 (Hours)
Teaching & assessment responsibilities:	As module lead, I am responsible for the design of the course content, delivery and assessment of the module including the formative MCQ examination and the marking of the structured review assignment. From ideation through delivery to assessment and evaluation.	As module lead, I am responsible for the design of the course content, delivery and assessment, in addition to the smooth delivery of the module my aim is to reduce the burden on supervisors by ensuring the students have a full understanding of the module requirements. I also acted as supervisor for two Pod projects.	As module lead, I am responsible for the design of the course content, delivery and assessment. My role in addition to the smooth delivery of the module my aim is to reduce the burden on academic supervisors by ensuring the students have a full understanding of the requirements of the module.	As module lead, my role is to be responsible for the delivery of the module and support the learning and development of the students to ensure they are prepared for the two examinations associated with this module. I am also responsible for setting and marking the two examinations.
Course evaluation Mean course rating:	4.7	4.2	4.4	4.6
Mean lecturer rating (for me):	Data no longer collected	Data no longer collected	Data no longer collected	Data no longer collected
Additional comments	The students are a mixture of international full-time students and domestic students from a wide range of professions, some are using the module for M level credits and CPD. I have to be flexible in my teaching approach to ensure all the students benefit from the module.	This is a challenging module, all the group projects are very different, I have to be responsive to student concerns and questions as well as smoothing over any difficulties that may arise by managing student anxiety.	This is a challenging module, all the group projects are very different, I have to be responsive to student concerns and questions as well as smoothing over any difficulties that may arise by managing student anxiety.	The first semester is an anxious time for our year 2 (level 5 students). I have to manage student expectation and ensure they have a full understanding of maximum safe dose calculations and the requirements of the POM exam.

Programme/Module (and code)	MEDI6107 Foundations of Diabetes	HLTH6147 Long Term Conditions and Partnership Care	Long Term Conditions BN5	Return to Practice (RTP) Nursing x2
Degree title (and code)	Diabetes Best Practice MSc	Postgraduate Diploma in Nursing	BSc Adult Nursing	Return to Practice Nursing
Students UG/PG:	PG	PG	UG	UG
Year of study:	Year 1 (level 7)	Year 1 (level 7)	Year 2 (level 5)	Post registration
Numbers:	15	50+	80+	20+
Contact hours overall	42	*	*	*
My contribution:	1.5 Hours	2 Hours	2 Hours	3 Hours
Teaching & assessment responsibilities:	Provide an evidenced based introduction to lower limb complications of Diabetes.	Provide a multidisciplinary overview of diabetes care, (diagnostic criteria, prevention and complications management). Provide an evidence-based introduction to lower limb complications. Pitched to level 7.	Provide a multidisciplinary overview of diabetes care, (diagnostic criteria, prevention and complications management). Provide an evidence-based introduction to lower limb complications. Pitched to level 5.	Provide a multidisciplinary overview of diabetes care, (diagnostic criteria, prevention and complications management). Pitched to level 6.
Course evaluation Mean course rating:	*	*	*	*
Mean lecturer rating (for me):	Data no longer collected	Data no longer collected	Data no longer collected	Data no longer collected

Additional comments	Most of these students are international from a wide variety of health care professions and settings. Full engagement requires time for introductions and flexibility with content to ensure a higher level of understanding across the group.	These students are very different from undergraduate nursing students and with the right level of engagement, sessions can be very interactive. Students have previous degrees and life experience so are more willing to be forthcoming with ideas and reflections.	There is a varying level of engagement with these students. I try to sense check the level of understanding by revisiting key learning points at set intervals to keep the interest up and ensure engagement.	These individuals have a huge amount to offer the Nursing profession and are generally very enthusiastic and a pleasure to teach. They have previous relevant experience and engage well with the latest thinking and progress in diabetes care. I always frontload the sessions with lots of questions to find the core level of knowledge then build on that.
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Year: 2018-2019

Sheet

3

of

3

Programme/Module (and code)	HLTH6160 Amputation Rehabilitation and Prosthetic Use	PODY3010 Complex Clinical Management	PODY3015 Business for Podiatrists	PODY10117 Principles of Podiatry Practice
Degree title (and code)	MSc Amputation and Prosthetic Rehabilitation	BSc(Hons) Podiatry	BSc(Hons) Podiatry	BSc(Hons) Podiatry
Students UG/PG:	PG	UG	UG	UG
Year of study:	Year 1 (level 7)	Year 3 (level 6)	Year 2 (level 5)	Year 1 (level 4)
Numbers:	15+	27	10	16
Contact hours overall	*	52	24	220
My contribution:	3 Hours	6 Hours	2 Hours	3 Hours
Teaching & assessment responsibilities:	Provide a multidisciplinary overview of diabetes care, (diagnostic criteria, prevention and complications management). Provide an evidence-based introduction to lower limb complications. Pitched to level 7.	Wound bed preparation and methods of debridement in the diabetic foot. Peripheral arterial disease, screening and assessment. The role of the multidisciplinary team.	Medicines in private practice. A general overview of the practicalities of using the POM certificate in private practice.	Interactive Journal club and introduction to critical appraisal

Course evaluation Mean course rating:	*	*	*	*
Mean lecturer rating (for me):	Data no longer collected	Data no longer collected	Data no longer collected	Data no longer collected
Additional comments	Most of these students are international from a wide variety of health care professions and settings. Full engagement requires time for introductions and flexibility with content to ensure a higher level of understanding across the group.	This is my particular field of expertise. I always try to open up discussion on new guidelines and research evidence. This is easier because most of my research students are engaged with issues surrounding the foot in diabetes, and wound prevention.	In these sessions I discuss the practicalities of prescribing in private practice. Some of this is a refresher from the year 2 POM module.	Teaching the first journal club in first year can be a shock for some of the students, however this is a great time for them to start looking at research papers and teasing out the limitations and strengths in a friendly environment. I present two arguments with different papers to create some class debate.

(b) Summary of Teaching & Education Responsibilities in the two Academic years prior to a) above

Year: **2017-18**

Programme/Module	Mean course rating	Mean lecturer rating (for me)	My contact hours
HLTH6092 Management of Adult Diabetes in Primary and Secondary Care	4.4	*	15
PODY3013 Research Methods 2	4.2	*	20
PHYSIO3034 Research Methods 2	4.6	*	20
MEDI6107 Foundations of Diabetes	*	*	1.5
PODY2030 Chronic Conditions	*	*	3
HLTH6147 Long Term Conditions and Partnership Care	*	*	2
Long Term Conditions. Bachelors of Nursing (Level 5)	*	*	2
Return to practice Nursing (RTP) x2	*	*	3
HLTH6160 Amputation Rehabilitation and Prosthetic Use	*	*	3
PODY3010 Complex Clinical Management	*	*	6
PODY10117 Principles of Podiatry Practice	*	*	6

Comments
During 2017-18 I continued to maintain high standards across my modules whilst focusing on my Practice placement lead role, postgraduate research student supervision and outward facing external roles. This year the Podiatry level 6 students joined the Physio students for the research methods joint module. I worked hard with my physio colleagues to ensure that all these students were successfully allocated to suitable supervisors and projects, while supervising a group myself. My strategy for this was to integrate the Physio and Podiatry students in group work to promote immersive shared learning across the two professions, by taking this approach students became interested in each other's projects and disciplines further underpinning multidisciplinary practice. Unfortunately, this year was a period of great change in our School/Faculty with much uncertainty. During this period my focus was on ensuring standards of education in the areas of learning and development that I had influence over both in podiatry and across the school whilst perusing organisational objectives.

Year: **2016-17**

Programme/Module	Mean course rating	Mean lecturer rating (for me)	My contact hours
NQCG3122 An Introduction to the Management of Adult Diabetes in Primary and Secondary Care	4.8	*	15
HLTH6092 Management of Adult Diabetes in Primary and Secondary Care	4.8	*	15
HPRS3013 Research Podiatry	4.4	*	28
PHYSIO3034 Research Methods 2	4.5	*	20
MEDI6107 Foundations of Diabetes	*	*	1.5
PODY2030 Chronic Conditions	*	*	3
HLTH6147 Long Term Conditions and Partnership Care	*	*	2
Long Term Conditions. Bachelor of Nursing (level 5)	*	*	2
Return to practice Nursing (RTP) x2	*	*	3
HLTH6160 Amputation Rehabilitation and Prosthetic Use	*	*	3
PODY3010 Complex Clinical Management	*	*	6
PODY10117 Principles of Podiatry Practice	*	*	6

Comments
<p>During 2016-17. I continued to contribute to the delivery of high-quality education including undergraduate and postgraduate teaching, delivery and administration. In this year I further consolidated my reputation as diabetes lead for the school, being invited to teach again into many of the nursing programmes (UG, PG and RTP), and also into the Amputation and Rehabilitation module and Foundations of Diabetes module in Medicine. My level 7 Diabetes module was a recommended option, and was becoming popular with nearly all the MSc Diabetes best Practice students from Medicine. This was the first year that the level 6 Physios conducted an empirical research project which replaced the protocol on the previous programme, as module lead, I successfully managed this transition ensuring the students were well informed and supported by liaising with supervisors and anticipating issues before they arose resulting in excellent evaluations. I was commended for this work by our AHP Director at the time. At the same time I managed the Podiatry level 6 students who were still rolling out on the old programme (protocol), despite some students feeling aggrieved that they were not having the same opportunities as the Physio students on the new programme, I managed to keep morale high and attain good evaluations for this module by seeing students individually and maintaining high standards of academic rigour.</p>

*Because I am not directly involved with the management of these modules, I do not have this information/data to hand. My teaching is well received and of a high quality, this can also be evidenced by recent peer review if required.

In addition to the above teaching I also facilitate a one hour placement preparation session for Clinical Practice 1/2/and 3 BSc (Hons) Podiatry (PODY1019/2029/3011) as part of my placement role 2016-Present. I also conduct clinical visits as required (estimated 10 hours).

c) Summary of significant personal achievements in education and teaching

In 2008 I was successful in obtaining funding from British Council as part of the Prime Minister's initiative for International Education (PMI2). We identified a remote clinical educator's network, and delivered training to 14 Podiatrists in Singapore. For the first part of the project, five third year students spent a month "hands on" placement in five different hospitals in Singapore (Jan-Feb 2009), repeat funding was sought and granted allowing further students to gain a similar experience. I presented this work at our National College of Podiatry conference in 2010. As project manager this was a significant achievement and It is widely recognised by collaborators and colleagues that this initiative demonstrated our interest in partnership working, and contributed to the subsequent steady stream of applicants from our partners and their associates in Singapore to date. As a result of these regular applications we have been graduating Podiatrists from Singapore for 10 years and we have over 20 Southampton working as podiatrists in Singapore working hard to contribute to reducing amputation rates which relates to my subject specific interests. In May this year I led a further delegation to Singapore in my role as Director of Internationalisation and we are working to renew clinical partnerships with all three health clusters and re-establish our relationship with the Ministry of Health in Singapore.

I was a named collaborator on an Erasmus exchange programme with the Karolinska institute in Stockholm Sweden and was invited to teach for 3 days with a second visit to conduct clinical MSK referral examinations as external examiner. 2 students from Karolinska spent their second year in Southampton obtaining their access and supply certification and administration of local anaesthetics annotation.

Another personal achievement in education relates to the development of my role as diabetes lead across the school (2015-Present) and in partnership with the Faculty of Medicine as a member of the senior leadership team on the MSc Diabetes Best Practice Programme. For the last three years I have been teaching into many of the undergraduate and postgraduate programmes across the school and I am module lead for the management of Adult Diabetes MSc module within the school.

I manage and chair the Clinical Educators Expert Reference Group (CEERG) which meets every quarter with our lead clinical educators from practice, this strategic group plans the annual conference and informs developments and policy for podiatry placements. Our clinical network and high level of engagement with external partners (primarily the NHS and Virgin Healthcare) has been commended by our external examiners as an excellent example of stakeholder engagement. I provide direct mentorship for the 8 lead clinical educators and provide onsite clinical educators training across south central and beyond. A number of years ago I developed a package of clinical education with an Occupational Therapy colleague which was based on

c) Summary of significant personal achievements in education and teaching

the APPLE (OT) and ACE (Physio) mode called PACE (Podiatry Accredited Clinical Education), this was adopted nationally by our professional body (College of Podiatry London) and accredited clinical educators are added to the register (RACE) which is held by the COP.

In addition to the MSc in Diabetes Best Practice I have been involved continuously in curriculum development within the school. As AHP placement lead I took a lead role in the C2009 revalidation answering all the questions and queries relating to AHP placements, I was also a member of the revalidation curriculum programme team. I was also present at the C2015 event answering questions on UG research, and the C2019 revalidation event in my capacity of admissions tutor and placement lead. For both these events I also reviewed and contributed to paperwork related to my own modules and to practice placement for C2019.

Please also see details of the two Student prizes in the Major Honours and distinctions section.

7. POSTGRADUATE SUPERVISION

a) Number of students

Degree	Current	Completed	Total to date
PhD	2	0	2
MSc Diabetes Best Practice	1	2	3
MRES	1	0	1
Pre-Registration MSc Physiotherapy	1	1	2
MSc Amputation and Rehabilitation	0	1	1
MSc Nursing	1	2	2

b) Details of the three most recent higher degree students supervised to completion

Student	Degree and title of thesis	Start date	Completion date
Gavinash Persaud	MSc Diabetes Best Practice: What are the patient and prescribing factors that influence the use of offloading devices for the diabetic foot? A systematic review.	2018	2019
Charlotte Matthews	MSc Amputation and Prosthetic Rehabilitation: Looking after the last leg: what can a scoping review tell us about practitioners' views on diabetic patients education in regards to preventing contralateral limb loss?	2017	2018
Benita Patel	MSc Diabetes Best Practice: Measuring the delay in the assessment and referral of wounds against existing set criteria in elderly people with diabetes in a hospital setting.	2017	2018

8. RESEARCH ACTIVITY

a) Summary of current research

I am currently second supervisor for two clinical academic PhD students. I had significant input into the design of one of these projects and this particular study is a continuation of my work in microvascular and neurological function (see section c) using novel technology which has the potential to change the way we measure these parameters in clinical practice. Both students are progressing well. Through my research students I am slowly developing a small-scale research strategy and programme of work related to the clinical assessment and management of foot disease in diabetes, which now also includes patient and practitioner perceptions in this field. As my role is primarily in teaching, I am slightly constrained in the development of these activities however I supervise 4 additional MSc/MRES students who are all researching in this field and I am currently the School expert in this area. I work closely with Professor Cathy Bowen and her postdoctoral researchers to identify where my advice can be best utilised within the research group without impacting too much on my other activities. Although I do not currently hold any research grants my contribution (particularly to the PG students I supervise) is not insignificant and we currently have two papers in preparation with findings from 2 M level student projects. I anticipate there will be many more academic outputs from the two PhD students once the come closer to completion.

I am part of a small group of academics lead by Debbie Thackray, we are currently looking for funding to pilot our "Sim for Success" programme of work which will enhance preclinical training for AHP students by utilising high fidelity simulation techniques to simulate the clinical environment. By introducing these modalities, we believe we will improve the student experience by preparing students for placement. I was a named applicant on a global partnership award application in May 2019 in collaboration with the University of Sidney which was unsuccessful, however we continue to seek funding for this important work which has the potential to improve the student experience. We will be supervising a group of undergraduate AHP research students as part of my module this year to evaluate a pilot of "Sim for success" in 15 AHP students prior to Placement 1 in June.

b) Summary of research in the previous three years

In the last three years my research activity has been very much linked to my undergraduate research modules (Podiatry and Physiotherapy level 6) and my postgraduate students as second supervisor for 2 PhD students and as supervisor for 6 MSc students across four level 7 programmes (MRES, MSc Diabetes Best Practice, Pre-Registration MSc Physiotherapy and MSc Nursing. My main interests are in vascular (micro and macro) and neurological function in the lower limb particularly in individuals with or at risk of diabetes. I am also interested in wound healing in diabetes, and structural musculoskeletal changes in diabetes.

c) Summary of significant personal achievements in research

Between 2010 and 2013 I spent three years at the Biomedical Research Centre for Nutrition (Southampton) as a clinical research on a large double blind randomised controlled trial investigating the effects of Omega 3 Fish oil on Fatty liver disease. My duties were many and varied including recruitment to the trial, working on databases, data collection using multiple clinical tests/modalities using standardised operating procedures, laboratory work and data analysis. I was also responsible for the day to day running of certain aspects of the trial. The patients recruited on the trial displayed many of the features of the metabolic syndrome and were at high risk of diabetes and potentially foot ulceration. For my own research I was able to conduct peripheral microvascular and neurological (blood vessel and nerve) function tests on these patients pre and post intervention resulting in novel findings which I were published with the support of my colleagues in a high-quality international Journal (Diabetologia). I was also privileged to be third author on the main publication of the study which showed a significant reduction in liver fat in the fish oil group, a finding of international importance. This paper was published in the journal Hepatology.

During my time working on this trial I learned a huge amount about diabetes, the metabolic syndrome and also about quantitative research methods. This augmented my knowledge from my MSc, my Warwick diabetes care qualification and my general knowledge as a podiatrist. This high-level learning has informed the teaching I am engaged with now across the School of Health Sciences in diabetes and research methods.

d) Research grants and contracts

Dates	Award holder(s)	Funding body	Title	Value
April 2011	Keith McCormick	Repeat Funding; Prime Minister's Initiative for International Education 2 (PMI2) British Council	Education Grant for International student Mobility. Collaboration between the University of Southampton and the Postgraduate Allied Health Institute Singapore.	£5600
January 2010	Keith McCormick Christopher Byrne Geraldine Clough	Diabetes UK Fellowship Award	The effect of purified n-3 fatty acids on peripheral neurological and microvascular function in people with insulin resistance.	£197,122
April 2008	Keith McCormick	Prime Minister's Initiative for International Education 2 (PMI2) British Council	Education Grant for International student Mobility. Collaboration between the University of Southampton and the Postgraduate Allied Health Institute Singapore.	£6880

9. PUBLICATIONS

Please refer to the guidance notes for the format of publications listings. All of your publications in chronological order within each category following the British Standard for bibliographic references. With multiple authorship, if one is the main author, that author's name appears in Italics.

- Please star (*) in the left margin what you consider were especially significant publications.
- Please enter a 'T' against those related specifically to publications about teaching.

Books - Authored

N/A

Books - Edited

N/A

Books - Short Works

T Managing diabetes in people with foot complications. / Patel, Mayank; **McCormick, Keith.** Management of Diabetic Foot Complications. Springer London, 2015. p. 39-49. Chapter

Conference Contributions - Refereed

T Inter and intra-rater reliability of the toe-pressure index (TBPI) in healthy individuals, Clark A., Price R., Tanyanyiwa S., **McCormick K.G.** Tissue Viability Society Conference Publication p52. 1st-2nd May 2019.

T The international mobility of UK podiatry students; a government funded initiative. **McCormick KG.**, Bowen C.J., Tong J., Potter M.J. 2010 SOCAP Conference Publication. Journal of Foot and Ankle Research 3. Suppl 1: O16.

Non-alcoholic fatty liver disease severity is related to increased cardiovascular risk independently of hyperglycaemia and obesity. Hudson S., Bhatia L.S., **McCormick K.G.**, Bateman A., Nash K., Curzen N.P., Clough G.F., Calder P.C., Byrne C.D.

Diabetologia. Conference: 47th Annual Meeting of the European Association for the Study of Diabetes, EASD 2011 Lisbon Portugal. Conference Start: 20110912 Conference End: 20110916. Conference Publication: (var.pagings). 54 (pp S110), 2011. Date of Publication: September 2011.

Microvascular and sensory dysfunction in individuals with non-alcoholic fatty liver disease (NAFLD) at risk of cardiovascular disease. **McCormick K.G.**, Bhatia L.S., Griffin M.J., Calder P.C., Nash K., Byrne C.D., Clough G.F.

Microcirculation. Conference: 61st Meeting of the British Microcirculation Society London United Kingdom. Conference Start: 20110418 Conference End: 20110419. Conference Publication: (var.pagings). 18 (5) (pp 418), 2011. Date of Publication: July 2011.

Liver fat content in non-alcoholic fatty liver disease is related to whole body insulin resistance independent of body fat percentage. Bhatia L.S., Fletcher A., **McCormick K.G.**, Umpleby A.M., Curzen N.P., Peebles C., Shojaee-Moradie F., Scorletti E., Darekar A., Clough G.F., Calder P., Nash K., Byrne C.D. Diabetic Medicine. Conference: Diabetes UK Professional Conference 2012 Glasgow United Kingdom. Conference Start: 20120307 Conference End: 20120309. Conference Publication: (var.pagings). 29 (pp 61-62), 2012. Date of Publication: March 2012.

Peripheral microvascular dysfunction is associated with cardiovascular risk independently of HbA1c and diabetes in non-alcoholic fatty liver disease. **McCormick K.G.**, Bhatia L.S., Scorletti E., Nash K., Calder P., Clough G.F., Byrne C.D.

Diabetic Medicine. Conference: Diabetes UK Professional Conference 2012 Glasgow United Kingdom. Conference Start: 20120307 Conference End: 20120309. Conference Publication: (var.pagings). 29 (pp 63), 2012. Date of Publication: March 2012.

Insulin resistance and glycaemic control are independently associated with increased risk of liver fibrosis. Scorletti E., Bhatia L.S., **McCormick K.G.**, Moyses H., Clough G.F., Nash K., Calder P., Byrne C.D. Diabetic Medicine. Conference: Diabetes UK Professional Conference 2012 Glasgow United Kingdom. Conference Start: 20120307 Conference End: 20120309. Conference Publication:

(var.pagings). 29 (pp 63), 2012. Date of Publication: March 2012.

***Simultaneous measurement of microvascular blood flux and oxygenation in human skin using a combined laser doppler fluximetry and white light reflectance spectroscopy probe. McCormick K.G., McDonald E.F., Valletta J.J., Gush R., Chipperfield A.J., Clough G.F. EmbaseMicrocirculation. Conference: 2nd Joint Meeting of the British and American Microcirculation Societies 62nd Meeting of the British Microcirculation Society. Oxford United Kingdom. Conference Start: 20120702. Conference End: 20120705. Conference Publication: (var.pagings). 20 (1) (pp 54-55), 2013. Date of Publication: January 2013. [Journal: Conference Abstract] AN: 71114445 (Oral Presentation Key Note)**

Microvascular blood flow and sensory function in individuals with non-alcoholic fatty liver disease (NAFLD). McCormick K.G. ,Scorletti E. ,Bhatia L.S. ,Nash K. ,Griffin M.J. ,Calder P.C. ,Byrne C.D.,Clough G.F. EmbaseMicrocirculation. Conference: 2nd Joint Meeting of the British and American Microcirculation Societies 62nd Meeting of the British Microcirculation Society Oxford United Kingdom. Conference Start: 20120702 Conference End: 20120705. Conference Publication: (var.pagings). 20 (1) (pp 88), 2013. Date of Publication: January 2013.

Insulin resistance and glycaemic control but not liver fat mass or visceral fat mass are associated with markers of liver fibrosis in non-alcoholic fatty liver disease. Scorletti E.S., Bhatia B.L., McCormick K., Moyses G.F.M., Clough G.C., Nash P.C.N., Calder P.C.C., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2013. Manchester United Kingdom. Conference Start: 20130313. Conference End: 20130315. Conference Publication: (var.pagings). 30 (pp 60), 2013. Date of Publication: March 2013.

[Journal: Conference Abstract] AN: 71018924

Simultaneous measurement of microvascular blood flux and tissue oxygenation in human skin. Clough G., Kuliga K., McCormick K., Gush R., Chipperfield A. EmbaseFASEB Journal. Conference: Experimental Biology 2013, EB. Boston, MA United States. Conference Start: 20130420. Conference End: 20130424. Conference Publication: (var.pagings). 27 (no pagination), 2013. Date of Publication: April 2013. [Journal: Conference Abstract] AN: 71156011

Benefits of docosahexanoic acid tissue enrichment in non-alcoholic fatty liver disease: Results from a randomised, double-blind, placebo-controlled study testing the effects of omega-3 fatty acid treatment. Byrne C.D., Scorletti E., Bhatia L., McCormick K., Clough G., Nash K., Hodson L., Calder P. EmbaseDiabetes. Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Start: 20140613. Conference End: 20140617. Conference Publication: (var.pagings). 63 (pp A468), 2014. Date of Publication: June 2014.

[Journal: Conference Abstract] AN: 71560190

Potential benefits of purified long chain omega-3 fatty acid treatment in non-alcoholic fatty liver disease (NAFLD): A potential treatment for early NAFLD in metabolic syndrome and Type 2 diabetes? Results from the WELCOME study. Scorletti E., Bhatia B., McCormick K.G., Clough G.F., Nash K., Hodson L., Calder P.C., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2014. Liverpool United Kingdom. Conference Start: 20140305. Conference End: 20140307. Conference Publication: (var.pagings). 31 (pp 1), 2014. Date of Publication: March 2014. [Journal: Conference Abstract] AN: 71554280

QTc duration is independently associated with tissue palmitoleic acid levels but is not affected by omega-3 fatty acid treatment in patients with non-alcoholic fatty liver disease and features of the

metabolic syndrome. Palmer C.E., Scorletti E., Clough G.F., **McCormick K.G.**, Bhatia L., Targher G., Curzen N.P., Calder P.C., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2014. Liverpool United Kingdom. Conference Start: 20140305. Conference End: 20140307. Conference Publication: (var.pagings). 31 (pp 2), 2014. Date of Publication: March 2014. [Journal: Conference Abstract] AN: 71554281

The patatin-like phospholipase domain-containing protein 3 (PNPLA3) G allele variant (148M) is associated with insulin resistance independently of diabetes status and liver fat quantity. Scorletti E.S., Bhatia L., McCormick K.G., Clough G.F., Nash K., Hodson L., Moyses H., Calder P.C., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2015. London United Kingdom. Conference Start: 20150311. Conference End: 20150313. Conference Publication: (var.pagings). 32 (pp 61), 2015. Date of Publication: March 2015. [Journal: Conference Abstract] AN: 71820981

Peripheral sensory nerve function is independently associated with microvascular function, but neither are improved by n-3 fatty acids. **McCormick K.G.**, Scorletti E.S., Bhatia L., Calder P.C., Griffin M.J., Clough G.F., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2015. London United Kingdom. Conference Start: 20150311. Conference End: 20150313. Conference Publication: (var.pagings). 32 (pp 99), 2015. Date of Publication: March 2015. [Journal: Conference Abstract] AN: 71821076

The combination of insulin resistance and the patatin-like phospholipase domaincontaining protein-3 (PNPLA3) 148m (G allele variant) is associated with markedly higher levels of liver fat. Scorletti E., Bhatia L., **McCormick K.G.**, Clough G.F., Hodson L., Nash K., Calder P.C., Byrne C.D. EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2016. Glasgow United Kingdom. Conference Start: 20160302. Conference End: 20160304. Conference Publication: (var.pagings). 33 (pp 28-29), 2016. Date of Publication: March 2016. [Journal: Conference Abstract] AN: 72230627

A clinical audit of a Dorset Type 2 diabetes education programme. Buckley K., Alicea S., **McCormick K.** EmbaseDiabetic Medicine. Conference: Diabetes UK Professional Conference 2016. Glasgow United Kingdom. Conference Start: 20160302. Conference End: 20160304. Conference Publication: (var.pagings). 33 (pp 123), 2016. Date of Publication: March 2016. [Journal: Conference Abstract] AN: 72230887

Conference Contributions – Other (Pre 2010)

McCormick KG. (1997) 'Do patients with POAD receive appropriate Podiatric care?' Poster presentation. National Podiatry Conference. Journal of British Podiatric Medicine, Vol. 52, No. 5, May, pp 65.

McCormick KG. & Young MJ (1999) 'A Clinical Audit of the Diabetic Foot Ulcer Clinic, at the Royal Infirmary of Edinburgh' Oral Presentation Society of Chiropodists and Podiatrists. Dublin. British Journal of Podiatry, Vol. 2, No. 3, August 1999, pp 95

McCormick KG (2003) 'A Retrospective Evaluation of Continuing Professional Development (CPD) Activity in NHS Podiatry in Scotland.' Society of Chiropodists and Podiatrists. Faculty of Management (Scotland). Royal Edinburgh Hospital. Oral Presentation

McCormick KG (2004) 'Clinical evaluation of a hydrofibre dressing with ionic silver in a series of 12 patients'. Oral poster presentation. Conference Proceedings Wounds UK.. Harrogate.

McCormick KG et al (2005) 'Are there predictors of future diabetic foot ulceration?' Poster presentation. Diabetes UK. Diabetic Medicine, Vol 22, Supp 2, pp 93

McCormick KG, Padmanabhan S, Hopkinson HE, McCallum RW. (2005) 'Are there predictors of future diabetic foot ulceration?' Oral presentation. Australasian Podiatry Conference Christchurch New Zealand. Book of Abstracts, September , pp 79

Panel Member, Professional Select Committee on the management of diabetic foot ulcers. Manchester Town Hall. December 2005

Invited Speaker: 'Managing the Neuropathic limb with limited resources' 2nd Affiliated Hospital of Kunming. Kunming. China. February 2006

McCormick KG (2007) 'A Critical Analysis of the Nail Surgery Service in a large Teaching Hospital'. Oral presentation. FIP World Congress of Podiatry. 26th - 28th May. Copenhagen.

McCormick KG (2007) 'An evaluation of the First Four Years of a Multidisciplinary Diabetic Foot Ulcer Clinic'. Poster presentation. Diabetic Limb Salvage Conference. 27th - 29th Sept. Washington DC.

Invited Speaker: 'Debridement, Wound bed Preparation and Dressing Selection'. Society of Chiropodists and Podiatrists Annual Conference. 17th - 19th October 2007. Harrogate.

Spruce ME, Sweet J, Bowen G, **McCormick KG** (2007) 'Multidisciplinary Debridement Course: A New Approach' Poster presentation. Wounds UK. 12th - 14th November. Harrogate.

McCormick KG (2007) 'An evaluation of the First Four Years of a Multidisciplinary Diabetic Foot Ulcer Clinic' Oral presentation. Wounds UK..12th - 14th November. Harrogate.

Invited Session Chair and Abstract Marker: Diabetes UK. 5th - 7th March 2008. Glasgow

Invited Speaker: 'Diagnostic Tests: What do they mean?' Regional Podiatry Conference. Ark Centre. Basingstoke General Hospital. 17th April 2008

'Multidisciplinary Management of Diabetic Foot Disease, a UK Perspective'. Continuing Professional Development Seminar. British Council. Singapore. 18th September 2008.

Invited Speaker: 'The Development of Podiatry and its role in the modern healthcare, the UK experience' Karolinska Institute. Sweden. 5th December 2008

Departmental/Research Working Papers

N/A

Edited Works: Contributions

N/A

Editorships - Journal

Although not appointed as editor, from 2006 - present I have reviewed papers for The Journal of Foot and Ankle Research, Journal of Tissue Viability, Journal of Lower Extremity Wounds and Podiatry Now.

Editorships - Newsletter

N/A

Journal Letters

N/A

Journal Papers - Academic Journals

Scorletti E, Bhatia L, **McCormick KG**, Clough GF, Nash K, Hodson L, Moyses HE, Calder PC, Byrne CD; on behalf of the WELCOME Study Investigators. Effects of purified eicosapentaenoic and docosahexaenoic acids in non-alcoholic fatty liver disease: Results from the *WELCOME study. *Hepatology*. 2014 Jul 4. doi: 10.1002/hep.27289. [Epub ahead of print]

*Scorletti E, Bhatia L, **McCormick KG**, Clough GF, Nash K, Calder PC, Byrne CD; on behalf of the WELCOME study Investigators. Design and rationale of the WELCOME trial: a randomised, placebo-controlled study to test the efficacy of purified long chain omega-3 fatty treatment in non-alcoholic fatty liver disease. *Contemp Clin Trials*. 2014 Mar; 37(2):301-11. doi: 10.1016/j.cct.2014.02.002. Epub 2014 Feb 18

Scorletti E., West A.L., Bhatia L., Hoile S.P., **McCormick K.G.**, Burdge G.C., Lillycrop K.A., Clough G.F., Calder P.C., Byrne C.D. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: Results from the WELCOME trial. EmbaseJournal of Hepatology. 63 (6) (pp 1476-1483), 2015. Date of Publication: 01 Dec 2015. [Journal: Article] AN: 607132419

***McCormick K.G.**, Scorletti E., Bhatia L., Calder P.C., Griffin M.J., Clough G.F., Byrne C.D. Impact of high dose n-3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. EmbaseDiabetologia. 58 (8) (pp 1916-1925), 2015. Date of Publication: 29 May 2015. [Journal: Article] AN: 604624091

*Clough G.F., **McCormick K.G.**, Scorletti E., Bhatia L., Calder P.C., Griffin M.J., Byrne C.D. Higher body fat percentage is associated with enhanced temperature perception in NAFLD: results from the randomised Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacer thErapy trial (WELCOME) trial. EmbaseDiabetologia. 59 (7) (pp 1422-1429), 2016. Date of Publication: 01 Jul 2016. [Journal: Article] AN: 610081933

Journal Papers - Professional Journals

Sharp A & **McCormick KG** (2002) 'Alginate dressings and the healing of diabetic foot ulcers' *The Diabetic Foot*, Vol 5, No 4, pp 179-186

Bristow IR. & **McCormick KG**. (2004) Report. 9th European Wound Healing Summer School. Oxford University. Podiatry Now, Vol. 7, No. 10, pp 36-37

Fox M, Smith L, **McCormick K** (2014) et al Palpating for abdominal aortic aneurysms within a specialist podiatrist and nurse-led peripheral arterial disease service: A pulse too far? *The Diabetic Foot Journal*. 17 (pp11-15). 2014 March.

Journal Papers - Popular Journals

N/A

Official Reports: Whole Report

N/A

Official Reports: Part of Report

N/A

Review Articles in Academic Publications

N/A

Reviews of Single Academic Books

N/A

Other Publications – Research

N/A

Other Publications - Research Equivalent

N/A

Other Media - Research : All Produced by Author

N/A

Other Media - Research : Part Produced by Author

N/A

Other Media - Research Equivalent: All Produced by Author

N/A

Other Media - Research Equivalent: Part Produced by Author

N/A

Exhibitions - Solo

N/A

Exhibitions - Group

N/A

Design Practice

N/A

Commissions

N/A

Public Appearances (research-related only)

NA

Consultancy

N/A

Citations

N/A

Web sites/Web site design/CD-ROM

N/A

Other

N/A

10. CONTRIBUTIONS TO LEADERSHIP, MANAGEMENT & ENGAGEMENT

A summary of significant contributions to the development and running of the University.

a) The Academic Unit/Department

Dates	Nature of contribution
2006 -2010	Podiatry Placement Lead
2006-2008	Member of the Clinical Placement Organisation Team (CPOT)
2008-2010	AHP Lead for Practice Placement
2008-2010	Chair of the Clinical Placement Organisation Team (CPOT) (As AHP Lead)
2008-2010	Member of the Programme Integration Group
2008-2009	Member of the Revalidation Curriculum Programme Team
2009-2010	Member of the Contract Monitoring Group (NESC)
2009-2010	International Student Staff Guidance Group
2009-2010	Strategic Retention and Attrition Group
2009-2010	Chair of the Clinical Educators Development Review
2014-present	Podiatry subcommittee meetings
2015-present	PhD supervisor
2015-present	AHP placement meetings

b) The Faculty or Budgetary Group

Dates	Nature of contribution
2013-present	MSC Advanced Clinical Practice Post Graduate Teaching Sub Committee (FoHS)
2014- 2016	Member of the Special Considerations Panel (FoHS)
2015-present	Practice Learning Committee (PLC) (FoHS)
2017-2018	C2018/19 Undergraduate Research Working Group (FoHS)
2018-present	Admissions Tutor Meetings
November 2018	Student Fitness to Practice Panel

2019-present	Senior Leadership Group Meetings
2019-present	School full Board Meetings

c) The University

Dates	Nature of contribution
2015-present	MSc Diabetes best practice Programme Committee (Faculty of Medicine).
2016-present	Podiatry NHS Clinical Educators Expert Reference Group (Chair)
2018-present	Admissions Tutor Forum
2019-present	FELS International planning meetings (Quarterly)

CONTRIBUTIONS TO ENTERPRISE

Dates	Nature of contribution
N/A	

11. STAFF DEVELOPMENT AND TRAINING

a) Staff development and training activities undertaken

Over the last three years (including current year) plus any significant activities in previous years.

Dates	Activity	Hours
24 th January 2017	Rethinking Strategies for Large Group Teaching	3 hours
6 th April 2017	Principles of Curriculum Design and Development	6 Hours
8 th May 2017	Let's Talk about Marking: levels and Standards	3 Hours
9 th November 2017	Part 2 Membership Examiner training. Royal College of Physicians and Surgeons(Glasg)	6 Hours
1 st July 2019	Building your educational Portfolio (Chep)	2 Hours
11 th July 2019	Student fitness to practice training (Field Fischer)	6 Hours
13 th September 2019	External Examiner Induction and Training. University of Ulster	4 Hours
25 th October 2019	Royal College of Physicians and Surgeons (Glasg). Regional Advisors Training	5 Hours
2016-2019	Mandatory Health and Safety/Diversity and Inclusivity on line training as requested	3 hours total

b) Staff development and training activities coordinated, tutored, led or initiated

Over the last three years (including current year) plus any significant activities in previous years.

Dates	Activity	Hours
2016	Member of a working group to develop and deliver two International student support staff training workshops within the Faculty (as was)	2 x 3Hours

2016	Invited workshop facilitator: International Office Seminar (UOS) - International student support “The Singapore Podiatry Experience”	1 Hour
October 2019	Training for members of the UOS outreach team. “Selling podiatry to potential applicants”	2 hours

c) Conference attendance

Major conferences attended over the last three years (including current year) plus any significant participation in previous years.

Dates	Title	Nature of involvement
Please see list of conference contributions. All conferences where I am first author (Poster or Oral presentation) were attended by me personally.		

d) Study leave and leave (including study leave/ sabbatical)

Taken over the last three years (including current year).

Dates	Purpose
N/A	

e) Activities and achievements

In the most recent period of leave including study leave/ sabbatical.

Dates	Purpose
N/A	

ACADEMIC AND PROFESSIONAL ACTIVITIES OUTSIDE THE UNIVERSITY

Details for the last three years (including current year) together with a summary of significant activities in previous years.
2008: External panel member for the validation of two new MSc routes at Huddersfield University; MSc Theory of Podiatric Surgery and MSc Podiatric Medicine.
2008: External Examiner for MSK clinical examination referral assessments. Karolinska Institute. Stockholm. Sweden.
2010 – Present: Wider Committee Foot in Diabetes UK (FDUK)
2011: External Panellist for the elective review of the MSc Musculoskeletal Studies (Lower Limb). Cardiff Metropolitan University.
2012 – Present: Member of the exams development group for the Faculty of Podiatric Medicine (FPM). Royal College of Physicians and Surgeons of Glasgow (RCPS).
2014: Represented the College of Podiatry as a professional body panel member for the validation of Graduate Cert/PG Cert Prescribing, MSc Physiotherapy with Independent and Supplementary prescribing, MSc Podiatry with Independent and Supplementary Prescribing. University of Brighton. Faculty of Health and Social Care.
2014-2018: External Examiner for the UG BSc (Hons) Podiatry course. London Centre for Podiatric Education. University of East London.

Details for the last three years (including current year) together with a summary of significant activities in previous years.

2016 – Present: External Examiner MSc Musculoskeletal Studies (Lower Limb) / Msc Advances Practice (Musculoskeletal Studies). Cardiff Metropolitan University.

2017: Appointed as Examiner for the FPM RCPS(Glasg)

Feb 2019: External Panellist for the Revalidation of the MSc Advancing Practice – Lower Limb preservation.

August 2019: Appointed as a Regional Advisor for the FPM RCPS(Glasg)

12. COMMUNITY ACTIVITIES

Details for the last three years (including current year) together with a summary of significant activities in previous years.

N/A

13. MEMBERSHIP OF PROFESSIONAL AND LEARNED SOCIETIES

Member of the College of Podiatry. (1997 – ongoing)

Registrant with the UK Health and Care Professions Council. (1997 – ongoing)

Committee Member (wider group) Foot in Diabetes UK (FDUK). 2010 –ongoing)

Fellow of the College of Podiatry (Podiatric Medicine). (2010 –ongoing)

Inaugural fellow of the Faculty of Pod Med, Royal College of Physicians and Surgeons (Glasg) (2012- ongoing)

Fellow of the Higher Education Academy 2012 –(ongoing)

14. OTHER RELEVANT INFORMATION

I am privileged to have worked as a lead extended scope practitioner in the NHS where I set up and managed an award winning multidisciplinary diabetic foot clinic, and reducing amputation rates significantly in a 400-bed hospital in Glasgow and the wider community. I have been committed to the learning and development of others for over 20 years. By presenting my clinical findings at national and international conferences I became interested in academia and I was fortunate to have the opportunity to bring my clinical and management experience to Health Sciences at the University of Southampton. Since then I have been rigorously trained in education and research and now have a wealth of knowledge and experience in both these domains. I have worked at the highest level of research (Biomedical research Unit for Nutrition Southampton) and have had my personal research findings published in International journals. I have a national and international reputation in my primary field of interest.

I have held leadership positions in the school/faculty in placements and admissions and I am now Director of Internationalisation for the School of Health Sciences. Through all these activities I have made myself simply better, and my outward facing activity in learning and development have contributed to building our reputation both in Podiatry and the wider health agenda.

I am a naturally compassionate person who is committed to the wellbeing of colleagues and students. I live by my own moral and ethical code and take pride in my honesty and integrity. I think that my activities in the work place help to contribute to the delivery of excellence, and the greater goal of providing exemplary learning and development opportunities for our students. I look forward to working together with the School and Faculty into 2020, setting new goals and confronting new challenges in the pursuit of excellence.

Signed:	
Date:	28 th October 2019

1. PERSONAL INFORMATION

Full name and title:	Professor Catherine Jane Bowen
Employee number:	11594664
Date of birth:	23.06.66

2. PRESENT APPOINTMENT

Present post & level:	Professor in Podiatry – level 7
Date of appointment to present post:	01.08.2016
Academic Unit/Division:	School of Health Sciences Active Living Research Theme
Faculty:	Environmental and Life Sciences

3. PREVIOUS SUBSTANTIVE APPOINTMENTS

Appointment	From	To
MRes, NIHR lead, Faculty of Health Sciences, University of Southampton	2010	2015
Professional Lead, Podiatry, School of Health Professions & Rehabilitation Sciences, University of Southampton	2008	2011
Programme Leader, BSc Hons Podiatry, School of Health Professions & Rehabilitation Sciences, University of Southampton	2003	2008
MSc Podiatry Course Leader, School of Health Professions & Rehabilitation Sciences, University of Brighton	2000	2003
Senior Lecturer, School of Health Professions, University of Brighton	1996	2000
Clinical Podiatry Team Leader & Research Rheumatology intern, Oxleas NHS Trust, Bexleyheath	1994	1996
Senior II Podiatrist, Optimum Health Services Trust, Lewisham	1992	1994
Senior I Podiatrist, Placement Instructor, Milton Keynes Health Authority	1990	1992
Senior II Podiatrist, Aylesbury Vale Health Authority	1987	1990

4. QUALIFICATIONS (Educational and Professional)

Date	Title of award	Subject	Class	Awarding body
2009	Doctor of Philosophy	Ultrasound imaging/foot and ankle rheumatology	N/A	University of Southampton
2002	POMS cert.	Access & supply of medicines.	N/A	The Chiropodists Board of the CPSM
2000	ILT membership	Learning & Teaching in Higher Education	N/A	Institute for Learning & Teaching
1998	PG Cert: Learning & Teaching	Higher Education	N/A	University of Brighton / SEDA
1996	Master of Science	Podiatry	N/A	University of Brighton
1992	Bachelor of Science with Honours	Podiatry	2:1	University of Brighton
1989	City & Guilds Certificate	Teaching in further education (730)	N/A	Aylesbury Vale College of FE
1987	Diploma	Podiatric Medicine (with State Registration)	N/A	Salford College of Further Education

5. MAJOR HONOURS & DISTINCTIONS

Honour/distinction	Date awarded
Invited appointment: Adjunct Professor Faculty of Health, Podiatry, at the Queensland University of Technology, Australia.	2020
The College of Podiatry 'Jewel in the Crown' National Conference presentation award. This award was given to my post-doctoral senior research fellow, Lucy Gates, in the prestigious keynote opening session. The award was in recognition of our work as the best research paper: 'The natural history of radiographic first metatarsophalangeal joint osteoarthritis: a nineteen-year population based cohort study' (1500 attendees).	2019
The College of Podiatry 'Jewel in the Crown' National Conference presentation award. This award was given to my PhD student, Annabelle Mizzi in the prestigious keynote opening session. The award was in recognition of our work as the best research paper: 'The progression rate of peripheral arterial disease in patients with intermittent claudication': (1500 attendees).	2018
Invited to deliver Keynote Address for the College of Podiatry Conference. I have been peer nominated to deliver the keynote address to the largest podiatry conference in Europe (1600+ delegates) on 'raising the profile of podiatry through robust evidence'.	2016
Invited to deliver Keynote Address for the Australasian Podiatry Association Annual Conference. I have been peer nominated to deliver the keynote address to the largest podiatry conference in the Southern Hemisphere with an overview of the development of diagnostic ultrasound techniques and research for the foot and ankle.	2016
National Institute for Health Research Career Development Fellowship. I am the first podiatrist in the UK to be awarded such a senior medical sciences prestigious Department of Health Fellowship.	2015
The Society of Chiropodists and Podiatrists Meritorious Medal for outstanding contribution to the Podiatry profession. I was one of four podiatrists (out of a 15,000 membership) peer nominated for this award in recognition of my significant and devoted service through sustained contribution to national and international clinical development and research in rheumatology.	2014
Appointed Chairperson of the Research and Development Committee, the College of Podiatry. This appointment was made in recognition of my sustained leadership in engaging my profession in research and development.	2014
The College of Podiatry 'Jewel in the Crown' National Conference presentation award. This award was given to my PhD student, Lucy Gates in the prestigious keynote opening session. The award was in recognition of our work as the best research paper: Defining a multidisciplinary musculoskeletal foot and ankle assessment: results of an international consensus statement (1500 attendees).	2014

Staff Achievement Award. I received this award for my leadership and ongoing development of our Faculty Athena SWAN agenda.	2014
University of Southampton (SUSU) nomination for the best lecturer awards. My undergraduate students nominated me for this award in recognition of my excellence in learning and teaching and my continued embedding of theory and research into clinical practice.	2013
Staff Achievement Award. I received this award in recognition of my development and leadership of our Faculty Athena SWAN agenda towards an application for a silver Charter award.	2013
Fellowship of the Faculty of Podiatric Medicine, The Royal College of Physicians and Surgeons, Glasgow. I was elected to this prestigious position in peer recognition of my academic national and international standing within podiatry, allied health and medical rheumatology.	2012
Faculty of Health Sciences Post-Graduate supervisor award. My Post-graduate research students nominated me for this award in recognition of my sustained support and enthusiasm for their research.	2012
National mentor for the National Institute for Health Research clinical academic Fellows' scheme. I was nominated by the College of Podiatry for this national positional and appointed as one of the first Podiatry NIHR clinical academic mentors in the UK.	2011
Department of Health Advancing Healthcare Award for Excellence in Allied Health Leadership. I received this national honor in being a highly commended finalist for the Department of Health 'Achieving Excellence in Leadership' for my role in the development and leadership of a National internship scheme to grow clinical rheumatology podiatry research.	2010
Honorary Research fellow to the National Institute for Health Research Musculoskeletal Biomedical Research Unit at the University of Oxford. This appointment was made in recognition of leadership in engaging allied health clinicians with musculoskeletal epidemiological research in this world-leading unit.	2009
Fellowship of the College of Podiatric Medicine, Society of Chiropodists & Podiatrists. I was elected to this position in peer recognition of my academic standing within podiatry,	2008
Fellowship of the Higher Education Academy/Institute for Learning and Teaching. I was elected to this position in peer recognition of my pedagogy in academia.	2006
The Basham Literary prize, The Institute of Chiropodists and Podiatrists. I was awarded this National prize for my contribution to academic writing in podiatric medicine.	2005

6. TEACHING ACTIVITY

(a) Teaching responsibilities for this and the last academic year

Year: 2019

Sheet 1 of 2

Programme/Module (and code)	Clinical Research in Practice HLTH 6114	Dissertation Module HLTH6037	Chronic Conditions PODY2023	Complex Clinical Management PODY3005
Degree title (and code)	All Faculty of Health Sciences Masters programmes	All Faculty of Health Sciences Masters programmes	BSc Hons Podiatry	BSc Hons Podiatry
Students UG/PG:	PG	PG	UG	UG
Year of study:	1 (level 7)	1 (level 7)	2 (level 5)	3 (level 6)
Numbers:	15	11	35	35
Contact hours overall	3 200	20 200	60 200	60 200
My contribution:	Keynote lecturer 3 hours	Dissertation supervisor	Keynote lecturer 6 hours	Keynote lecturer 6 hours
Teaching & assessment responsibilities:	My teaching strategies are focussed towards students exploring translation of the research process into their clinical practice. The session I now lead is based on applying for funding.	My responsibilities are in the facilitating of the action learning set in the design, implementation and evaluation of a master's level research project. I am also responsible for the direct supervision of two students dissertations.	Utilising my rheumatology clinical and research scholarly activity I am responsible for teaching current concepts in the pathogenesis of rheumatological diseases.	Utilising my clinical experience and research scholarly activity I am responsible for teaching current concepts in the management of foot and ankle manifestations of rheumatological diseases
Additional comments	With the different pathways I introduced an assessment in which students evaluate an area of their own clinical research in practice they have found challenging. Alongside this they produce an action plan with recommendations that can be taken back to their clinical teams.	Through my experiences in developing a research programme I support MRes students in their clinical research learning and research development skills.	Within this module I have integrated a case based learning approach with a novel extended case building examination on diagnostics and clinical reasoning. I enjoy embedding my own clinical research within the content of this module, instigating positive debates from students surrounding current clinical practices.	Utilising group work and vicarious case-based learning approaches, I enjoy the interaction of students in discussing current concepts in rheumatology.

Programme/Module (and code)	Research methods 1	Research methods 2
Degree title (and code)	BSc Hons Podiatry	BSc Hons Podiatry
Students UG/PG:	UG	UG
Year of study:	2 (level 5)	3 (level 6)
Numbers:	35	35
Contact hours overall	60 200	60 200
My contribution:	Project supervisor 20 hours	Project supervisor 20 hours
Teaching & assessment responsibilities:	My responsibilities are in the facilitating of two action learning sets (n=10) in the design of a bachelor's level research project.	My responsibilities are in the facilitating of two action learning sets (n=10) in the application to ethics, project implementation, analysis and write up of a bachelor's level research project.
Additional comments	Through my leadership of the foot and ankle research programme I support BSc Hons students to embed clinical research skills in their learning and to participate in research development with leading researchers in the field.	

7. POSTGRADUATE SUPERVISION

a) Number of students

Degree	Current	Completed	Total
MSc / MRes	1	14	15
MPhil	0	1	1
PhD	3	4	7
PhD (external)*	2	2	4

* 1 PhD student as external supervisor at Queen Margaret University, Edinburgh (completed 2009);

* 1 PhD student at the University of East London; * 1 PhD student at the University of Malta; *PhD student at Auckland University of Technology, New Zealand.

For each of these external students I was invited to provide supervision specifically related to my expertise in advanced podiatric practice and research.

b) Details of the three most recent higher degree students supervised to completion

Student	Degree and title of thesis	Start date	Completion date
Saed Al Bimani	PhD (Oman Government scholarship) <i>Investigation of factors affecting return to play following acute lateral ankle sprains</i>	Oct 2014	Dec 2019
Alexander Izod	PhD <i>The impact of early adult rheumatoid arthritis on the biomechanical and functional characteristics of the foot and lower limb</i>	Oct 2013	Feb 2019

Charlotte Dando	PhD (Clinical Academic) <i>The diagnosis of symptomatic forefoot neuroma from a clinical diagnostic protocol for podiatric assessment</i>	Oct 2012	Sep 2018
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c) Details of higher degree students examined

Student	Degree and Title of Thesis	Institution	Date
Conor Power	Improving Movement Quality of Military Personnel to Protect Hips and Lower Limbs from Injury	University of Southampton	April 2020
Patcharin Chaisurin	DClinP A qualitative study exploring influences on physical activity for musculoskeletal health among Thai surgical nurses	University of Southampton	Jan 2019
Nadine Booyesen	PhD Exercise programmes for hip control to improve lower limb movement quality in young footballers: a proof of concept and feasibility trial	University of Southampton	July 2018
Andrea Graham	PhD by published works Foot health education for people with rheumatoid arthritis	University of Salford	Nov 2017
Sarah Stewart	PhD A sonographic and clinical investigation of the first metatarsophalangeal joint in gout and asymptomatic hyperuricaemia: a comparison with normouricaemic individuals	Auckland University of Technology, New Zealand	Mar 2017
Ryan Causby	PhD <i>Making 'sense' of dexterity: its role in scalpel skill acquisition in podiatry students.</i>	University of South Australia	Jan 2016
Angela Brenton-Rule	PhD <i>Foot and ankle characteristics associated with falls and falls risk in adults with rheumatoid arthritis.</i>	Auckland University of Technology, New Zealand	Nov 2015
Thomas Downes	Intercalated Medical degree/ MPhil <i>The natural history of foot osteoarthritis phenotypes: a prospective study in community-dwelling adults</i>	University of Keele	Oct 2015
Jo Coates	PhD <i>Identification of Quantitative Kinetic Measures for Assessment of the Efficacy of Functional Foot Orthoses</i>	University of Northampton	April 2014
Lisa Newcombe	PhD <i>Foot involvement in early arthritis (FIRST): A prospective ultrasound study</i>	Glasgow Caledonian University	Dec 2013
Hannah Jarvis	PhD <i>Investigation of the Podiatric Model of Foot Biomechanics</i>	University of Salford	April 2013

8. RESEARCH ACTIVITY

Summary of current research

Catherine is principal applicant in the following current projects:

OptiFooT: Optimisation of foot care for people living with arthritis.

Supported by The College of Podiatry UK and a Career Development Fellowship from the National Institute for Health Research this project formed a four year multi-phase research design to develop an optimal model of foot care for people living with arthritis.

MSKInterns: Graduate Rheumatology Research Internships for Nurses and Allied Health Professionals.

The aim of this project is about developing a national network of healthcare professional research internships in rheumatology. Funded by the UK charity Versus Arthritis the governance of the programme is overseen by Professor Catherine Bowen at the University of Southampton, who is joined by expert colleagues from a network of universities including Leeds, Salford, Oxford, the West of England, Keele and Glasgow Caledonian.

ELFOAB / Epidemiology and lifetime risk of osteoarthritis within the foot and biomechanical functional outcomes

It has been recognized that osteoarthritis (OA) of the foot may have a detrimental effect on patients' health related quality of life and that foot OA may cause significant morbidity. Funded by the Dr W.M.Scholl Podiatric Research & Development fund, the specific aims of this research were to develop a detailed understanding of the epidemiology, risk factors and associations of OA occurring within the feet in the general population at middle and older age. An additional aim was to determine lower limb biomechanical factors associated with radiographic foot OA.

SPIDERSOLE: Optimal insole design for people who have foot arthritis.

The SpidersoleTM project has a primarily focus on further developing a novel insole design for management of foot osteoarthritis through investigation of appropriate materials and methods of printing and construction to a device that is wearable. A second phase of the study is being led by undergraduate BSc (Hons) Podiatry students and involves testing the 'SpidersoleTM' to determine its wearability and efficacy in terms of structure, performance, density and support during gait in the human performance laboratory and outdoors on different terrain.

Catherine has been principal applicant in the following project:

FeeTURA.

Forefoot complications in patients with rheumatoid arthritis: identification, impact and intervention through novel imaging techniques. The project, set up in 2003 by Professor Bowen with radiologists [Dewbury, Sampson], rheumatologists [Arden, Edwards] was the first to identify diagnostic ultrasound imaging as an additional skill that could be used reliably by podiatrists, particularly those working in musculoskeletal health. The subsequent programme of work, involving podiatrists [Cherry, Gates and Dando] from Solent NHS Trust, University of Southampton and University of Oxford has evolved to increase understanding of foot problems in rheumatic diseases. Findings indicate that the use of DUSI of the foot would be more beneficial than clinical examination alone in the refinement of diagnosis and the implementation of effective care pathways for patients who have foot symptoms and those starting biologic therapies. The fourth phase, led by Dr Lindsey Cherry and funded by the National Institute for Health Research and Pfizer has involved reliability testing of DUSI by Cherry [NIHR Research fellow 2010-2016] and Charlotte Dando [NIHR HEE Wessex funded PhD student 2015- 2017] and enabled production of diagnostic protocols for investigation of forefoot musculoskeletal pathology and validation of DUSI against MRI.

Catherine is co-applicant in the following:

The Centre For Sport, Exercise and Osteoarthritis Research Versus Arthritis.

The Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis is led by Nottingham University Hospitals NHS Trust in collaboration with Versus Arthritis and is a consortium of six Universities: Bath, Leeds, Loughborough, Nottingham, Oxford and Southampton.

Funded by the UK charity Versus Arthritis the aim is to build a Centre of Excellence made up of a group of world-leading researchers in sport and exercise medicine and science, bone and cartilage biology, orthopaedics, rheumatology, nutrition, skeletal muscle biology, psychology, physiotherapy, podiatry, occupational therapy, medicine, epidemiology, bioengineering and physiology.

Specific to the foot and ankle is the aim of keeping individuals physically active for longer by understanding arthritis in the feet and modifying footwear and in-shoe devices.

<http://www.sportsarthritisresearchuk.org>

Summary of current research

SHOES:

People with Stroke and Parkinsons: Home and Outdoor shoES. *Funder: RfPB National Institute for Health Research.*

Shoes can protect and support the foot as well as help with walking but bad shoes can increase fall risk in older people. The aims of this study were to find out which shoes people with Parkinson's (PwP) and people with stroke (PwS), wear indoors and outdoors; to find out whether balance and walking change when wearing indoor or outdoor shoes and to explore patients' views on the challenges they face when wearing and buying shoes. In the first part of the study, we found out more about people's views about shoes and foot problems using a postal survey and face-to-face interviews. In the second part, PwS and PwP attended an assessment at the hospital gait laboratory and we looked at their balance whilst completing walking and balance tests in their own indoor and outdoor shoes.

Most people wore slippers indoors and shoes fitted badly in about half the sample. Many had never received foot care support. Participants felt that there was a need for more advice and support when buying shoes. Current shoe choices were based on trial and error. Balance and walking was better in outdoor shoes and worse in indoor shoes. Foot problems and worse balance in indoor shoes was more common amongst fallers. Findings highlighted an unmet need for foot-health advice/foot-care for PwS and PwP, a need for further research to explore the best ways to provide foot-care support on selecting safe and appropriate shoes. Addressing these unmet needs may help to improve current fall prevention treatments. Improved balance performance in outdoor shoes suggests that it may be possible to improve indoor balance performance through improved indoor shoe choices. HCP's could be trained to give footwear advice and to refer people with foot problems to specialist podiatry services where appropriate.

Research grants and contracts

Dates	Award holder(s)	Funding body	Title	Value
Feb 2020-Dec 2020	Mark Cole, Keith McCormick Prof Cathy Bowen (Co-applicant)	Health Education England	Initiatives to support Podiatry and Therapeutic Radiography Workforce Supply	£20,000
April 2020 – March 2021	Prof Cathy Bowen (PI)	Versus Arthritis	Impact of physical activity, sport and injury on the foot and ankle.	£10,000
Oct 2019 – Aug2020	Prof Cathy Bowen (PI) Dr Lucy Gates	Versus Arthritis	Defining radiographic foot and ankle osteoarthritis according to clinically important outcomes	£10,981
April 2019-July 2020	Prof Cathy Bowen (PI) Prof Maria Stokes	Uos REF impact accelartion	Ultrasound Imaging research drives expertise in Podiatry and Physiotherapy musculoskeletal services	£6,000
Oct 2018 -Sep 2021.	Prof Cathy Bowen (PI) (Southampton) [Univ Southampton], [Univ Leeds], [Univ Salford]', [Univ Oxford]', [Univ West of England]; [Univ Keele]; [Glasgow Caledonian Univ]	Versus Arthritis	Nurse and AHP career development internship scheme -	£175,000
Jan 2018-Dec 2022	Professor Mark Batt (Lead Applicant) Prof Cathy Bowen (Co-applicant) [Univ Nottingham], [Univ Leeds], [Univ Bath]', [Univ Oxford]', [Univ	Arthritis Research UK	Centre of Excellence for Sports Injuries and Osteoarthritis Prevention	£1,998,626.65

	Loughborough]; [Univ Southampton].			
Nov 2017-July 2018	Prof Cathy Bowen PI	PERU (Public engagement in research unit), University of Southampton	Feet for Life: creation of a mobile lab-pod	£3146.25
Nov 2016-March 2017	Prof Cathy Bowen* (PI) Dr Lucy Gates* Angela Masson* (*Southampton) Simon Wickes (Cynapse) Will Howden (SO3D)	FortisNet: Impact Acceleration fund	Spidersole 3D print insole	£4,785
Jan 2015-March 2015.	Dr Cathy Bowen* (PI) Louise McCulloch* Angela Masson* (*Southampton) Simon Wickes (Cynapse) Steve Perkins (SO3D)	FortisNet Pump-prime funding	3D Orthotics printing	£2,000
Dec 2015- Nov 2019	Dr Cathy Bowen (PI) Prof Judith Petts Prof Christopher Edwards (Southampton) Prof Nigel Arden (Oxford)	NIHR / Career Development Fellowship	Optimisation of foot care for people living with arthritis	£468,066
Oct 2015-Sep 2018.	Dr Cathy Bowen (PI) (Southampton) Prof Anthony Redmond (Leeds); Prof Nigel Arden (Oxford); Prof Sarah Hewlett (West of England); Dr Anita Williams (Salford); Prof Afsie Sabooker (Oxford)	Arthritis Research UK	Nurse and AHP career development internship scheme - [Univ Southampton], [Univ Leeds], [Univ Salford]', [Univ Oxford]', [Univ West of England]	£120,000
Oct 2015 – Sep 2018	Prof Sue Latter Dr Bronagh Walsh Dr Cathy Bowen Dr Christopher Bailey Prof Jonathan Drennan Prof Alison Richardson (all Southampton)	National Institute for Health Research	MRes Clinical Academic Training Pathway for nurses, midwives and AHPs	£2.5 million
Feb 2015- Jan 2016	Dr Cathy Bowen (PI) Dr Alan Borthwick, (Southampton); Prof Anthony Redmond, (Leeds); Dr Andrew Judge*, Dr Rafael Pinedo-Villanueva*, Dr Daniel Prieto Alhambra*, Prof Nigel Arden*, (Oxford)	The College of Podiatry, UK	Are podiatry services clinically and cost effective?	£116,000
July 2014-Sep 2014	Dr Cathy Bowen (PI) Lucy Gates	FoHS Enterprise and Innovation grant.	Innovation internship	£6,000
April 2013- Mar 2016	Prof Christopher Edwards* (PI) Dr Lindsey Hooper* Dr Leonard King* Dr Matthew Thomas* Dr Cathy Bowen* (*Southampton) Prof Nigel Arden (Oxford) Prof Mikkel Ostergaard (Denmark)	Pfizer	The epidemiology of MRI-detected rheumatoid arthritis disease activity within the forefoot	£100,000

	Dr Frank Roemer (Germany)			
April 2013-Mar 2016	Professor Ann Ashburn Dr Cathy Bowen Prof Dan Bader Dr Maggie Donovan Hall Dr Julia Potter Mr Mark Cole (all Southampton)	National Institute for Health Research: Research for Patient Benefit	SHOES (People with Stroke and Parkinson's Disease: Home and Outside Shoes)	£249,767
Jan 2013 - Dec 2017	Prof Mark Batt (Nottingham) Prof Nigel Arden (Oxford) <i>et al</i> Dr Cathy Bowen: collaborator	Arthritis Research UK	Centre of Excellence for Sports Injuries and Osteoarthritis Prevention	£3million (+ £5million added value investment)
Jan 2013 - Dec 2015	Dr Lindsey Hooper, (Solent NHS Trust) Dr Cathy Bowen (Southampton) Prof Nigel Arden (Southampton/ Oxford), Dr Christopher Edwards (Southampton)	National Institute for Health Research: Clinical Lecturer Fellowship	Forefoot complications in patients with rheumatoid arthritis: identification, impact and intervention	£110,000
Oct 2012 – Sep 2015	Dr Cathy Bowen (PI) (Southampton) Dr Wendy Dreschler (University of East London) Dr David Stephenson (University of East London) Prof Nigel Arden (Oxford) Prof Mike Doherty (Nottingham)	Dr W,M Scholl Podiatric Development and Research fund.	The epidemiology and lifetime risk of foot osteoarthritis and associated lower limb biomechanical factors	£214,000 + £35,000 (Jan 2015) + £15,000 (Nov2015)
Oct 2012 – Sep 2015	Prof Sue Latter Dr Bronagh Walsh Dr Cathy Bowen Dr Debbie Craddock Prof Alison Richardson Dr Steve Tee (all Southampton)	National Institute for Health Research	MRes Clinical Academic Training Pathway for nurses, midwives and AHPs	£2.2 million
Sep 2012 – Oct 2016.	Mr Alex Izod (University of East London) Dr Wendy Dreschler (University of East London) Dr David Stephenson (University of East London) Dr Cathy Bowen (Southampton)	Dr W,M Scholl Podiatric Development and Research fund.	The effect of biologic drug therapy on the kinematics of the lower limb in rheumatoid arthritis	£221,153
Oct 2011 – Sep 2014	Miss Lucy Gates (Portsmouth City PCT) Dr Cathy Bowen (Southampton) Prof Nigel Arden (Southampton/ University of Oxford), Prof Mark Jones (Southampton)	Southampton Rheumatology Trust	Can we use clinical foot and ankle assessment to improve the prediction of patient reported outcomes in Total Knee Arthroplasty?	£11,196
Oct 2011 – Sep 2014	Miss Lucy Gates (Portsmouth City PCT)	Arthritis Research UK AHP Fellowship	Foot and ankle biomechanics as	£169,983

	Dr Cathy Bowen (Southampton) Prof Nigel Arden (Southampton/ Oxford), Prof Mark Jones (Southampton)		predictors of knee arthroplasty outcomes	
Dec 2009 – Dec 2012	Miss Lindsey Hooper, (Lewisham PCT) Dr Cathy Bowen (Southampton) Prof Nigel Arden (Southampton/Oxford), Dr Christopher Edwards (Southampton)	National Institute for Health Research: Clinical Doctoral Research Fellowship	The epidemiology, aetiology and clinical importance of forefoot bursae in patients with rheumatoid arthritis	£120,077
July 2009 – June 2010	Mrs Cathy Bowen (PI) (Southampton) Prof Nigel Arden (Southampton/Oxford) Dr A.C Redmond (Leeds)	Arthritis Research Campaign	Arc research career development internships in podiatry (Continuity funding)	£12,000
July 2009 – July 2010	Mrs Cathy Bowen (PI) (Southampton) Prof Nigel Arden (Southampton/Oxford), Dr Christopher Edwards (Southampton)	Southampton Rheumatology Trust	The clinical importance of forefoot bursitis in patients with rheumatoid arthritis	£17,554
2008	Mrs Cathy Bowen (PI)	Canonbury Healthcare UK	Professional practice for podiatry students	£12,000
Dec 2007 – April 2009	Mr K McCormick (Southampton) Mrs Cathy Bowen (Southampton) Mr Mike Potter (Southampton)	British Council (BC) Prime Ministers Initiative Phase 2 (PMI2)	The International mobility of UK podiatry students	£7,750
Dec 2003 – June 2009	*Dr A.C Redmond (Leeds) * Mrs Cathy Bowen (Southampton) Dr Nigel Arden (Southampton) Prof Philip Helliwell (Leeds) Dr Julia Potter, (Southampton) *main co-applicants	Arthritis Research Campaign	Arc research career development internships in podiatry: a collaborative strategy for developing podiatry researchers in rheumatology.	£30,000

9. PUBLICATIONS

- Please star (*) in the left margin what you consider were especially significant publications.
- Please enter a 'T' against those related specifically to publications about teaching.

Books - Short Works (3)
T 1. Bowen CJ . Foot and ankle in rheumatology: core reading material on the Postgraduate Diploma in Musculoskeletal Medicine (PG Dip MsMed) offered by Middlesex University, London. The physiotherapist, occupational therapist and podiatrist.
T 2. Bowen CJ , Graham AS, Williams AE: Rheumatology. Chapter in 'A textbook of Podiatric Medicine'. Eds Hayes C, Barbaro-Brown J. M&K Publishing Sep 2017, ISBN: 9781905539321.
T 3. T Cherry LC, Gates L, Bowen CJ . Clinical Assessment. Chapter in 'Foot and Ankle in Rheumatology'. Helliwell P, Backhouse M, Siddle H (Eds). (In press).

Conference Contributions – Refereed (74)

4. **Bowen C.J**, Dewbury K, Sampson M, Sawyer S, Bennet S.P, Burridge J, Edwards C.J And Arden N.K Bursitis of the foot: a common and under diagnosed problem in patients with rheumatoid arthritis. *Rheumatology* 2006, 45, (4): Abstracts supplement: i95.

5. **Bowen C.J**, Dewbury K, Sampson M, Sawyer S, Bennet S.P, Burridge J, Edwards C.J And Arden N.K. Inter-observer reliability of a podiatrist and radiologist: results of ultrasound imaging of the plantar forefoot in patients with rheumatoid arthritis. *Rheumatology* 2006, 45, (4): Abstracts Supplement: i184.

6. **Bowen C.J**, Dewbury K, Sampson M, Sawyer S, Bennet S.P, Burridge J, Edwards C.J, Arden N.K. Bursitis of the foot: a common and under diagnosed problem in patients with rheumatoid arthritis. Poster presentation. (Nov 2006) The Society of Chiropodists and Podiatrists Annual Conference.

7. Backhouse, M, **Bowen, C.J.** Effect Of Prefabricated And Custom Orthoses On Plantar Loading Of The First Metatarsophalangeal Joint During Gait. Poster presentation. (Nov 2006) The Society of Chiropodists and Podiatrists Annual Conference.

*8. **Bowen CJ**, Arden NK. Imaging, Injections and Enhanced Clinical Practice: an emerging concept: Invited key note presentation. (Nov 2006) The Society of Chiropodists and Podiatrists Annual Conference.

9. **Bowen CJ**, Arden NK. Diagnostic Ultrasound Imaging and forefoot pressure analysis. Invited oral presentation. The British Society for Rheumatology, Foot and Ankle Specialist Interest group, Birmingham, April 2007.

10. **Bowen CJ**, Backhouse M, Burridge J.H, And Arden N.K. Observations of in-shoe plantar pressures in patients with rheumatoid arthritis. *Rheumatology* 2007, 46, (4): Abstracts Supplement: i155. (Poster presentation. British Society for Rheumatologists Annual Conference, Birmingham, April, 2007).

11. **Bowen CJ**, Backhouse M, Burridge J, and Arden NK. Forefoot bursitis in patients with rheumatoid arthritis: is there a link to peak plantar pressures? *Rheumatology* 2007, 46, (4): Abstracts Supplement: i93. (Poster presentation. British Society for Rheumatologists Annual Conference, Birmingham, April, 2007).

12. **Bowen CJ**, Dewbury K, Sampson M, Sawyer S, Bennet S.P, Burridge J, Edwards C.J And Arden N.K. Does bursitis of the forefoot improve in patients with rheumatoid arthritis on anti-tnf- therapy? *Rheumatology* 2007, 46, (4): Abstracts Supplement: i30. (Poster presentation. British Society for Rheumatologists Annual Conference, Birmingham, April, 2007).

13. ***Bowen CJ**, Backhouse M, Burridge J, Arden NK. Observations of in-shoe plantar pressures in patients with rheumatoid arthritis. Oral Presentation. World Congress of Podiatry, Copenhagen, May 2007

*14. **Bowen CJ**, Backhouse M, Burridge J, Arden NK. Inter-metatarsal bursitis in patients with rheumatoid arthritis is there a link to peak plantar pressures? Oral Presentation. World Congress of Podiatry, Copenhagen, May 2007.

15. Hooper L, **Bowen CJ**, Taylor P, Sawyer S, Arden NK. Changes in metatarsal bone mineral density following 12 weeks anti-TNF therapy in RA patients. Poster presentation. The Society of Chiropodists and Podiatrists Annual Conference, Oct 2007.

16. **Bowen CJ**, Dewbury K, Sampson M, Sawyer S, Bennet S.P, Burridge J, Edwards C.J, Arden N.K Does anti-TNF therapy affect the presence of foot symptoms in patients with rheumatoid arthritis? Oral presentation. The Society of Chiropodists and Podiatrists Annual Conference, Oct 2007.

17. Gay A, **Bowen CJ**, Hooper L, Edwards CJ, Arden NK. An Investigation into the Clinical Lifespan of the FScan sensor. Poster presentation. The Society of Chiropodists and Podiatrists Annual Conference, Oct 2008.

*18. **Bowen, C.J**, Burridge, J.H, Dewbury K, Culliford D, Arden, N.K. Bursitis of the foot is a clinically relevant factor. *Rheumatology* 2008, 47, (Supplement2), ii24. (Oral presentation. British Society for Rheumatologists Annual Conference, Liverpool, April, 2008).

19. Hooper L, **Bowen CJ**, Taylor P, Arden, N.K. A preliminary study of changes in metatarsal bone mineral density following anti-TNF α therapy in patients with rheumatoid arthritis. *Rheumatology* 2008, 47, (Supplement 2), ii34. (Poster presentation. British Society for Rheumatologists Annual Conference, Liverpool, April, 2008).

*20. **Bowen CJ**, Culliford D, Dewbury K, Sampson M, Burridge JH, Edwards CJ, Arden NK. Diagnostic Ultrasound Imaging Reveals Relevant Subclinical Disease In The Burden Of Rheumatoid Foot Disease: Oral presentation. Australasian Podiatry Conference, Gold Coast, May, 2009.

21. Gay A, **Bowen CJ**, Hooper L, Edwards CJ, Arden NK. Plantar foot pressures are not related to disease activity in rheumatoid arthritis. *Rheumatology* 2009, 48, (Supplement1), i129. (Poster presentation. British Society for Rheumatologists Annual Conference, Glasgow, April, 2009).

22. Allen RP, Beacroft J, **Bowen CJ**, Gay A, Hooper L, Burridge JH, Edwards CJ, Arden NK. A controlled study of plantar foot pressures in patients with rheumatoid arthritis. *Rheumatology* 2009, 48, (Supplement1), i28. (Oral presentation. British Society for Rheumatologists Annual Conference, Glasgow, April, 2009).

23. **Bowen, C.J**, Morgan J, Hooper L, Burridge, J.H, Edwards CE, Arden, N.K. An Investigation of Changes in Patient Reported Foot Impact of Rheumatoid Arthritis after One Year. (Poster presentation. World Congress of Podiatry, Amsterdam, May, 2010).

*24. **Bowen CJ**, Culliford D, Dewbury K, Sampson M, Burridge J.H, Hooper L, Edwards C.J, Arden N.K. Investigation of the Natural History of Forefoot Bursitis Detected by Musculoskeletal Ultrasound and

Predictors of its Change after One Year. *Rheumatology* 2009, 48, (Supplement1), i132. (Oral presentation. British Society for Rheumatologists Annual Conference, Birmingham, April, 2010).

25. *Bowen CJ, Allen RP, Beacroft J, Gay A, Hooper L, Burridge JH, Edwards CJ, Arden NK. A longitudinal investigation of plantar foot pressures in patients with rheumatoid arthritis. Oral presentation. World Congress of Podiatry, Amsterdam, May, 2010.

26. Hooper L, Warner M, Goulston L, Gates L, **Bowen CJ**, Edwards CJ, Arden NK. Within-subject foot motion variability in patients with rheumatoid arthritis. JFAR (Poster presentation, The Society of Chiropodists and Podiatrists Annual Conference, 2010).

T 27. McCormick K, **Bowen CJ**, Spruce MC, Potter MJ. The International mobility of students: Results of a British Council PMI project to support clinical placement of UK podiatry students in Singapore. (Oral presentation, The Society of Chiropodists and Podiatrists Annual Conference, 2010).

28. Williams A, Graham A, Davies S, Longrigg K, Dagg A, Lyons C, **Bowen CJ**. Guidelines for the Management of The Foot Affected by Rheumatoid Arthritis. *Rheumatology* 2011, 50, (Supplement1), iii80. (Poster presentation. British Society for Rheumatologists Annual Conference, Brighton, April, 2011).

T 29. Naidoo S, **Bowen CJ**, Arden NK, Helliwell P, Redmond A. Graduate AHP Research Internships in Rheumatology: A preliminary Evaluation. *Rheumatology* 2011, 50, (Supplement1), iii83. (Poster presentation. British Society for Rheumatologists Annual Conference, Brighton, April, 2011).

T*30. **Bowen CJ**. Resources for Implementing Research. *Rheumatology* 2011, 50 (Supplement1) iii9. (Invited speaker. *Invited workshop/oral presentation* British Society for Rheumatologists Annual Conference, Brighton, April, 2011).

31. Goulston L, Hooper L, Gates L, Metcalf C, **Bowen CJ**, Warner M, Culliford D, Maskell J, Leyland K, Burridge JH, Stokes M, Arden NK. Static and dynamic knee alignment in osteoarthritis. *Ann Rheum Dis* 2011;70(Suppl3):702. (Abstract, European League Against Rheumatism, Annual Conference, London, May 2011).

32. Hooper L, **Bowen CJ**, Ball C, Costello P, Culliford D, Edwards CJ, Arden NK. The Prevalence of Forefoot Bursae in Rheumatoid Arthritis and Osteoarthritis. *Ann Rheum Dis* 2011;70(Suppl3): (Poster presentation. European League Against Rheumatism, Annual Conference, London, May, 2011).

T 33. Naidoo S, **Bowen CJ**, Arden NK, Redmond A. Training the next generation of clinical researchers: Qualitative evaluation of a graduate AHP research internship in Rheumatology. The Society of Chiropodists and Podiatrists Annual Conference, 2011 (oral presentation).

34. Gates L, **Bowen CJ**, Hooper L, Goulston L, Warner M, Arden NK. The association between static Foot Posture and dynamic knee alignment in unilateral knee OA. The Society of Chiropodists and Podiatrists Annual Conference, 2011 (poster presentation).

35. Hooper, L, **Bowen CJ**, Gates L, Culliford DJ, Ball C, Edwards CJ, Arden NK. Prognostic indicators of foot related disability in patients with RA. *Rheumatology* 2012. 51 (Supplement 3), iii31. (Oral presentation. British Society for Rheumatology Annual conference, Glasgow, May 2012).

*36. **Bowen CJ**. The Chingford Womens study: A proposal for comprehensive epidemiological investigation of foot OA. *Invited oral presentation*. British Society for Rheumatology Foot and Ankle Research Interest Group, Annual conference, Glasgow, May 2012.

37. Gates L, **Bowen CJ**, McCulloch L, Arden NK. Many musculoskeletal foot and ankle assessments do not show adequate reliability between examiners: results of a systematic review. *Journal of Foot and Ankle Research* Oct 2012. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

38. Hooper L, King L, Thomas M, Roemer F, Culliford D, **Bowen CJ**, Arden N.K, Edwards C.J. The prevalence of MRI-detected bursa-like lesions of the forefoot in patients with rheumatoid arthritis and associations with structural or clinical disease manifestations. *Journal of Foot and Ankle Research* Oct 2012. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

39. Hooper L, King L, Thomas M, Roemer F, Culliford D, Edgson L, **Bowen C.J**. Forefoot inflammatory activity in patients with rheumatoid arthritis under remission receiving biologic therapy. *Journal of Foot and Ankle Research* Oct 2012. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

40. Merriman R, **Bowen C.J**, Judge A, Arden NK. A reliability study of defining osteoarthritis retrospectively in a population cohort using the Australian foot atlas. *Journal of Foot and Ankle Research* Oct 2012. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

41. Kamis AS, Adams J.E, **Bowen C.J**. The Prevalence of Foot Symptoms In Patients With Rheumatoid Arthritis At The Raja Isteri Pengiran Anak Saleha (Ripas) Hospital, Brunei Darussalam. Oral presentation. FIP World Congress of Podiatry, Rome, Oct, 2013.

*42. Gay A, Culliford D, Leyland K, Arden N.K, **Bowen C.J**. Associations between body mass index and foot joint pain in middle-aged and older women: A retrospective analysis of a longitudinal cohort. Oral presentation. FIP World Congress of Podiatry, Rome, Oct, 2013.

*43. **Bowen C.J**, Culliford D, Leyland K, Arden NK. Footwear Habits and General Health in Middle-Aged Women: A Retrospective Ten Year Study. Oral presentation. FIP World Congress of Podiatry, Rome, Oct, 2013.

44. Kamis AS, Adams J, **Bowen CJ**. Critical appraisal of clinical practice guidelines for foot and ankle management in rheumatoid arthritis. *Rheumatology* 2013. 52 (Supplement 1), iii139 (Poster presentation. British Society for Rheumatology Annual conference, Birmingham, April 2013).

45. Gates L, **Bowen CJ**, McCulloch L, Arden NK. An investigation into the prevalence of disabling foot pain in patients awaiting total knee arthroplasty. *Rheumatology* 2013. 52 (Supplement 1), iii134. (Poster presentation. British Society for Rheumatology Annual conference, Birmingham, April 2013).

T*46. **Bowen CJ**. Training issues for AHPs and nurses in musculoskeletal diagnostic ultrasound imaging. *Rheumatology* 2013. *Invited oral presentation*. British Society for Rheumatology Annual conference, Birmingham, April 2013.

47. McQueen PL, **Bowen CJ**, Daniels M, Cherry L, Doherty M, Arden NK Radiographical abnormality of hallucal sesamoids in middle-aged females. *Journal of Foot and Ankle Research* Oct 2013. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

48. Culliford DC, Gates L, **Bowen CJ**, Arden NK. Is foot pain considered in the decision to treat knee osteoarthritis with arthroplasty? *World Congress of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases*, Seville (poster presentation). April 2014.

49. Gates L, **Bowen CJ**, McCulloch L, Arden, NK Defining a musculoskeletal foot and ankle assessment protocol to be used within the investigation of lower limb osteoarthritis: results of an international consensus statement. *World Congress of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases*, Seville (poster presentation). April 2014.

50. Mukherjee S, Cherry L, Culliford D, **Bowen CJ**, Arden NK and Edwards CJ. The epidemiology and clinical importance of forefoot inflammation in patients with systemic lupus erythematosus. (Poster presentation. British Society for Rheumatology Annual conference, Liverpool April 2014). *Rheumatology* 53 (suppl 1), i182-i182.

*51. Gates L, **Bowen CJ**, Arden NK. Defining a multidisciplinary musculoskeletal foot and ankle assessment: results of an international consensus statement. *Journal of Foot and Ankle Research* Nov 2014. (The Society of Chiropodists and Podiatrists Annual Conference, oral presentation prize: **Jewel in the Crown**).

52. McQueen PL, **Bowen CJ**, Daniels M, Doherty M, Arden NK (2014) Orthoses; the honest problem with patient success when proving the value of a key podiatric treatment. *Journal of Foot and Ankle Research* Oct 2014. (The Society of Chiropodists and Podiatrists Annual Conference, poster presentation).

T 53. Adams J, Woods - Townsend K, Grace M, Warner M, **Bowen CJ**, McQueen P, Dando C, Stokes M. (2015) Raising teenagers awareness of musculoskeletal health through LIFELAB: a collaboration between school students, teachers and clinical academic researchers. *Rheumatology* 54(S1):i37

54. Culliford, D. Gates, L. **Bowen, C.** Ball, C. Chan, K. Cooper, C. Arden, N. Is Foot Pain considered in the decision to treat Knee Osteoarthritis with Arthroplasty? *World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases*, April 2015.

55. Gates, L. **Bowen, C.** Arden, N. A musculoskeletal foot and ankle assessment protocol to be used within the investigation of lower limb osteoarthritis: results of an international consensus statement. *World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases*

56. **Bowen CJ**, Kunkel D, Cole M, Donovan-Hall M, Pickering R, Burnett M, Bader D, Robison J, Mamode L, Ashburn A. (2015) A survey exploring footwear habits in people with stroke and people with Parkinson's. *Journal of Foot and Ankle Research* Nov 2015. The College of Podiatry Annual Conference, Harrogate.

57. McQueen P, Daniels M, Doherty M, Arden NK, **Bowen CJ**. Painful foot osteoarthritis: a common symptom in a common pathology. *Journal of Foot and Ankle Research* Nov 2015. The College of Podiatry Annual Conference, Harrogate.

58. Dando C, Cherry L, **Bowen CJ**. Clinical diagnosis of symptomatic forefoot neuroma in the general population: Delphi based recommendations. *Journal of Foot and Ankle Research* Nov 2015, The College of Podiatry Annual Conference, Harrogate.

59. Sanders L, Donovan-Hall M, Borthwick A, **Bowen CJ**. Experiences of mobility for people living with rheumatoid arthritis who are receiving biologic drug therapy: implications for podiatric practice. *Ann Rheum Dis* 2016;75(Suppl 2):1272-1273. (European League Against Rheumatism, Annual Conference, London, June 2016).

60. Al Bimani S, Gates L, Warner M, **Bowen C.J.** Prognostic Factors for return to play following conservatively treated ankle sprain: a systematic review. *Journal of Foot and Ankle Research Supplements* Vol 10 , The College of Podiatry Annual Conference, Glasgow Nov 2016.

61. Edwards K, Borthwick A, McCulloch L, Redmond AC, Pinedo-Villanueva R, Arden NK, **Bowen CJ.** Evidence for current recommendations concerning the management of foot health for patients with chronic long-term conditions: a systematic review. *Journal of Foot and Ankle Research Supplements* Vol 10, The College of Podiatry Annual Conference, Glasgow Nov 2016.

62. Dando C, Bailey J, Ferguson R, Jones S, Bowen G, Jones L, Hussain B, **Bowen C.J.**, Cherry L. Implementation and evaluation of an innovative diagnostic musculoskeletal ultrasound pathway in a UK Community Trust. *Journal of Foot and Ankle Research Supplements* Vol 10 , The College of Podiatry Annual Conference, Glasgow Nov 2016.. **Innovations in Practice Prize Winner.**

63. Bailey J, Dando C, Ferguson R, Jones S, Bowen G, **Bowen C.J.**, Cherry L. Can Podiatrists safely and competently embed diagnostic musculoskeletal ultrasound within clinical practice? *Journal of Foot and Ankle Research Supplements* Vol 10 , The College of Podiatry Annual Conference, Glasgow Nov 2016.

Mizzi A, Cassar K, **Bowen C.** Formosa C. The progression rate of peripheral arterial disease in patients with intermittent claudication: a systematic review. *Journal of Foot and Ankle Research Supplements* Vol 12, The College of Podiatry Annual Conference, Liverpool Nov 2017.

64. Ferguson R, Culliford D, Prieto-Alhambra D, Judge A, Delmestri A, Arden NK, Bowen CJ. The UK burden of foot and ankle pain on GPs: An observational overview. *Journal of Foot and Ankle Research Supplements* Vol 11, The College of Podiatry Annual Conference, Liverpool Nov 2017. *Journal of Foot and Ankle Research* 2018. 11(Suppl 1):4

65. Yardley S, Gates L, Warner M, Bowen CJ. A proof of concept study for the investigation of the kinetic effect of variable-hardness insoles on external knee adduction moment during walking. *Journal of Foot and Ankle Research Supplements* Vol 11, The College of Podiatry Annual Conference, Liverpool Nov 2017. *Journal of Foot and Ankle Research* 2018. 11(Suppl 1):4

66. Ashburn A, Donovan-Hall M, Robison J, Cole M, Bowen C, Burnett M, Mamode L, Pickering R, Bader D, Kunkel D. A qualitative study of the views and experience of people with Parkinson's disease regarding their footwear. **ORAL PRESENTATION.** ACPIN International Neurophysiotherapy Conference: Manchester, 19th-20th March 2018.

67. Kunkel D, Burnett M, Mamode L, Pickering R, Bowen C, Bader D, Robison J, Donovan-Hall M, Cole M, Ashburn A. The effects of wearing usual indoor and outdoor footwear on balance and gait performance in people with Parkinson's disease using clinical tests and instrumented movement analysis. **POSTER PRESENTATION.** ACPIN International Neurophysiotherapy Conference: Manchester, 19th-20th March 2018.

*68. Mizzi A, Cassar K, **Bowen CJ.** Formosa C. Characteristics and treatment of patients with intermittent claudication. A comparison between UK and Maltese populations. *Journal of Foot and Ankle Research Supplements* Vol 12, The College of Podiatry Annual Conference, Bournemouth Nov 2018. **Best scientific paper prize: Jewel in the Crown.**

69. Uhan J., Gates L., Arden N., Doherty M., and **Bowen CJ.** The Prevalence of Foot Pain - a study taken from the general population of Nottingham. *Journal of Foot and Ankle Research Supplements* Vol 12, The College of Podiatry Annual Conference, Bournemouth Nov 2018.

70. Smith M, McCormick K, **Bowen CJ.**, Cherry L. Podiatry led encounters of Charcot Neuropathic Osteoarthritis at an NHS hospital in south east England: a service evaluation. *Journal of Foot and Ankle Research Supplements* Vol 12, The College of Podiatry Annual Conference, Bournemouth Nov 2018.

71. Tanyanyiwa ST, McCormick K, **Bowen CJ.** Neurological assessment using a portable nerve conduction device in a clinical setting. *Journal of Foot and Ankle Research Supplements* Vol 12, The College of Podiatry Annual Conference, Bournemouth Nov 2018.

72. Wright D, Fry ML, Adams JA, Bowen CJ. Training the next generation of clinical rheumatology researchers: evaluation of a graduate Allied Health Professional and Nurse internship programme. **British Society for Rheumatology Annual Conference**, Liverpool April 2018. *Rheumatology* (suppl 1).

73. Gates L, McQueen P, Daniels M, Delmestri A, Drechsler W, Stephensen D, Doherty M, Arden N, **Bowen CJ.** The natural history of radiographic first metatarsophalangeal joint osteoarthritis: a nineteen-year population based cohort study. *Journal of Foot and Ankle Research Supplements* Vol 13, The College of Podiatry Annual Conference, Harrogate Nov 2019. **Best scientific paper prize: Jewel in the Crown.**

74. Dando C, Bacon D, Borthwick A, **Bowen CJ.** Stakeholder views of podiatry services in the UK for people living with arthritis: a qualitative investigation. *Journal of Foot and Ankle Research Supplements* Vol 13, The College of Podiatry Annual Conference, Harrogate Nov 2019.

75. Mizzi A, Cassar K, **Bowen CJ.** Formosa C. 2-year outcome of patients with intermittent claudication - a longitudinal observational study. *Journal of Foot and Ankle Research Supplements* Vol 13, The College of Podiatry Annual Conference, Harrogate Nov 2019.

76. Wright D, Fry ML, Adams JA, Bowen CJ. Training the next generation of clinical rheumatology researchers: evaluation of a graduate Allied Health Professional and Nurse internship programme. The College of Podiatry Annual Conference, Harrogate Nov 2019.

77. Cherry L, Siddle HJ, Wong E, Arden NK, Edwards CJ, **Bowen CJ**. Persistent rheumatoid arthritis disease activity in the feet of people treated with biologic therapy. The College of Podiatry Annual Conference, Harrogate Nov 2019.

78. Smith M, McCormick K, **Bowen CJ**, Cherry L. The use of musculoskeletal ultrasound to evaluate the Achilles tendon in people with diabetes: A structured literature review. The College of Podiatry Annual Conference, Harrogate Nov 2019.

79. Eltaraboulsi R, Nelson AE, Alvarez C, Renner JB, **Bowen CJ**, Gates L, Golightly YM. Incidence and progression of foot osteoarthritis: the Johnston County osteoarthritis project. OARSI Congress, Vienna, April 2020.

Conference Contributions – Other (38)

79. **Bowen C.J.** (1998) Evaluation of foot pressure measurement techniques in Clinical Rheumatology. Podiatry Rheumatic Care Association Annual Conference.

80. **Bowen C.J.** (1999) Podiatric Rheumatology: workshop, Belgium Podiatrists and Holland Society of Podiatrists. University of Gent, Belgium.

81. **Bowen C.J.** (2000) Outcome Measures: Conference Chair. Podiatry Rheumatic Care Association Annual Conference, University of Salford, UK.

82. **Bowen C.J.** (2001) Clinical Assessment Tools for Podiatrists and other Allied Health Professionals: Conference Chair. Podiatry Rheumatic Care Association Annual Conference, University of Keele, UK.

83. **Bowen C.J.** (2002) Clinical Education Competencies: Podiatry Teachers Annual Conference, University of Manchester UK.

84. **Bowen C.J.** (2002) Clinico-pathological Case conference: Dermatomyositis. Podiatry Rheumatic Care Association Annual Conference, University of Salford, UK.

85. **Bowen C.J.** (2002) Consultant Posts In Podiatric Rheumatology. Podiatry Rheumatic Care Association Annual Conference, University of Salford, UK.

86. **Bowen C.J.** (2003) Podiatry & Rheumatology. Southern Podiatry Annual Conference, ARK Centre, Basingstoke, UK.

*87. **Bowen C.J.** and McCulloch L. (2003) Uncovering the Sole: The role of Podiatry in Rheumatology. **Invited keynote speaker**. The Royal Society for Medicine National Conference, University of Warwick, UK.

88. **Bowen C.J.** (2003) Uncovering the Sole: The role of Podiatry in Rheumatology. The Institute of Chiropodists & Podiatrists National Conference, UK.

89. **Bowen C.J.** (2004) Rheumatology and Podiatry: A Cinderella Service? The Podiatry Open Study Group Conference, Birmingham, UK.

90. **Bowen C.J.** (2004) Ultrasound uses in Podiatry workshop. Southern Podiatry Annual Conference, ARK Centre, Basingstoke, UK.

91. **Bowen C.J.** (2005) Ultrasound uses in Podiatry workshop. The Fife Post Graduate Study Group Conference, Dunfermline, UK.

*92. **Bowen C.J.** (2004) Musculoskeletal ultrasound uses in Podiatry: **Invited keynote workshop**. The Society of Chiropodists and Podiatrists Annual Conference, Glasgow, UK.

93. **Bowen C.J.** (2005) Rheumatology and Podiatry: The Cinderella Service. **Invited keynote speaker**. The Jubilee Conference of The Institute of Chiropodists and Podiatrists, UK.

94. **Bowen C.J.** (2006) Experiences of a specialist musculoskeletal ultrasound foot and ankle clinic: **Invited oral presentation**. The British Society for Rheumatologists specialist foot and ankle interest group. The British Society for Rheumatologists National Conference, Glasgow, UK.

95. **Bowen C.J.** (2007) Foot pressures and ultrasound imaging: **Invited oral presentation**. The British Society for Rheumatologists foot and ankle specialist interest group. The British Society for Rheumatologists National Conference, Birmingham, UK.

96. **Bowen C.J.** (2008) Ultrasound guided injections of the foot: *Invited oral presentation*. The British Society for Rheumatologists foot and ankle specialist interest group. The British Society for Rheumatologists National Conference, Liverpool, UK.

T 97. **Bowen C.J.** (2010) The lived experience of the first Allied Health Professions NIHR CATP application. Allied Health Professions research forum, The College of Occupational Therapists, NIHR CATP fellowship training event, London UK.

* 98. **Bowen C.J** and Murphy N. (2010) Plantar foot pressure measurement in rheumatoid arthritis: key variables. *Invited keynote workshop*. World Congress of Podiatry, Amsterdam, NL.

99. **Bowen C.J.** (2010) Disarticulation? Modern treatment of rheumatological conditions and podiatric biomechanical paradigms. *Invited keynote speaker*. Langer Biomechanics Summer School, University of Stafford, UK.

100. **Bowen C.J.** (2010) Imaging techniques and biomechanics: Chickens or eggs? *Invited keynote speaker*. Langer Biomechanics Summer School, University of Stafford, UK.

T 101. **Bowen C.J.** (2010) Accessing grants for clinical Podiatrists. *Invited keynote workshop*. The Society of Chiropodists and Podiatrists Annual Conference, Bournemouth, UK.

102. **Bowen C.J.** (2011) Rheumatology update (foot & ankle): *Invited speaker*. The Society of Chiropodists and Podiatrists Guildford Branch Annual Meeting, UK.

T 103. **Bowen C.J** and Naidoo S. (2011) Arthritis Research UK career development internships in podiatry: a strategy for developing podiatry research and researchers in rheumatology and musculoskeletal rehabilitation. The Arthritis Research UK Medical Educators Conference. University of Southampton, UK.

104. **Bowen C.J.** (2011) Walking on marbles: Are we closer to understanding what patients who have arthritis mean? *Invited speaker*. The Society of Maltese Podiatrists' Annual Meeting. Valetta, Malta.

* 105. **Bowen C.J.** (2013) Advanced Imaging in Podiatry: The Society of Hong Kong Podiatrists Annual Conference. Hong Kong.

106. **Bowen C.J.** (2013) Advanced Imaging in Podiatry: An introduction to diagnostic ultrasound imaging of the foot. The Society of Maltese Podiatrists' Annual Meeting. Valetta, Malta.

107. **Bowen C.J.** (2015) Ultrasound Imaging for the foot and ankle: *Invited speaker*. The Society of Chiropodists and Podiatrists Surrey Branch Annual Meeting, UK.

108. **Bowen C.J.** (2015) Diagnostic Ultrasound performed by podiatrists: a game changer in management of musculoskeletal foot and ankle pathology. *Invited keynote speaker*. The Northern Ireland Society of Chiropodists and Podiatrists Annual Conference. Belfast, UK.

109. **Bowen C.J.** (2015) The development of research skills within allied health and nursing. *Invited speaker*. The Isle of Wight showcase conference for National nurses day, UK.

* 110. **Bowen C.J.** (2016) Challenging and defining effectiveness of 'podiatry' for long term conditions. *Invited keynote speaker*. Australasian Podiatry conference

* 111. **Bowen C.J.** (2016) Ultrasound imaging of the foot and ankle: a game changer for podiatric musculoskeletal practice. *Invited keynote speaker*. Australasian Podiatry conference

112. **Bowen CJ.** (2016) People with Stroke and Parkinson's disease: Home and outdoor shoes - the SHOES project. *Invited speaker*. The Bournemouth and District Branch of the Society of Chiropodists and Podiatrists Annual Meeting.

113. **Bowen CJ.** (2016) Wounds UK Annual Conference. Harrogate, *Invited speaker*.

* 114. **Bowen CJ.** (2016) OptiFoot: The College of Podiatry Project that takes on the challenge of demonstrating evidence for the effectiveness of podiatry. The UK College of Podiatry Annual Conference. *Invited Keynote speaker*.

115. **Bowen C.J** (2017) Evidence informed practice: Opportunities for AHPs. Isle of Wight AHP conference. *Invited speaker*.

116. **Bowen CJ**, Buldt A. The Journal of Foot and Ankle Research (JFAR) Tenth Anniversary Review. The College of Podiatry Annual Conference, Bournemouth Nov 2018.

117. **Bowen CJ.** Making your research International and building International collaborations. The College of Podiatry Annual Conference, Bournemouth Nov 2018.

Departmental/Research Working Papers (1)

118. Gates L, Arden NK, McCulloch LA, **Bowen CJ**. An evaluation of musculoskeletal foot and ankle assessment measures. Working papers in Health Sciences 1:11.

Editorships – Journal (2)

Journal Papers - Academic Journals (46)

121. **Bowen C.J.** A pharmacological case history of a patient with rheumatoid arthritis with particular reference to podiatric practice. *British Journal of Podiatric Medicine* 1997, 2 (7): 97-100.

122. **Bowen C.J.** Case Study Challenge: Dermatomyositis. *Podiatry Now* 2002, 5, (8): 437.

123. Robinson C.J, Otter S.J, **Bowen C.J.** Clinical misdiagnosis of Morton's Neuroma: a case of early rheumatoid arthritis. *British Journal of Podiatric Medicine* 2003, 6, (3): 85 – 87.

*124. **Bowen C.J.** Extending the Scope of Practice for Podiatrists: A consideration of the use of Diagnostic Ultrasound Imaging. *British Journal of Podiatric Medicine* 2003, 6, (4): 92-95.

125. Lang C, **Bowen C.J.** The use of acupuncture in the management of rheumatoid arthritis: a case study. *International Journal of Therapy and Rehabilitation*. 2004; 11(4):176-178.

126. Otter S.J, **Bowen C.J** and Young A. Forefoot plantar pressures in Rheumatoid Arthritis. *Journal of the American Podiatric Medical Association* 2004, 94, (3): 255-260.

127. **Bowen C.J.** Burridge J.H, Arden N.K. Critical Review: Podiatry interventions in the rheumatoid foot. *British Journal of Podiatric Medicine* 2005, 8, (3): 76-82.

128. Backhouse M, **Bowen C.J.** Effect of Interpod and custom orthoses on plantar loading of the 1st metatarsophalangeal joint during gait. *Algeos* 2006,
<http://algeos.com/pdfs/Southampton%20Interpod%20Study.pdf>

129. Cryer J.R, Otter S.J, and **Bowen C.J.** The Use of Quantitative Ultrasound Scans of the Calcaneus to Diagnose Osteoporosis in Patients with Rheumatoid Arthritis. *Journal of the American Podiatric Medical Association* 2007, 97: 108-114.

*130. **Bowen C.J**, Dewbury K, Sampson M, Sawyer S, Burridge J.H, Edwards C.J Arden N.K. Musculoskeletal ultrasound imaging of the plantar forefoot in patients with rheumatoid arthritis: Inter-observer agreement between a podiatrist and a radiologist. *Journal of Foot and Ankle Research* 2008, 1:5 (28 Jul 2008).

*131. **Bowen C.J**, Edwards C.J, Hooper L, Dewbury K, Sampson M, Sawyer S, Burridge J.H, , Arden N.K. Improvement in symptoms and signs in the forefoot of patients with rheumatoid arthritis treated with anti-TNF therapy. *Journal of Foot and Ankle Research* 2010, 3:10 doi:10.1186/1757-1146-3-10

132. **Bowen C.J**, Culliford D, Dewbury K, Sampson M, Burridge J.H, Hooper L, Edwards C.J, Arden N.K. The clinical importance of ultrasound detectable forefoot bursae in rheumatoid arthritis. *Rheumatology (Oxford)*. 2010 Jan;49(1):191-2. Epub 2009 Sep 30.

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Journal Papers - Professional Journals (9)

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Official Reports: Whole Report (2)

178. National College of Podiatry Research and Development Strategy. College of Podiatry, London, UK. 2017.

179. Core Podiatry project: recommendations for evidence of effectiveness of podiatry: College of Podiatry, London, UK. 2016

Official Reports: Part of Report (2)

180. North West Clinical Effectiveness Group Guidelines for management of foot health in rheumatoid arthritis 2011.

181. National College of Podiatry Research and Development Strategy 2012, College of Podiatry, London, UK.

Review Articles in Academic Publications (1)

182. **Bowen C.J.**, Hooper L, Edwards C.J, Arden N.K. Using ultrasound to image the foot in rheumatoid arthritis: current understanding, challenges and future scope. *Imaging in Medicine* 2013, 5:4.

Exhibitions - Group (9)

183. Aimhigher: Raising teenagers' awareness of musculoskeletal health through LIFELAB (2014)

184. Foot and Ankle Research and imaging: The Faculty of Health Sciences Rehabilitation Health Technologies Research Group Open Day (2014)

185. Aimhigher: Raising teenagers' awareness of musculoskeletal health through LIFELAB (2015)

186. Foot and Ankle Research: The Faculty of Health Sciences and Wessex Health Research group exhibition at the New Forest Show (2015)

187. Foot and Ankle Research and foot pressure measurement: The Faculty of Health Sciences Rehabilitation Health Technologies Research Group Open Day (2015)

188. University of Southampton Science open day – physics engagement (14-15 year olds) (2018)

189. GCSE student science workshop (2018)

190. Arthritis Research UK Centre for sport, exercise and osteoarthritis – public engagement day, Friends House, London (2018).

191. Feet forvLife: Science and Engineering Fare, University of Southampton (2018)

Consultancy (2)

T 192. Consultant to the City and Guilds: Development of a National Diploma qualification in foot health 2008.

T 193. Consultant to Canonbury Health Care UK / Simply feet involving advice on new and existing foot products, 2007 - 2011.

Web sites/Web site design/CD-ROM (4)

T 194. Athena SWAN at Health Sciences <http://blog.soton.ac.uk/athenaswan/>

195. Southern Central hub of the Council for Allied Health Professions Research <http://www.southampton.ac.uk/ahprnhub>

196. Research project: MSKInterns: Graduate Rheumatology Research Internships for Nurses and Allied Health Professionals. <https://www.southampton.ac.uk/healthsciences/research/projects/mskinterns.page>

197. International Foot and Ankle OA Research Group.

<http://www.sportsarthritisresearchuk.org/international-foot-and-ankle-group/international-foot-and-ankle-group.aspx>

Other (4)

198. Interview for Singapore Women's Magazine. Footwear and high heels. 2009.

199. Radio Interview: Solent Radio. 'Walking on marbles'. December 2013.

200. YouTube media interview. Foot and ankle research as part of the rehabilitation health technologies open day 2015.

201. Lower Extremity Review (United States). Obesity and foot pain/foot disorders. 2016.

Webinar hosted by ARC Wessex: <https://vimeo.com/415098956> "Academic Career Development - applying for PhD Scholarships"

Research project: MSKInterns: Graduate Rheumatology Research Internships for Nurses and Allied Health Professionals. <https://www.southampton.ac.uk/healthsciences/research/projects/mskinterns.page>

You Tube: ARMA hosted Webinar "[Addressing the burden of rheumatic and musculoskeletal foot and ankle pain](#)", in May 2019.

10. CONTRIBUTIONS TO LEADERSHIP, MANAGEMENT & ENGAGEMENT

A summary of significant contributions to the development and running of the University.

a) The Academic Unit/Department

Dates	Nature of contribution
2008-2009	Member of the Programme Advisory Board for the revalidation of the Allied Health Professions programmes.
2002 - ongoing	Personal/pastoral tutor for undergraduate and postgraduate students
2004 - 2010	Attendance and participation in South Central podiatry managers forum to link educational developments with workforce / PCT initiatives.
2008 - 2010	Professional Lead, Podiatry
2009 - ongoing	PhD students supervision
2009 - ongoing	Member of the rehabilitation health technologies research group, active living technologies cluster.
2010 - 2016	MRes NIHR Clinical academic pathway lead.
2011- ongoing	Lead for SOLLAR (Southampton Oxford Lower Limb Arthritis Research) group.

b) The Faculty or Budgetary Group

Dates	Nature of contribution
2009 - 2010	Member of the Course Approvals Sub Committee
2005 - 2010	Professional Lead for Podiatry at the NES South Central contract management negotiations
2009 - 2013	Member of the Faculty of Health Sciences, Education Strategy Group

2010 - 2013	Member of the Faculty of Health Sciences Ethics Committee
2012 - 2016	Member of the South Central Clinical Academic Careers Steering Group
2012 - 2015	Chair for the Faculty Athena SWAN committee
2012 - 2013	Project lead for the application of an Athena SWAN silver award (Bronze)
2014 - 2016	Project lead for the application of an Athena SWAN silver award (Bronze renewed)
2015 - 2017	Chair of the Faculty Equality and Diversity Committee
2018 - present	Fellowship Champion
2019- present	Academic Career Development Lead : NIHR Wessex Applied Research Collaboration

c) The University

Dates	Nature of contribution
2003 - ongoing	Honorary clinical contract with Southampton Universities Hospital Trust (SUHT) for the implementation and delivery of a specialist rheumatology ultrasound foot clinic.
2004 - 2010	Collaboration with the University of Leeds Musculoskeletal Unit in the implementation of a twinned internship for new graduates to further develop their research training.
2006 - 2007	AHP representative at the Faculty of Medicine & Life Sciences strategic planning meetings with respect to proposals for an Institute for Health and The Institute for Life Sciences.
2007 - ongoing	Member of the OARS (osteoarthritis research syndicate) group as part of the Southampton/Oxford musculoskeletal research partnership.
2007 - ongoing	Research collaboration with the MRC epidemiology resource centre, University of Southampton and the NIHR Biomedical research Unit, University of Oxford involving the investigation of osteoarthritis within the foot and ankle.
2010 - ongoing	Member of the shadow Musculoskeletal Biomedical Research Unit, University Hospitals Southampton.
2012 - ongoing	Member of the Institute for Life Sciences
2012 - 2016	Member of the University Athena Swan Committee (silver award)
2014 - 2016	Member of WISET

d) Enterprise

Dates	Nature of contribution
2006 - ongoing	Development and Leadership of a National Internship programme, funded by Versus Arthritis (formerly Arthritis Research UK), to grow musculoskeletal research capacity within allied health and nursing
2008 - 2010	CPD4Me: Contribution of two foot and ankle rheumatology online foot modules
2010 - 2013	British Council - Singapore podiatry student exchange placement programme

2014	The introduction of innovation interns to the Faculty of Health Sciences. Established the patenting and marketing of a new International protocol for musculoskeletal foot and ankle assessment (IMFAA).
2013	Leadership of the design of an off shore podiatry programme partnership with Singapore.
2015 - ongoing	On line access website for the International Foot and Ankle Assessment (IMFAA) protocol.
2015 - ongoing	Proof of concept investigation of design of 3D printed foot orthoses: Collaboration with 'SO3D' and Cynapse Ltd.
2015 - 2017	Leadership of the Singapore – Faculty of Health Sciences partnership Allied Health Alumni

11. STAFF DEVELOPMENT AND TRAINING

a) Staff development and training activities undertaken

Over the last three years (including current year) plus any significant activities in previous years.

Dates	Activity	Hours
Jan 2015	EndNote training (PDU)	2 hours
Jan 2015	Appraisal training for managers	3 hours
Mar 2015	Introduction to Information Governance (on-line hscic)	3 hours
June 2015	Fellowship interview training workshop	One day
Oct 2015 – Jan 2016	Springboard Leadership programme for women	Four days
Oct 2016	Good Clinical Practice update training	3 hours
Dec 2016	NVIVO training: University of Surrey	2 days
April 2017	Advanced statistical methods in epidemiology	3 days
Dec 2017 – May 2018	Developing leaders: Athena Programme, Kings Fund, London	4 x 1 week modules
June 2018	Oxford trials course, University of Oxford	1 x week module

b) Staff development and training activities coordinated, tutored, led or initiated

Over the last three years (including current year) plus any significant activities in previous years.

Dates	Activity	Hours
May 2015	Clinical practice and research: a culture shift in nursing and allied health. Isle of Wight, Nurse Day Conference.	1 hour

Nov 2016	Introduction to diagnostic ultrasound for foot and ankle pathologies (University of Malta, Level 6 podiatry students))	2 days
Jan 2017	Evidence Informed Practice: Opportunities for Allied Health Professionals. Isle of Wight Allied Health Conference.	2 hours
Feb 2017	Careers in clinical research. Council for Allied Health research South Central Hub.	1 hour
Mar 2017	Challenges in Podiatry and providing evidence. Hampshire Branch Meeting of the College of Podiatry.	3 hours
May 2017	The NIHR fellowship journey: Kings NIHR CLARHC conference, London.	1 day
June 2018	Addressing the burden of rheumatic and musculoskeletal foot and ankle pain: Arthritis and Musculoskeletal Alliance	Webinar
November 2018	The status of Podiatry Research: South Central CAHPR hub, Southampton	Webinar
April 2020	Fellowships: what are they and how to access support?	Webinar

c) Conference attendance

Major conferences attended over the last three years (including current year) plus any significant participation in previous years.

Dates	Title	Nature of involvement
May 2016	The Australasian Podiatry Conference, Melbourne, Australia (500 delegates)	Invited Keynote speaker
Nov 2016	Wounds UK Conference, Harrogate.	Invited workshop lead
Nov 2016	College of Podiatry UK, Glasgow UK. (1600 delegates)	Invited keynote speaker Session Chair, Research masterclass convener, oral and poster presentations. Poster tour chair. Scientific abstracts Chair
April 2017	British Society for Rheumatology, Birmingham, UK. (3000 delegates)	Session Chair, research oral and poster presentations. Scientific abstracts reviewer.
Nov 2017	College of Podiatry UK, Harrogate UK. (1600 delegates)	Session Chair, Research masterclass convener, oral and poster presentations. Scientific abstracts Chair
April 2018	OARSI: Osteoarthritis Research Society International, Liverpool.	Delegate
April 2018	British Society for Rheumatology, Birmingham, UK. (3000 delegates)	Session Chair, research oral and poster presentations. Scientific abstracts reviewer.
Nov 2018	College of Podiatry UK, Liverpool UK. (1600 delegates)	Session Chair, Research masterclass convener, oral and poster presentations. Scientific abstracts Chair
May 2019	OARSI: Osteoarthritis Research Society International, Toronto.	Foot and Ankle Discussion Group Session Chair

Nov 2019	College of Podiatry UK, Harrogate UK. (1600 delegates)	Session Chair, oral and poster presentations.
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d) Study leave and leave (including study leave/ sabbatical)

Taken over the last three years (including current year).

Dates	Purpose
6 weeks	Advanced epidemiology statistics; course; NIHR fellowship training (Athena Leadership programme; Oxford Trials course)

12. ACADEMIC AND PROFESSIONAL ACTIVITIES OUTSIDE THE UNIVERSITY

Details for the last three years (including current year) together with a summary of significant activities in previous years.
<p>2015: appointed mentor status by ILIAD, University of Southampton.</p> <p>2011-15: lead for Southern-Central hub, Council for Allied Health Professions Research.</p> <p>2012: Deputy Editor UK for the Journal of Foot and Ankle Research (Impact factor 1.83).</p> <p>2011: UK NIHR Clinical Academic Training Fellowship Mentor.</p> <p>2012: Co-convener for the British Society for Rheumatologists Foot and Ankle Specialist Interest Group.</p> <p>2014: Appointed Chair of the UK College of Podiatry Research and Development Committee.</p> <p>2014: Implementation of the UK Chartered Scientists awards for podiatrists (I was the first ever podiatrist to receive such an award).</p> <p>2014: UK professional body representative on the EULAR (European League against Rheumatism) foot and ankle group.</p> <p>2015: Member of the UK Council for Allied Health Professions Research (CAHPR) strategy committee.</p> <p>2015: Chair of the UK College of Podiatry Professoriate.</p> <p>2018: appointed Editor in Chief, Journal of Foot and Ankle Research (Impact factor 1.83).</p> <p>2018: Appointed Chair for the OARSI (Osteoarthritis Research Society International) foot and ankle discussion group.</p> <p>2019: Appointed Academic Career Development Lead: NIHR Applied Collaboration Wessex.</p>

13. COMMUNITY ACTIVITIES

Details for the last three years (including current year) together with a summary of significant activities in previous years.
<p>I have supported the local branches of the Society of Chiropodists and Podiatrists as well as those of Age Concern and Arthritis Research UK. I often give talks/presentations related to my scholarly and research activity. I also support a local podiatry network of clinicians involved in rheumatology who have regular quarterly meetings. The latest talk I gave to Winchester Women's 'Inner Wheel' (the wives of the Rotary club). This involved giving an after dinner speech on behalf of the Faculty of Health Sciences, explaining where and how funding from Arthritis Research UK is used within our research activities.</p>

14. MEMBERSHIP OF PROFESSIONAL AND LEARNED SOCIETIES

Member of the Society of Chiropodists and Podiatrists, UK. (1987 – ongoing)
Registrant with the UK Health and Care Professions Council. (1987 – ongoing)
Member of the British Health Professionals in Rheumatology, UK. (1997 – ongoing)
Fellow of the Higher Education Academy UK (2006 – ongoing)
Fellow of the College of Podiatry UK. (2008 – ongoing)
Fellow of the Royal College of Physicians and Surgeons, Glasgow, UK. (2012-ongoing)
Member of the Science Council, UK. (2014 – ongoing)

Member of the Osteoarthritis Research Society International (2018 - ongoing)

Signed:	
Date:	08.07.2020

Feedback	Response
1 Exact temporal sequences of the test protocol are not clear 1.1 e.g. 10 minutes may not prove appropriate for equilibration of the transcutaneous devices 1.2 Use of VMS-Oxy in reperfusion phase	<p>The data shows that both devices take about 8 minutes to reach equilibrium; and</p> <p>1.1 by 10 minutes the Medicap does so sooner than the TCM rewrite "ABOUT" and clarify in protocol to say "UP TO 20 Minutes. [deng et al] [page 13]"</p> <p>1.2: CLARITY IN WRITING ON USING VMS-OXY: MEDICAP REFERENCES ON CALIBRATION OF MEDICAP LAB STUDIES / MANUFACTURERS LITERATURE AS APPENDIX ETC: POINT IS NOT TO ACCPET BLINDLY WHAT MANUFACTURERS TAKE YOU. Since the two devices challenge the microvascular supply and trigger dilation through heating; it was useful to check if microvascular dilation had been effective. This was done by measuring flux at both sites, hence the use of the VMS-Oxy.</p>
2 Protocols assume Medicap has been calibrated against gas tension in phase 1. What if this is not the case?	<p>Both devices have been calibrated; the TCM by the Medical Physics department and also serviced by Radiometer; and the Medicap by the manufacturer against a laboratory blood gas analyser. prior to phase 1. (UoS Hospital Labs : Canisius Christopher)</p>
3 Study suggests there will be a comparison between Medicap values and nerve conduction velocity and amplitude. The two systems measure distinct physiological responses of the patient group.	<p>Earlier work by McCormick et al. (2015), had found an association between peripheral large nerve fibre function and microvascular reactivity. PROTOCOL UPDATED TO EXPLAIN PHYSIOLOGICAL PATHWAY RELATING NERVE FUNCTION AND ARTERIAL SUPPLY / DILATION. This work could explore any further relationships. [McCormick, K.G., Scorletti, E., Bhatia, L. et al. Diabetologia (2015) 58: 1916. doi:10.1007/s00125-015-3628-2]</p>
4 Uncertain who the "other examiners" are, in assessing intra-observer reliability of each of the measuring devices	<p>4. EXAMINERS CLARIFIED IN UPDATE PROTOCOL</p>

Faculty of Health Sciences

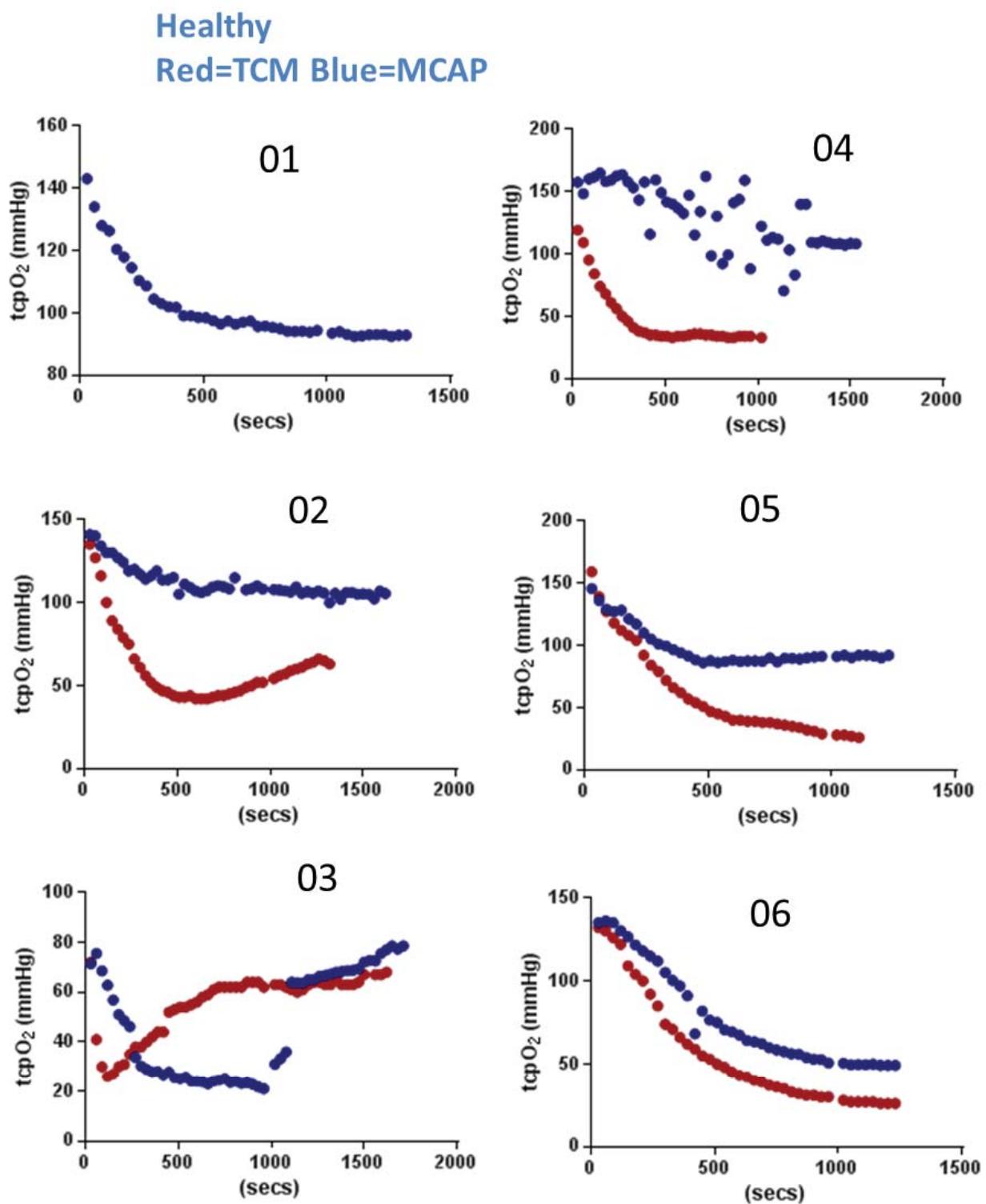
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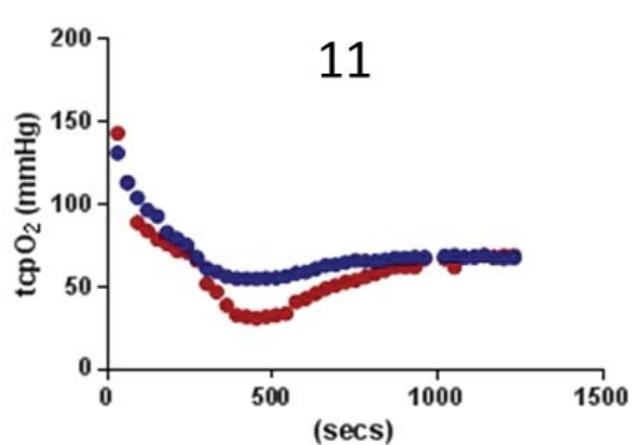
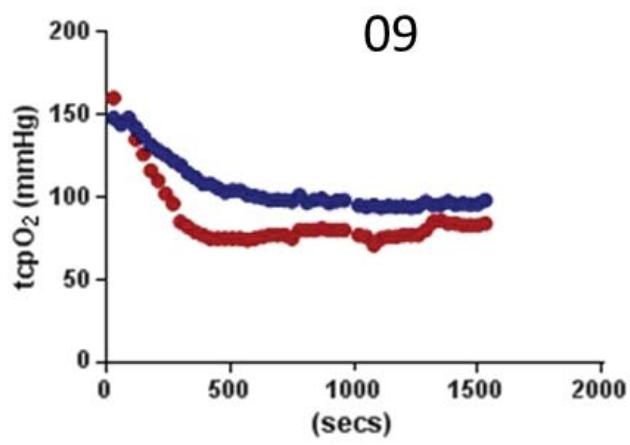
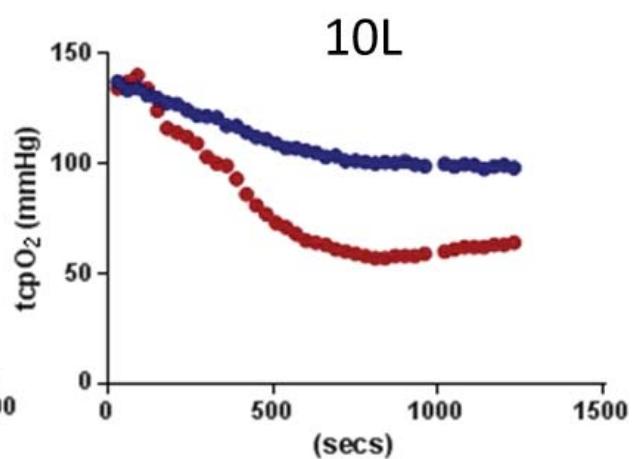
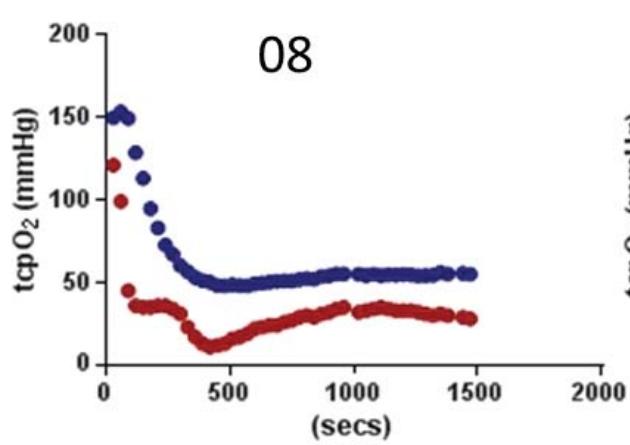
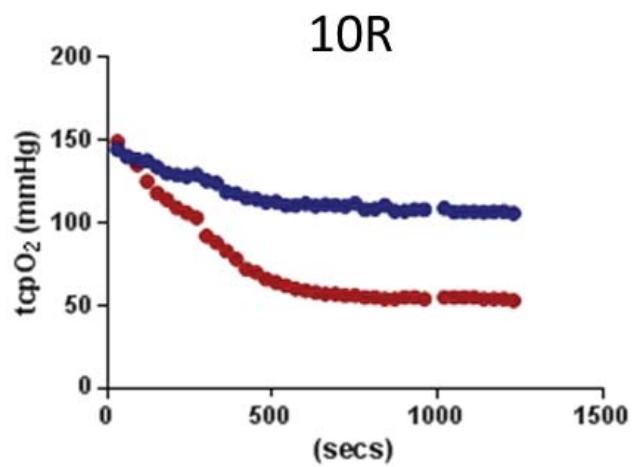
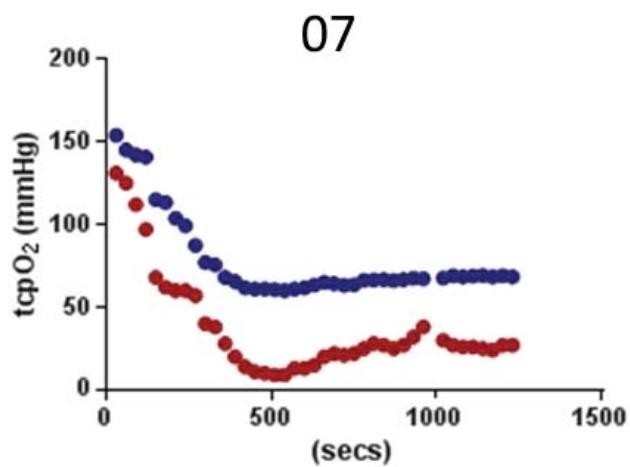
Name of Applicant	Simba R Tanyanyiwa
Title of Proposal	Can novel neurovascular devices (DPN-Check and Medicap) detect diabetic neurovascular changes earlier than current tools?

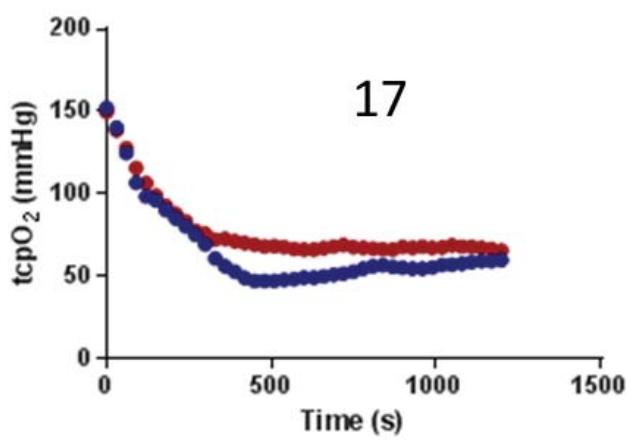
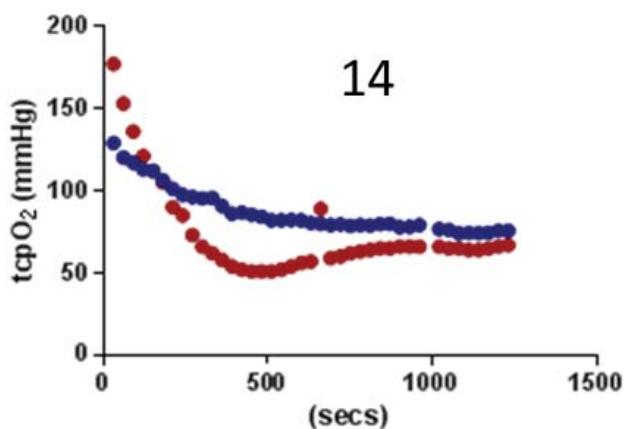
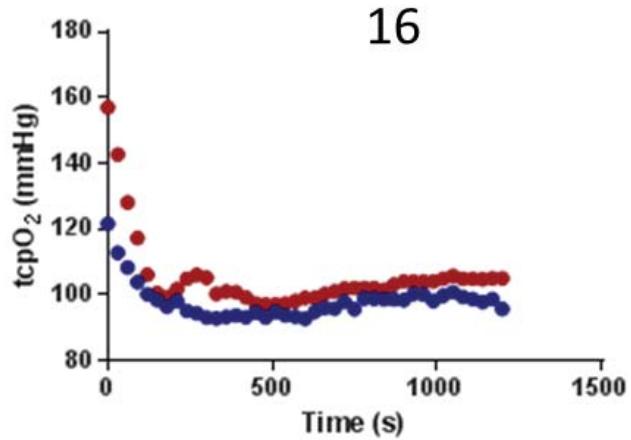
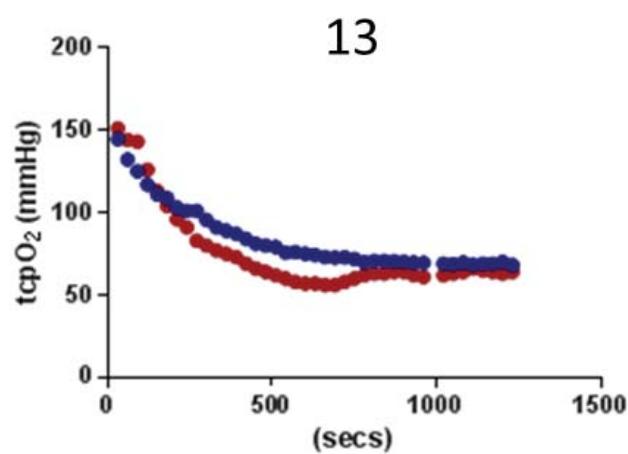
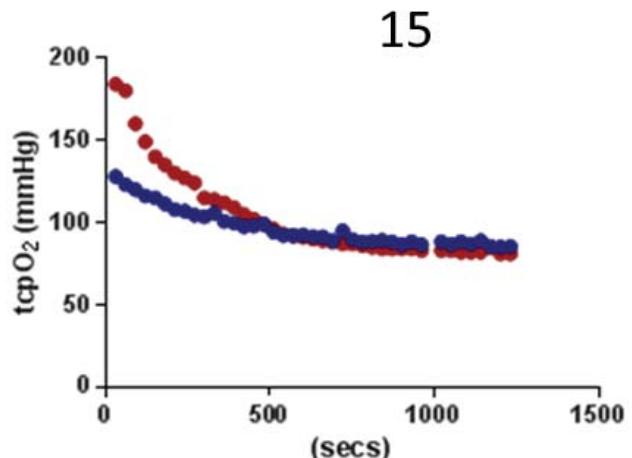
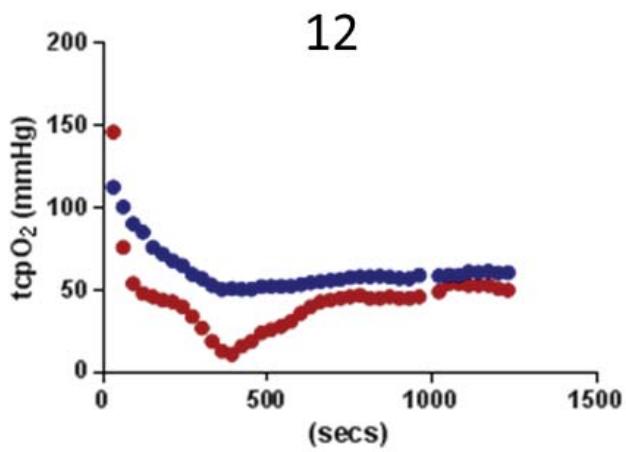
Research Quality			
Questions:	Yes / No	Peer-reviewer's Comments	Submitter's Answers
1. Background & Literature: Is the current state of knowledge outlined, well structured, coherent and well referenced?	Partially	<p>On the whole a reasonable introduction. Not all references are listed so these need checking. There is a more recent Marion Kerr paper published Jan 2017 with updated economic data - recommend this be used.</p> <p>In the background I feel there is limited information on neuropathy (2 pages) compared to vascular (4 pages) - this feels unbalanced. There is limited discussion around screening / diagnosis of neuropathy with only monofilaments and tuning forks discussed as alternative to NCS. No mention of other assessment tools e.g. Neuropad for sudomotor dysfunction (currently being evaluated by NICE).</p>	

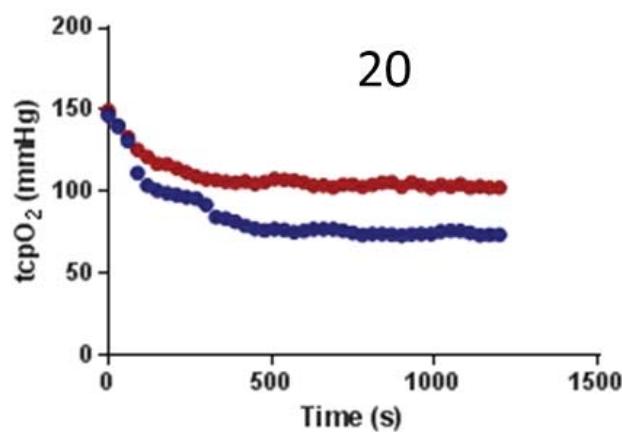
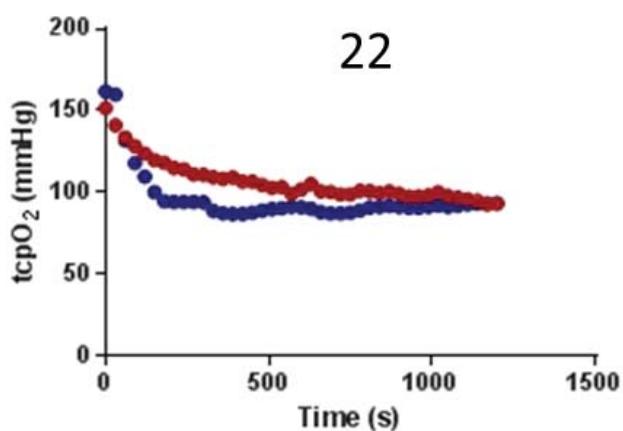
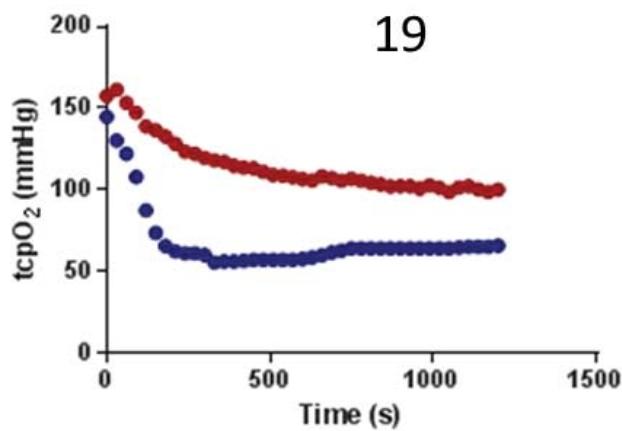
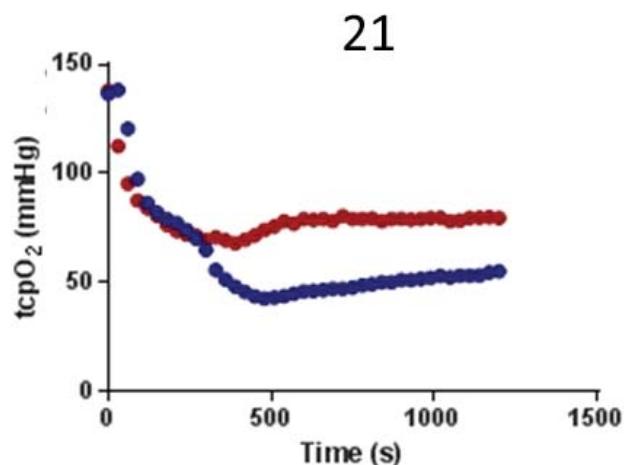
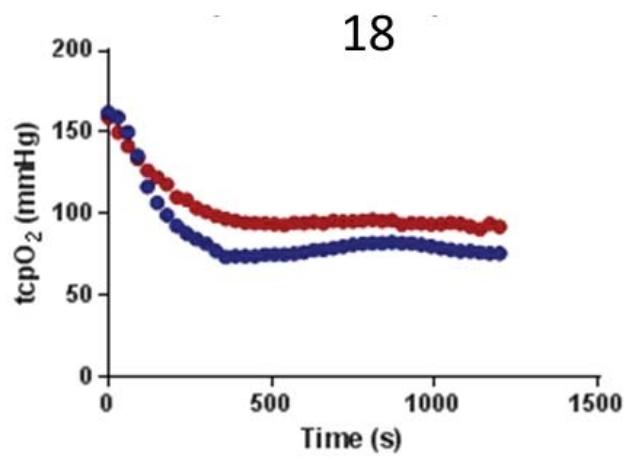
Experimental Study		Identified	DNA	Attended	Withdrawn	Reason
1	Reliability of DPNCheck	21	0	21	1 declared exclusion criteria after assessment	
2	Validity Medicap in Healthy	22	0	22	4 faulty equipment	
3	Validity Medicap in Diabetes L-Risk	unsure. About 30	0	21	0	
4	Reliability of TBI in healthy	31	0	31	0	
5	Validity and Reliability of DPNCheck, 10g MNF; TBI, Medicap			part of final study		
6	Effectiveness of DPNCheck	unsure. About 120	about 20	93	1 declined DPNCheck	
7	Effectiveness of Medicap					
Σ =				188	6	
Final				182		

APPENDIX B4: - Experimental Study 2 : Supplementary data of individual plots from n=22 Healthy Individuals for Medicap vs TCM400



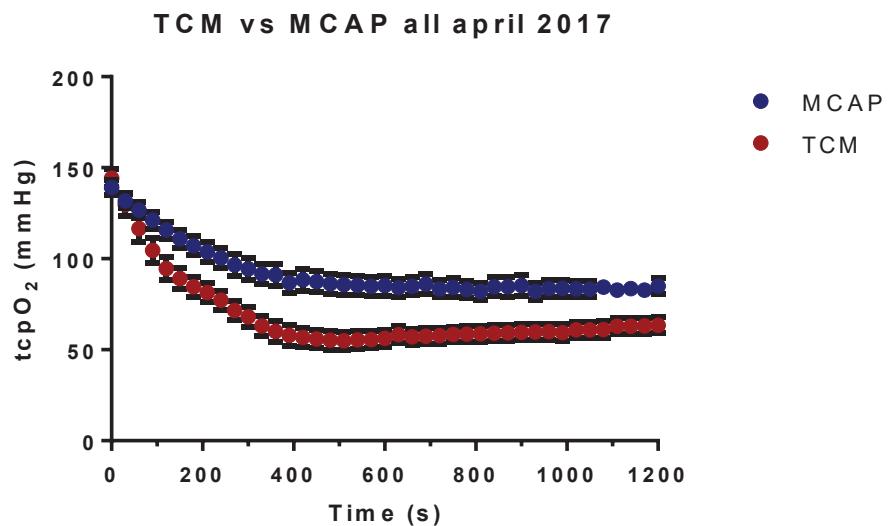






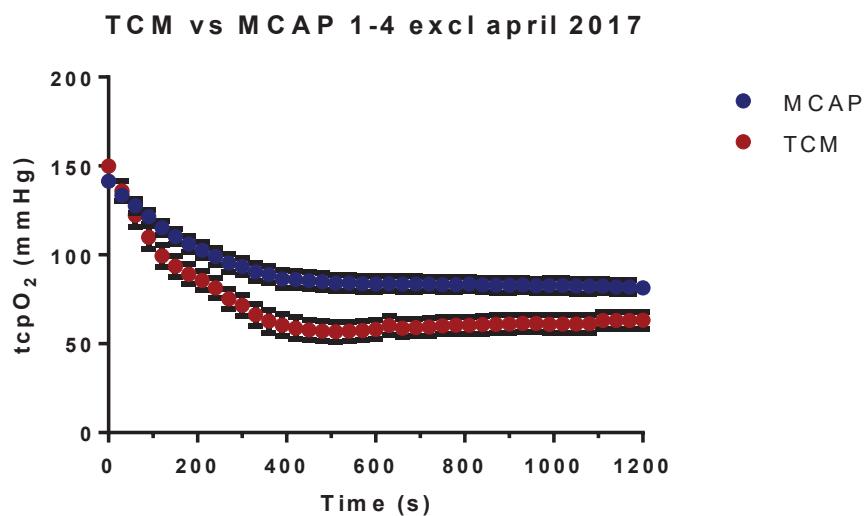
Summary

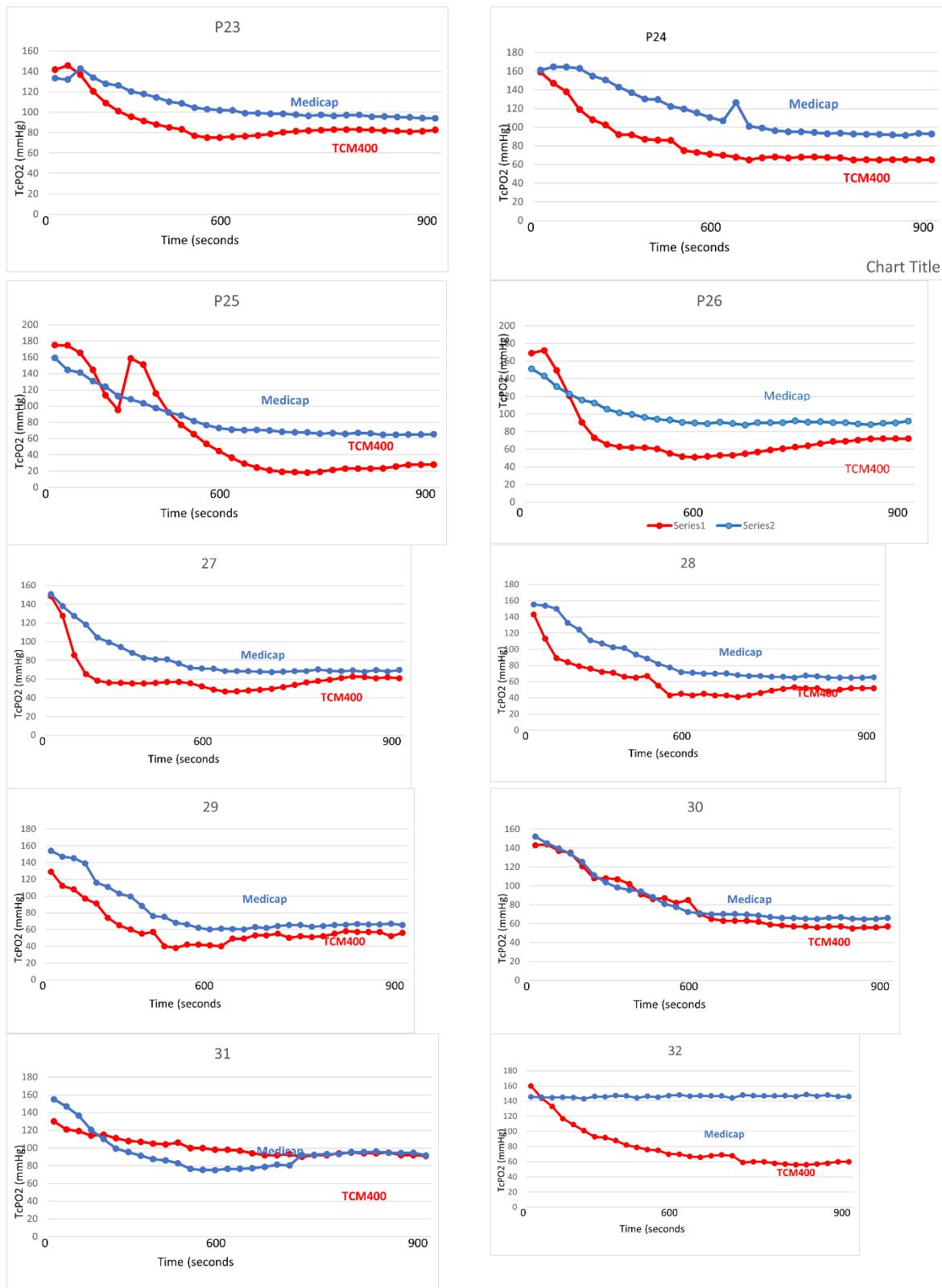
ALL N=22

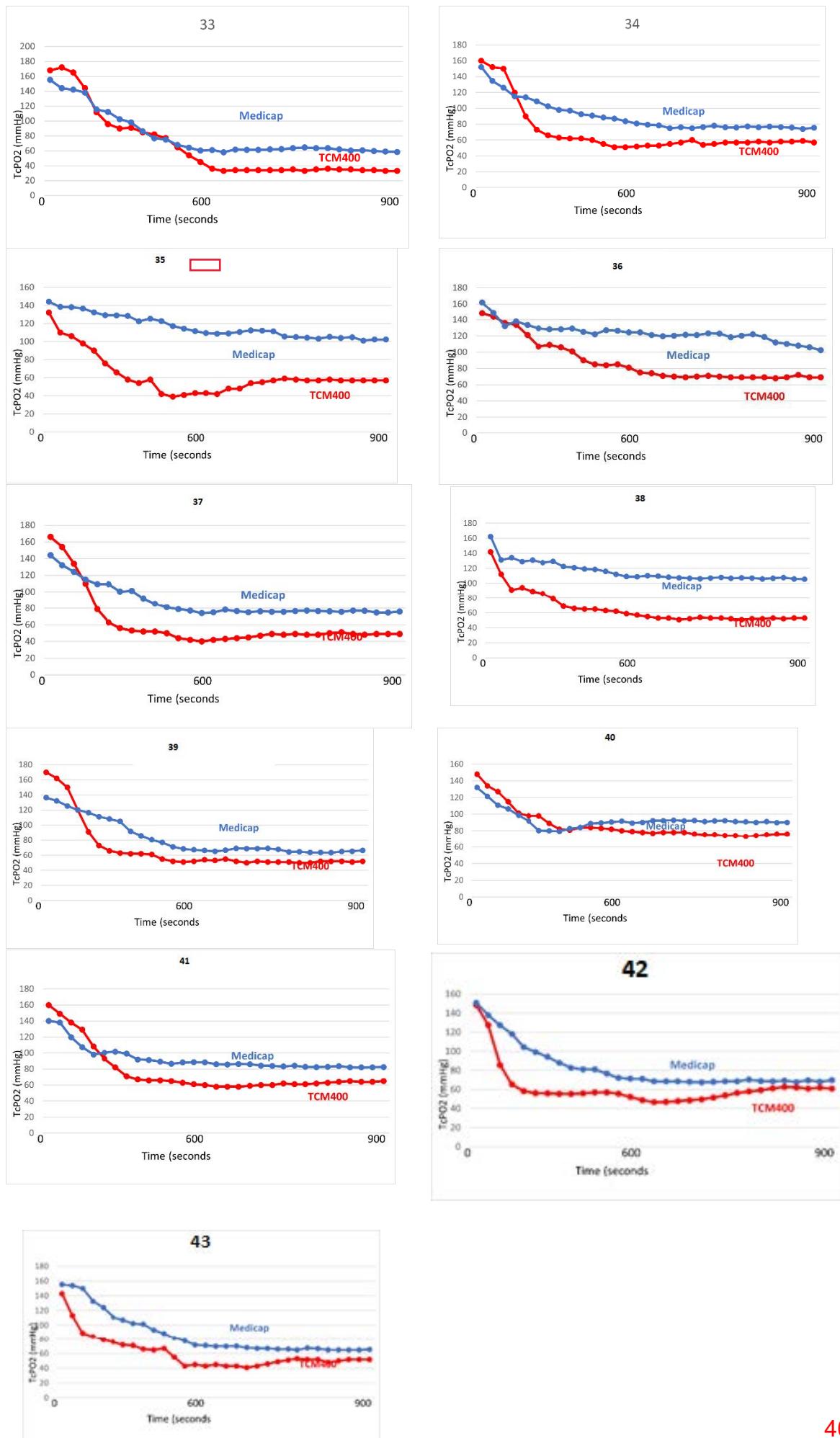


Excluding v1,v2,v3,v4

N=18







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