CLINICAL OUTCOMES AND PATIENT EXPERIENCE OF BIOSIMILAR TO BIOSIMILAR INFLIXIMAB SWITCHING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE

BY

DR CLARE HARRIS

CLINICAL AND EXPERIMENTAL SCIENCES

FACULTY OF MEDICINE

UNIVERSITY OF SOUTHAMPTON

STUDENT ID 32125259

SUPERVISORS: DR FRASER CUMMINGS & PROF SUSAN LATTER

ORCID 0000-0002-8233-7509

JUNE 2025

Abstract

University of Southampton

Faculty of Medicine

Clinical and Experimental Sciences

Thesis for the degree of Doctor of Medicine

Clinical outcomes and patient experience of biosimilar to biosimilar infliximab switching in patients with inflammatory bowel disease

Background & aims:

Regulatory pathways compare biosimilars with originator molecules only and not with other biosimilars. With the development of multiple infliximab biosimilars, patients may be asked to transition between them. Data is emerging but there is still a gap in the evidence on switching between infliximab biosimilars. Our aim was to conduct a full evaluation of switching a cohort of IBD patients from one biosimilar (CT-P13) to another (SB2) in a real-world setting including clinical, patient experience, molecular and drug immunogenicity aspects of the process. The study was sponsored by University Hospital Southampton NHS Foundation Trust and financially supported by Biogen Idec Limited.

Method:

Prospective, phase IV interventional study of patients on CT-P13 switched to SB2. Demographics, disease history, validated disease activity scores, patient reported outcome measures and laboratory measurements were collected. Semi-structured qualitative interviews were also conducted.

Results:

133 out of 158 patients agreed to participate. Thirty-five subjects discontinued. Mean disease duration was 9.2 years. There was no difference in mean haemoglobin, platelet

count, albumin and C-reactive protein before and after switching. Mean faecal calprotectin at baseline and at week 30/32 was 306ug/g versus 210ug/g. Mean partial Mayo Clinic Score and modified Harvey Bradshaw Index at baseline were 1.54 and 3.14 versus 1.18 and 2.91 at week 30/32 respectively. There were 16 serious adverse events. Thematic analysis of interview transcripts from 26 participants identified six major themes that reflected the patient experience – trust, clinical status at the point of switching, past experience, general disposition, information provision and concerns/anxiety.

Conclusions:

Switching from CT-P13 to SB2 is safe and effective. Certain factors must be considered in supporting patient decision-making and enabling trust in the process. The results from this study support the development of a clear, stream-lined and well-monitored biosimilar switching programme.

Table of Contents

List of Tables

List of Figures

Declaration of Authorship

I, Dr Clare Harris, declare that this thesis and the work presented in it are my own unless stated otherwise and the work has been generated by me as the result of my own original research.

Title of thesis:

Clinical outcomes and patient experience of biosimilar to biosimilar infliximab switching in patients with inflammatory bowel disease

I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this university.
- 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.
- Where I have consulted the published work of others, this is always clearly attributed.
- 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.
- I have acknowledged all main sources of help.
- 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.
- Parts of this work have been published as:

  Harris C, Harris RJ, Young D, McDonnell M, Clancy B, Harvey J, et al. Clinical Outcomes and Patient Experience of Biosimilar to Biosimilar Infliximab Switching in Patients with Inflammatory Bowel Disease: A Prospective, Single-Centre, Phase IV Interventional Study with a Nested Qualitative Study. GastroHep. 2023, 1248526, 14 pages, 2023. http://doi.org/10.1155/2023/1248526

  ORCID 0000-0002-8233-7509

Signed:

Date: 17th June 2025

Acknowledgements

There are many people who have supported this research journey of mine over the last seven years or so. First and foremost, thank you Fraser for giving me the opportunity to come and work with you again. You know that this not only provided me with an avenue to develop myself academically but also allowed me to come back to Wessex and be where I needed to be. You've been an inspiration and a huge supporter of me from my very first day as a junior doctor and I cannot thank you enough.

Thank you, Sue, for guiding me through my first foray in to qualitative research and showing me the wealth of information that can be gained from it. It has certainly been an experience which I have enjoyed and I thank you for being so kind, attentive and patient along the way.

To the lower GI research team and all the staff at Victoria House – you are all wonderful and it wouldn't have happened without you. Thank you to all the collaborators on this project and for your hard work and dedication. To all the lovely friends I've gained along the way, thank you for putting up with my incessant rants and lamenting about this thesis. Richard, Martin and David – you've had to bear the brunt of it and I thank you for the 'therapy sessions'!

And then of course my lovely family. Thank you for helping me get through this. It's been a long ol' time and I feel like you all deserve this as much as I do! Many, many hours of baby sitting and providing cups of tea and biscuits – none of it has gone unnoticed. To my little people, Maya and Miri, you've certainly contributed to my delaying tactics on submitting this but I would not have had it any other way! And Matthew – I would not have done this without you, my number one fan. Thank you for dealing with all my dramas and helping me get here. You are the best.

Abbreviations

5-ASA	5-Aminosalicylates
ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASUC	Acute Severe Ulcerative Colitis
ATI	Antibodies to Infliximab
BSG	British Society of Gastroenterology
CARD15	Caspase Recruitment Domain-containing protein 15
CCT	Certificate of Completion of Training
CCUK	Crohn's and Colitis United Kingdom
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CI	Chief Investigator
COVID-19	Coronavirus Disease Pandemic
CRF	Case Report Form
CRP	C-reactive Protein
CT	Computed Tomography
CTA	Clinical Trials Assistant
ECCO	European Crohn's and Colitis Organisation
eCRF	electronic Case Report Form
EEN	Exclusive Enteral Nutrition

EFCCA	European Federation of Crohn's and Ulcerative Colitis Association
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FBC	Full Blood Count
FC	Faecal Calprotectin
FDA	Food and Drug Administration
HBI	Harvey Bradshaw Index
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
IBD-U	Inflammatory Bowel Disease – unclassified
iBiSS	IBD Biosimilar to Biosimilar Switching Study
IBS	Irritable Bowel Syndrome
ICB	Integrated Care Board
ID	Identification
IEC	Intestinal Epithelial Cells
IFN	Interferon
IFX	Infliximab
IL	Interleukin
IMID	Immune Mediated Inflammatory Disorders
IPQ-R	Revised Illness Perception Questionnaire
JAK	Janus Kinase
LOR	Loss of Response
mAb	Monoclonal Antibodies
MCID	Minimal Clinically Important Difference
MCS	Mayo Clinic Score

MDT	Multi-Disciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
mHBI	modified Harvey Bradshaw Index
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NAb	Neutralising Antibodies
NHS	National Health System
nm	nanomolar
NOD2	Nucleotide-binding Oligomerisation Domain-containing protein 2
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PIS	Patient Information Sheet
PK	Pharmacokinetics
pMCS	partial Mayo Clinic Score
PROM	Patient Reported Outcome Measures
PTM	Post Translational Modifications
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBCE	Small Bowel Capsule Endoscopy
SES-CD	Simple Endoscopic Score for Crohn's Disease
SMD	Small Molecule Drug
SRQR	Standards for Reporting Qualitative Research
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumour Necrosis Factor
TNF-alpha	Tumour Necrosis Factor alpha

TSQM	Treatment Satisfaction Questionnaire for Medication
UC	Ulcerative Colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ug/ml	microgram per millilitre
UHS	University Hospital Southampton
UoS	University of Southampton
US	United States
VAS	Visual Analogue Scale

Chapter 1 Introduction

1.1 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the gastrointestinal tract. The two main types are Crohn's Disease (CD) and ulcerative colitis (UC). The incidence and prevalence of IBD continues to increase with time with a current prevalence of 0.5% of the general population in Western countries(1). CD can affect the entire gastrointestinal tract from the mouth to the anus although it has a propensity for the terminal ileum. It is characterised by transmural granulomatous inflammation and can lead to the formation of strictures and/or fistulae. UC only affects the large bowel and is characterised by inflammation and ulceration of the colonic mucosa extending proximally from the rectum(2, 3). A small proportion of patients with UC can present atypically and have rectal sparing disease although this is more common in CD(4). Patients with UC typically experience a waxing and waning course of their disease. IBD-unclassified (IBDU) is a label given to 5-15% of patients with IBD when it is not possible to distinguish the endoscopic and histological findings as either CD or UC(5). There are an estimated 2.5-3 million people in Europe alone who are affected by IBD with an estimated direct healthcare cost of 4.6-5.6 billion euros per year(6). This represents a global public health problem because of the chronicity of the disease, with no increased mortality, and the need for expensive treatments and surgeries.

1.2 Pathogenesis

The exact cause of IBD remains unknown. However, in recent years significant progress has been made in our understanding of the disease process. Immunological abnormalities triggered by genetic and environmental factors, in particular the gut microbiome, are thought to be important in its pathogenesis (7). The intestinal immune system consists of innate and adaptive responses. It is a complex system that aims to protect the gut against pathogenic

invasion but at the same time tolerate commensal flora. The intestinal epithelium is a single-cell layer that forms the surface of the small and large intestine and separates the tissue from the luminal content. It is made of intestinal epithelial cells (IEC). The role of the IEC is to act as a physical and biochemical barrier and protect from invading pathogens, antigens and toxins but at the same time allow the passage of nutrients and water. Disintegration of this cell layer and loss of this protection can lead to intestinal inflammation like we see in IBD(8). Intestinal homeostasis is thus achieved by intricate interactions between the microbiota, the intestinal epithelium and the host immune system.

The innate immune response is rapid but offers no immunological memory. It consists of anatomical barriers, toll-like receptors, immune cells (including neutrophils, monocytes, macrophages, dendritic cells and natural killer T cells) and cytokines that all respond to invading microbes by producing a rapid inflammatory response. The innate immune system activates the adaptive immune response which in contrast is pathogen specific and mediated by a T-cell response. This response is delayed and can take up to seven days to develop. IBD is strongly immune mediated(9). Th1 cells secrete interferon(IFN)-gamma and tumour necrosis factor (TNF). Macrophages and dendritic cells produce interleukin(IL)-12. These cytokines are induced by IL-12 and thought to be associated with CD(10). Th2 cells secrete IL-4, IL-5 and IL-13 and are induced by IL-13 and are linked to UC(11).

Carswell et al first described TNF-alpha in 1975 when studying tumour regression and necrosis in the sera of mice(12). TNF-alpha has been extensively studied and is well known to be one of the most significant pro-inflammatory cytokines in a wide range of pathological conditions including infection, injury, inflammation and tumour development(13). It exerts its effects by controlling cellular processes such as cell proliferation, survival and death. Over production of TNF-alpha in patients with IBD leads to a pro-inflammatory response which dysregulates immune cells and leads to tissue damage(14, 15). Targeting TNF-alpha in the

management of IBD was one of the major breakthroughs in treatment and will be discussed later in this chapter.

A positive family history is a well-known risk factor for IBD which supports the genetic contribution to the pathogenesis of IBD. Familial concordance in monozygotic twins is higher in CD (30-35%) compared to UC (10-15%)(16). Genome-wide association studies have successfully shown genetic risk loci for IBD with multiple shared between CD and UC(17, 18). Nucleotide-binding oligomerisation domain 2 (NOD2) gene, previously known as caspase recruitment domain-containing protein 15 (CARD15), located on chromosome 16 was the first gene found to be associated with CD(19). Approximately a third of patients with CD have a mutation in NOD2 and these patients often present earlier with a more aggressive disease phenotype(20, 21). NOD2 is also closely associated with the regulation of both the innate and adaptive intestinal immune system(22).

One of the key points genetic research has highlighted is that genetic susceptibility alone is not enough to manifest disease. There are other key non-genetic risk factors that are implicated, of which the diversity and composition of the microbiome is one of the most important(23). The gut microbiome consists of bacteria, fungi, viruses and protozoa. Firmicutes, Bacteroides, Proteobacteria and Actinobacteria are the four main phyla of bacteria. The colon has the highest diversity and number of species(24). Both CD and UC commonly present in areas of the gastrointestinal tract with the highest concentration of microbiota such as the colon and terminal ileum. Dysbiosis is the imbalance in the composition of the gut microbiome. It is not clear if dysbiosis is a cause or a result of IBD. However significant changes in the gut microbiota have been associated with IBD(23). Many of the other environmental factors linked to the pathogenesis of IBD are intimately related to the microbiome and dysbiosis. These include but are not limited to early antibiotic use, smoking, diet, exposure to gastroenteritis and breast-feeding.

1.3 Clinical features

Diarrhoea, abdominal pain and weight loss classically occur in most patients with CD. In active disease patients can also experience lethargy, malaise, fever and loss of appetite. However, the presentation is largely influenced by the site of disease, as in perianal CD which can present with perianal pain, recurrent abscesses and fistulae. The cardinal symptom of UC is bloody diarrhoea and the passage of mucous per rectum. Other symptoms include systemic features of weight loss, fever and malaise as like CD. It can also present acutely as acute severe UC (ASUC), a life-threatening medical emergency with significant morbidity(25). ASUC is defined by the Truelove and Witts criteria and requires immediate treatment and prompt consideration of colectomy if medical therapy fails(26). Truelove and Witts criteria include: number of bloody stools per day, pulse, temperature, haemoglobin and erythrocyte sedimentation rate to assess severity. Patients with IBD can also present with extra-intestinal manifestations of the disease linked to the skin, eyes, joints and hepatobiliary system. Some are directly related to disease activity like aphthous ulceration, erythema nodosum and episcleritis. Others are independent of active disease, for example sacroiliitis and small joint arthritis.

1.4 Disease classification

Crohn's disease can be classified according to the Montreal classification based on age at diagnosis (<16, 17-40, >40), location (ileal, colonic, ileocolonic and upper gastrointestinal tract disease) and behavior (non-stricturing or penetrating, stricturing, penetrating and presence of perianal disease) of disease. UC can also be classified using the Montreal classification which looks at the extent of the disease only (proctitis, left sided and extensive)(27). The macroscopic extent of disease in UC is important as it guides management and prognosis especially in terms of the risk of dysplasia(28).

1.5 Clinical disease activity

There are several research tools available to assess disease activity in IBD. In CD, two common tools are the Crohn's disease activity index (CDAI) and the Harvey-Bradshaw Index (HBI)(29-31). The CDAI was developed in 1976 and consists of eight domains which have individual weightings and are totalled to provide a score as shown in the table below (

Table 1). A CDAI <150 indicates clinical remission, 150-219 mild disease, 220-450 moderate disease and >450 severe disease.

Clinical or laboratory variable	**Weighting factor**
Total number of liquid/soft stool each day for 7 days	x2
Average daily rating for abdominal pain each day for 7 days (0=none, 1=mild, 2=moderate, 3=severe)	x5
Average daily rating for general well-being each day for 7 days (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	x7
Anti-diarrhoeal use	x30
Presence of an abdominal mass (0=no, 1=questionable, 2=definite)	x10
Haematocrit	x6
Presence of complications (One point for each complication)	x20
Percentage deviation from standard weight	x1
TOTAL	

Table 1: Crohn's Disease Activity Index (CDAI)

The validity of the CDAI has been vigorously verified and is considered the gold standard. However, there are problems with this score(32, 33). Firstly, several of the domains used to calculate the score are highly subjective which can affect the reliability. In addition, the CDAI requires a seven-day period of diary data from patients which is often not accurate and also can prove difficult in day to day clinical practice. The CDAI is also not applicable to patients with ileostomies or colostomies. Finally, the correlation between the score and objective markers of disease such as endoscopic evaluation and biomarkers is not well described. The HBI on the other hand is more commonly used and was designed as the CDAI was

considered too complex. The HBI provides a score based on a patient's general wellbeing, severity of abdominal pain, number of liquid stools, presence of an abdominal mass and complications related to CD. The subjective symptoms are based on the 72 hours prior to calculating the score. The modified HBI (mHBI) is a tool used which excludes the physical examination aspect and can therefore be calculated by the patient themselves. The Mayo Clinic Score (MCS) has four components and is commonly used to asses disease activity in UC(34). It takes in to account stool frequency, rectal bleeding, a physician's global assessment (PGA) and an endoscopic assessment of mucosal inflammation. This score is simple and easy to use. However, it has not been fully validated. A partial Mayo Clinic Score (pMCS) that does not include the endoscopic evaluation has also been developed for use in UC as this is not always feasible(35). The mHBI and pMCS tools are discussed in more detail later in this thesis.

The above tools measure severity in terms of clinical and endoscopic markers. Increasingly there has been importance placed on patient reported outcome measures (PROM) which are standardised and validated surveys filled in by patients. Tools such as the CDAI and HBI are unable to objectively capture a patient's perspective of their health condition. PROMs on the other hand are measures that come directly from the patient with no interpretation of their response by a clinician or other individual(36). The major benefit of these assessments is in supporting patient-centred care and thus providing a good quality IBD service. This study used the IBD Control PROM which is discussed in more detail in chapter 3.

1.6 Investigations

In clinical practice the diagnosis of IBD is based on a combination of clinical, endoscopic, radiological, biochemical and histological features. These should allow the differentiation between the two conditions and allow a diagnosis to be made. All patients with a new

diagnosis of IBD should be fully investigated to establish the extent and pattern of disease. Ileocolonoscopy with mapping biopsies is the mainstay of both diagnosis and assessment of IBD. Several scoring systems exist to aid endoscopic assessment by quantifying mucosal appearances and behavior with an aim to standardise reporting. The CD Endoscopic Index of Severity (CDEIS) and the Simplified Endoscopic Activity Score for CD (SES-CD) are two systems used in both clinical practice and research for CD(37). The SES-CD is much less complex to calculate compared to the CDEIS and therefore easier to use. It assesses the size of mucosal ulceration, affected surface, endoscopic extension and the presence of stenosis. Rutgeerts score is used to assess for recurrence of CD at the neo-terminal ileum post-surgery(38). If upper GI tract CD is suspected then endoscopic evaluation is indicated to aid diagnosis. Small bowel capsule endoscopy (SBCE) can also be used to assess the small bowel in CD(39). The Mayo Clinic endoscopy sub score is a commonly used scoring system for UC which classifies disease activity in to normal, mild, moderate or severe based on the most severely inflamed part of the colon macroscopically. Another scoring system used to assess UC is the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) which looks at three descriptors: vascular pattern, bleeding and ulceration(40).

According to the British Society of Gastroenterology (BSG) guidelines samples should be taken from the ileum, at least four colonic sites and the rectum with a minimum of two biopsy samples from each(41). Ideally there should be areas of both normal and abnormal mucosa. Histological assessment, in conjunction with endoscopic and clinical findings, is valuable for a number of reasons. These include confirming the diagnosis of IBD, differentiating between CD and UC, assessing disease extent/activity and excluding other non-IBD mimics as well as dysplasia. Typical findings in UC include distortion of crypt architecture, crypt abscess, inflammatory infiltrates and mucin depletion with the findings limited to the mucosa. Conversely CD shows transmural involvement and mucosal discontinuity with ‘skip lesions’. There are also typically the presence of granulomas to distinguish CD from UC(42).

Radiological investigations again complement endoscopic findings, especially in CD to establish the presence of more proximal small bowel involvement. Cross-sectional imaging including computed tomography (CT) and magnetic resonance imaging (MRI) as well as ultrasonography are all used in the assessment of the small bowel in CD(43, 44).

1.7 Treatment

Treatment is aimed at achieving long-term control by gaining complete clinical, biochemical, histological and endoscopic remission by tailoring evidence-based strategies to individual cases. There is no consensus on the definition of remission and in more recent years the concept of mucosal healing as a treatment target has been considered. However, this puts considerable burden on endoscopy departments, patients themselves and healthcare systems due to the need for regular endoscopic assessment.

1.7.1 Medical management

There are two aims in the medical management of IBD – firstly to induce remission of active disease and then to maintain that remission and prevent further 'flares' of disease. There are now five classes of drugs used in the treatment of IBD which include 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, biologics and small molecules. The approach to medical management is dependent on the severity of each individual case but broadly can take a "bottom-up" (for mild disease) or "top-down" (for aggressive disease) approach with early use of advanced therapies in the course of the disease.

A combination of oral and topical 5-ASA is the standard treatment for mild to moderate UC. 5-ASAs are chemically related to aspirin and aim to dampen down the inflammatory response in order to allow healing. Mesalazine is the most widely used preparation and is

generally well tolerated compared to sulfasalazine. Side effects of mesalazine include nausea, diarrhoea, abdominal pain and headache. 5-ASAs can be nephrotoxic and so baseline renal function must be checked and then monitored regularly(45). Although historically 5-ASAs were used in the treatment of CD they have no role now with increasing evidence to show a lack of efficacy of these drugs in CD(46).

Corticosteroids can be administered orally and intravenously and have been extensively studied and used for the induction of remission in IBD since the 1950s(26). The major concern with steroids is the significant side effect profile which includes but is not limited to the development of opportunistic infections, diabetes mellitus, hypertension and osteoporosis(47). Drugs such as budesonide, which are second generation oral corticosteroids, are becoming much more popular. Their role is in the treatment of mild to moderate IBD. The aim with these drugs is to deliver the drug to the site of inflammation and therefore reduce systemic side effects(48).

Immunomodulators are drugs used for the long-term treatment and maintenance of remission in patients with moderate to severe IBD. Largely they include thiopurines, methotrexate (MTX) and calcineurin inhibitors. MTX is not used in UC(49). Immunomodulators can be used alone, although this is less fashionable now, or more commonly in combination with biologics to reduce the risk of immunogenicity.

Biological drugs are products that are derived from or contain components of living organisms. They are a diverse group of medicines that are generally proteins purified from living culture systems and include vaccines, growth factors, immune modulators and monoclonal antibodies. They are produced by a biological process, versus a chemical one, and target specific parts of the immune system that trigger inflammation. There are multiple

biologics available for physicians to use to treat patients with IBD in clinical practice. These include anti- TNF-alpha molecules (infliximab (IFX), adalimumab, golimumab and certolizumab), anti-integrin molecules (vedolizumab) and anti-interleukin molecules (ustekinumab, risankizumab, mirikizumab). The main focus of this thesis is the use of biosimilars of infliximab and this will be discussed in more depth in Chapter 2.

As our understanding of the mechanisms involved in the pathogenesis of IBD have evolved there has been increasing interest in new small molecules drugs (SMD). SMDs are organic compounds that have a low molecular weight of <900 Daltons. They rapidly diffuse across cell membranes and are absorbed into the systemic circulation(50). SMDs are orally administered, have a rapid onset of action, are more stable in terms of their structure and have a short half-life. This is particularly useful when rapid drug elimination is required such as pre-surgery or with concurrent infection. These drugs also have more predictable pharmacokinetics and immunogenicity is not an issue. The main SMD in use in IBD are the Janus Kinase (JAK) inhibitors with tofactinib, filgotinib and upadacitinib currently licensed for use in IBD.

Nutritional therapy can also be used in the treatment of IBD. Primarily this is used in paediatric populations with robust evidence for inducing remission as well as promoting growth(51). Exclusive enteral nutrition (EEN) is guided by specialist dietitians and involves a complete liquid diet, as the sole source of nutrition, for a prolonged period of up to 12 weeks. These can be elemental (individual amino acids), semi-elemental (peptides) or polymeric (intact proteins). The main drawback to enteral nutrition is the palatability and tolerance by patients. The exact mechanism of EEN is not clear although there is increasing evidence to suggest it alters the microbiome to re-establish intestinal homeostasis(52).

1.7.2 Surgical management

Clearly there are now extensive medical treatment options available for patients with IBD compared to several years ago. However, the option of surgical management is still present and must not be overlooked. In fact, the timing of surgery can be critical and delays due to further trials of medical therapies can be catastrophic for patients. The specific procedures pertaining to the surgical management of CD and UC will not be discussed in this thesis as this is an extensive subject with no specific implications on biosimilar switching which is the focus of this thesis.

1.8 Structure of thesis

This thesis is based on the IBD Biosimilar to Biosimilar Switching Study (iBiSS) which is a prospective, single-centre, phase IV interventional study conducted at University Hospital Southampton. Recruitment started in August 2018 and the final follow-up visit was in February 2020. The results of this study are presented in two sections. The first section looks at the quantitative data from the switch and the second analyses the data from the nested qualitative study of the patient experience of switching.

1.9 Hypothesis and objectives

Hypothesis:

There is no difference in clinical outcomes for adult patients with IBD treated with infliximab who are switched from one biosimilar of infliximab (CT-P13) to another (SB2).

Objectives:

- To evaluate the clinical outcome of switching a cohort of patients with IBD from CT-P13 to SB2 at week 30/32 using validated disease activity scores (pMCS for UC and mHBI for CD), patient reported outcome measures (IBD Control PROM) and

laboratory measurements (full blood count [FBC], C-reactive protein [CRP], albumin and faecal calprotectin[FC])(30, 35, 53, 54).

- To evaluate the safety of switching from one biosimilar to another.
- To assess drug trough levels and evaluate the risk of developing immunogenicity after switching.
- To explore the patient experience of switching medication including their general beliefs about their condition and treatment.

1.10 Thesis timeline

I started my Clinical Research Fellow post at University Hospital Southampton (UHS) NHS Foundation Trust in 2018 at which point this project was a concept that required much development. I was appointed as lead Research Fellow for the project and registered with the University of Southampton (UoS) for a Doctor of Medicine to be completed based on this work. In March 2020, as a result of the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, work slowed as I was re-deployed to the wards for several months.

I successfully submitted and passed my first progression review in May 2021 and shortly afterwards suspended my candidature whilst I was on maternity leave with my second daughter Miri. I returned to clinical training in April 2022 and have continued my research alongside this. I completed clinical training and obtained my Certificate of Completion of Training (CCT) in Gastroenterology and General Internal Medicine in June this year. In September this year, I started my consultant job at the Royal Hampshire County Hospital in Winchester having had a three month break in between jobs which gave me dedicated time to bring my thesis together.

Admittedly, my progress has waxed and waned during my candidature as I have balanced my research deadlines with clinical work and family life. Despite this I have completed all the required milestones and progression reviews and have submitted my final thesis as planned at the end of my candidature with no extensions to this deadline other than for maternity leave. The timeline below outlines my progress whilst conducting this Doctor of Medicine (Figure 1).

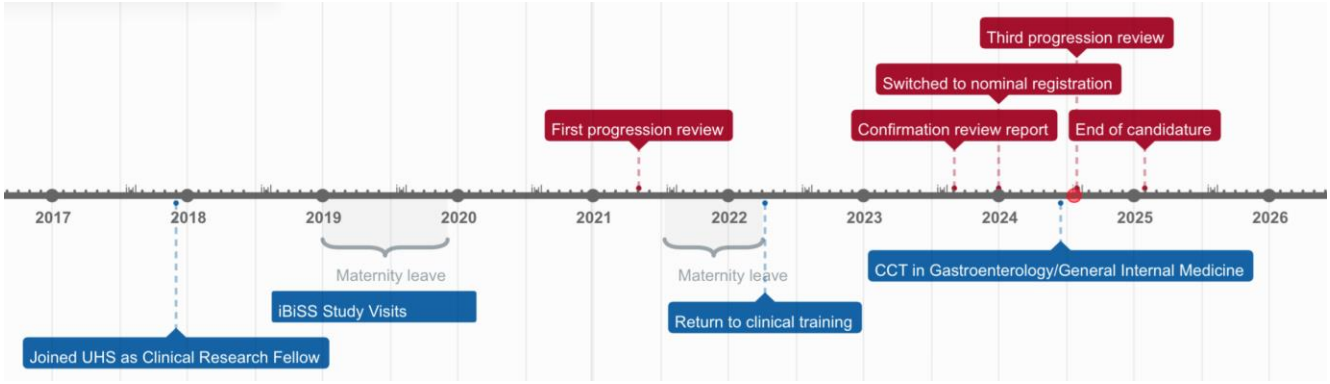


Figure 1: Thesis timeline

Chapter 2 Literature review

2.1 Infliximab

IFX is a chimeric, human-murine monoclonal antibody (mAb) against the pro-inflammatory cytokine TNF-alpha and is a highly effective treatment for IBD. IFX was the first anti-TNF to be approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 1998 and 1999 respectively(55, 56). The introduction of these targeted biological therapies has significantly improved the outcomes of patients with IBD as well as other immune-mediated inflammatory disorders (IMID). However, these biological medicines were under patents which were expensive(57). This was a barrier to all patients who might benefit from these treatments having access to them. The expiry of the patents on these drugs has allowed the development of biosimilar molecules(58, 59). Remicade, marketed by Janssen Biotech, is the trade name of originator infliximab and came off its patent in February 2015 in Europe and September 2018 in the US(60). Originator adalimumab was marketed by AbbVie as Humira and came off patent in Europe in October 2018(61).

2.2 Biosimilars

Biosimilars are biological medicines which were developed to be highly similar to the active substance of another biological product, also known as the reference or originator medicine, at a lower cost. However, due to the nature and complexity of how biologics are manufactured, they are impossible to replicate exactly. Unlike generic small molecule medications such as paracetamol or aspirin, biological drugs are derived from living cells or organisms using recombinant DNA technology and are relatively large, complex proteins. These engineered living cells make numerous copies of the therapeutic protein with the same primary amino acid sequence. However, very small changes can occur to these amino acids during manufacture through a process known as post-translational modification (PTM).

PTMs can change the functional diversity of the molecule by adding proteins, cleaving regulatory subunits or degrading entire proteins. These include, but are not limited to phosphorylation, glycosylation, methylation, acetylation and proteolysis. The resulting molecule is therefore slightly different to the reference. The aim therefore in development of these products is to demonstrate *high similarity* in terms of structure, biological activity, efficacy, safety and their immunogenicity profile under a defined regulatory pathway.

The FDA and EMA have developed a specific biosimilar regulatory pathway which has assessed >50 biosimilar products since 2006(62, 63). This process, which includes >200 separate assays, demonstrates that the performance and characteristics of a biosimilar product lie within certain strict parameters. The process ensures comprehensive physicochemical and biological characterisation of the molecule and ensures the biosimilar drug has no clinically meaningful difference when compared to the reference molecule. An important part of this regulatory pathway to be noted is that it compares the biosimilar product with the originator only and not with other biosimilars.

CT-P13, manufactured by Celltrion, was the first of the four biosimilars of IFX approved by the EMA in 2013. It was approved for use in the same indications as originator IFX, CD and UC. SB2, manufactured by Samsung Bioepis, was the second biosimilar of IFX approved by the EMA. SB2 is a chimeric human-murine monoclonal IgG1 antibody. Preclinical studies showed that SB2 was comparable in terms of structural, physicochemical and biological properties to reference IFX although it was acknowledged there were a number of clinically non-significant differences between the molecules(64, 65). These included differences in the primary structure, higher-order structure, glycosylation, aggregation, fragmentation, charge heterogeneity, Fab-related biological activity and Fc-related biological activity. These are summarised below in

Table 2 adapted from the original paper by Hong et al (2017).

Category	Attribute	Assessment
Primary structure	Molecular weight Amino acid sequence Terminal sequence Methionine oxidation Deamidation C-terminal and N-terminal variants Disulfide linkage mapping	Similar to reference product
Higher-order structure	Protein secondary and tertiary structure	Similar to reference product
Glycosylation	N-linked glycosylation site determination N-glycan identification and profile analysis	Minor differences observed but not clinically meaningful
Aggregation	Soluble aggregates	Similar to reference product
Fragmentation	Low molecular weight	Similar to reference product
Charge heterogeneity	Acidic variants Basic variants	Minor differences observed but not clinically meaningful
Fab-related biological activity	TNF-alpha neutralisation and binding activity	Similar to reference product
Fc-related biological activity	Multiple Fc-related binding	Similar to reference product

Table 2: Comparison of SB2 to originator IFX in terms of structural, physicochemical and biological properties. Adapted from Hong et al (2017).

Choe et al (2017) conducted a randomised, double-blind, multinational phase III trial in adult patients with moderate to severe rheumatoid arthritis despite MTX therapy. The primary efficacy endpoint was the proportion of patient who achieved at least a 20% reduction in the American College of Rheumatology (ACR) scores (a scale to measure changes in rheumatoid arthritis symptoms) after 30 weeks of treatment. SB2 and reference IFX demonstrated equivalent efficacy(66). Further work also showed that safety and tolerability of SB2 were consistent with reference IFX(67-69). The EMA Committee for Medicinal Products for Human Use reviewed SB2 and concluded that it was comparable in terms of quality, safety and effectiveness to the originator IFX Remicade and it was therefore given marketing authorisation in 2016(66-70).

The availability of these biosimilar products has led to increasing drug acquisition cost competition. In the United Kingdom, the NHS list price for Remicade is £419.62 per 100mg vial. The price for a 100mg vial of Remsima is £377.66 and Flixabi is £377.00. This has raised the possibility of patients being asked to transition from one biosimilar product to another. Interchangeability, as described by the EMA, refers to the possibility of exchanging one medicine for another with the expectation that it will have the same clinical effect(63). This can either be by '*switching'* which is a prescriber decision or by '*substitution'* which is at pharmacy level and is independent of the prescriber. The EMA does not make recommendations on the interchangeability of biosimilars. This decision is left at individual member state level due to different national health systems and budgets. They only compare the originator with the biosimilar in question and do not compare with other biosimilar molecules.

At the inception of this study, the bulk of the literature on CT-P13 and SB2 compared these biosimilars of IFX to the *originator molecule* (Figure 2). The body of research pertaining to this type of switching is vast and a systematic review of the data is beyond the scope of this thesis. The original trials looking at originator to biosimilar switching were conducted in patients with ankylosing spondylitis and rheumatoid arthritis (with an inadequate response to MTX) being switched to CT-P13. These two trials, the PLANETAS and PLANETRA studies, concluded that CT-P13 demonstrated equivalent efficacy to originator IFX at week 30. The pharmacokinetic profile and immunogenicity were also comparable. In addition, the biosimilar was well tolerated and safe(71, 72). Since then multiple peer-reviewed studies have been published looking at originator to biosimilar (both CT-P13 and SB2) switching in a wide range of IMID. These have provided an abundance of good quality data which has given clinicians the confidence to switch their patients. They are also further supported in their clinical practice by the official position statements released, based on the evidence, by

bodies such as the European Crohn's and Colitis Organisation (ECCO) and the BSG(49, 73). In contrast, there were far fewer studies on biosimilar to biosimilar switching and certainly no policy documents from the main governing bodies.

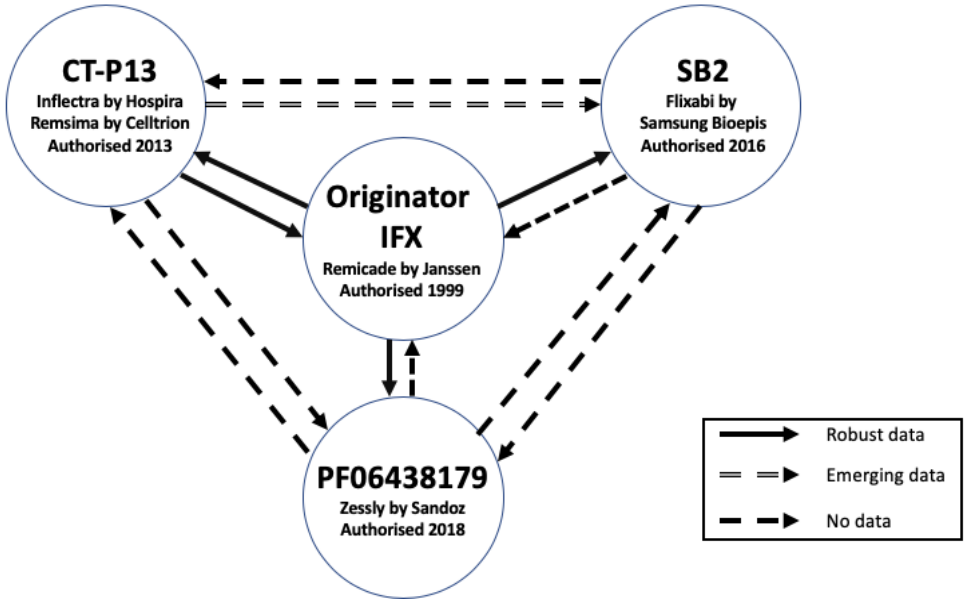


Figure 2: European Medicines Agency approved biosimilars of infliximab and level of evidence to support their use at the inception of iBiSS in 2018

In this chapter I will first review the current evidence base for this type of switch and then provide an overview of the research problem and the rationale for this project. The second part of this literature review will look at the available literature on the experiences of adult patients with IBD, as well as other IMID, having their biologic medication switched.

2.3 Biosimilar to biosimilar infliximab switching

I used the PICO-S framework as below to frame my research question to facilitate the first part of this literature search(74). This framework is primarily used for quantitative research.

Patient/population	Adults with IBD or other IMID
Intervention	On infliximab
Comparison	Biosimilar (CT-P13) versus biosimilar (SB2)

Outcome	Ascertain if they are equivalent in terms of clinical outcomes
Study design	Randomised controlled trials, observational studies

Research question: Is there a difference in clinical outcomes for adult patients with immune mediated inflammatory disorders who are switched from one biosimilar of infliximab (CT-P13) to another (SB2)?

This literature review was performed using the Pubmed, Medline and Embase databases. The search was conducted in two parts – for IBD related studies and non-IBD related ones. The key search terms used for the studies related to IBD were (inflammatory bowel disease* OR Crohn's OR ulcerative colitis OR IBD) AND (infliximab OR CT-P13 OR SB2) AND (biosimilar*) AND (switch*). The Medical Subject Heading (MeSH) terms were used for all databases and all MeSH terms were exploded. Studies were excluded if there was no clear evidence of a switching process from one biosimilar of IFX to another biosimilar in the methodology. The initial search identified 20 studies in IBD. This search is illustrated in the PRISMA flowchart below (Figure 3)(75). Of those, ten were excluded on review with the reasons shown in Table 3.

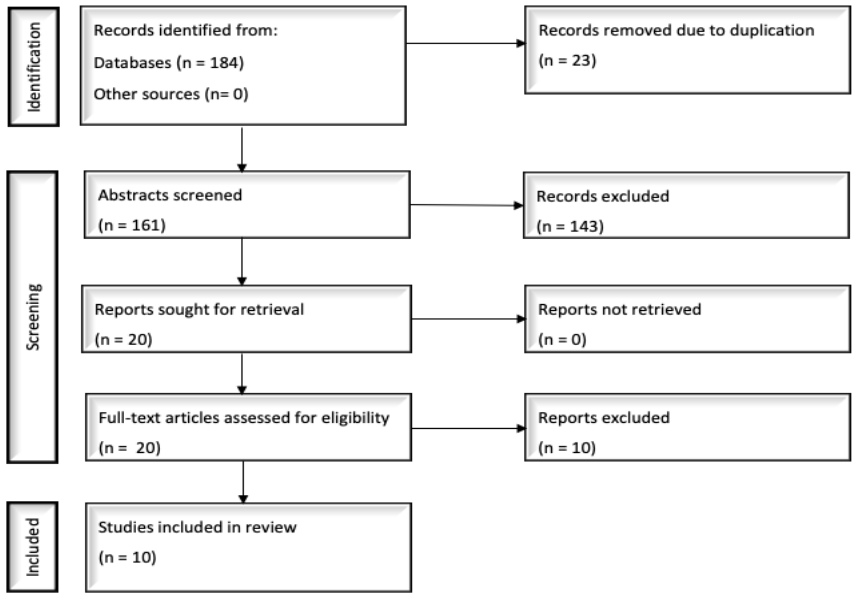


Figure 3: PRISMA flowchart – Biosimilar to biosimilar infliximab switching in IBD

Authors	Year	Reason for exclusion
Schulze-Koops et al	2017	Review article
Danese et al	2017	Review article
Moots et al	2017	No evidence of biosimilar to biosimilar switch
Gargallo et al	2017	Review article
Azevedo et al	2017	No evidence of biosimilar to biosimilar switch
Fiorino et al	2018	No evidence of biosimilar to biosimilar switch
Katsanos et al	2018	Letter in response to Fiorino et al article
Milassin et al	2019	No evidence of biosimilar to biosimilar switch
Queiroz et al	2020	No evidence of biosimilar to biosimilar switch
Gisondi et al	2020	Not IBD. Included in review of non-IBD studies

Table 3: Articles excluded from analysis with reasons for exclusion - Biosimilar to biosimilar infliximab switching in IBD.

2.3.1 Biosimilar to biosimilar infliximab switching – in IBD

The studies included in this review are shown in

Table 4 below. As mentioned, the initial concept for this study was developed in 2018 at which point there was *no* data on biosimilar to biosimilar infliximab switching. To demonstrate this clearly the studies have been presented in chronological order using a narrative approach to describe the studies and assess their strengths and weaknesses. I used the Critical Appraisal Skills Programme (CASP) checklist to assess the studies which are presented in Appendix A.

Authors	Year	Study design	Population	Intervention	Outcome measures	Summary
Macaluso et al	2020	Prospective Observational	IBD n=276	Originator IFX to CTP13 to SB2 (double switch)	Safety Effectiveness	Safety and effectiveness of SB2 was overall in line with originator IFX and CT-P13.
Pagnini et al	2020	Case report	IBD n=1	CTP13 to SB2 (single switch)	Not applicable	Caution advised in switching between biosimilars especially in IBD patients with comorbidities.
Lauret et al	2020	Prospective Observational	IBD n=265	Originator IFX to CTP13 +/- SB2 (single and double switch)	Immunogenicity	Overall, immunogenicity is not favoured. However, the consequences of immunogenicity are not negligible with risk of allergic reactions and treatment discontinuation.
Lovero et al	2021	Retrospective Observational	IBD n=36	CTP13 to SB2 (single switch)	Disease activity Safety Loss of response	Switching between CT-P13 and SB2 seems to be safe and effective either in patients with a single switch or multiple switches between IFX compounds.
Trystram et al	2021	Prospective Observational	IBD n=158	Originator IFX to CTP13 to SB2 (double switch)	Effectiveness Safety Pharmacokinetics	No major clinical or biological changes observed after the switch. Multiple switches did not promote immunogenicity.
Mazza et al	2021	Retrospective	IBD n=52	Originator IFX to CTP13 to SB2 (double switch)	Safety Efficacy	Double switching is safe and effective in patients with IBD.
Luber et al	2021	Prospective	IBD n=186	CTP13 to SB2 (single switch)	Disease activity Safety IFX trough levels	Switching from one biosimilar of IFX to another had no adverse impact on trough levels or disease activity whether switching for the first or second time.
Tursi et al	2021	Retrospective	IBD n=380	CTP13 to SB2 (single switch)	Safety Effectiveness	IFX biosimilars CT-P13 and SB2 are safe and effective in managing IBD.
Hanzel et al	2022	Prospective Cohort	IBD n=176	Originator IFX to CTP13 +/- SB2 (single and double switch)	Clinical remission Safety	Multiple successive switches from originator IFX to biosimilars are safe and effective, particularly if patients are in remission at the time of the switch.
Dispasquale et al	2022	Retrospective Observational	IBD (paediatric) n=87	Originator IFX to CTP13 +/- SB2 (single and double switch)	Clinical remission Adverse events Treatment persistence	Biosimilar IFX is efficacious in children with IBD with high treatment persistence and low incidence of non-serious adverse events.

Table 4: Summary of study characteristics of articles included in review - Biosimilar to biosimilar infliximab switching in IBD.

The first group to report on switching between CT-P13 and SB2 were Macaluso et al in the SPOSIB SB2 Sicilian Cohort study in February 2020(76). This was a multi-center, prospective, observational study involving 276 patients with IBD. Participants were divided in to five groups based on their previous IFX and anti-TNF exposure. Of note, group D (n=43) was a cohort switched from CT-P13 to SB2 and group E (n=24) was a cohort switched multiple times (from originator to CT-P13 and then to SB2). The primary endpoint of this study was the assessment of safety and the secondary endpoint was an evaluation of effectiveness. There were 11 serious adverse events (SAE) in 11 participants in group D and 4 SAE in 4 patients in group E. The highest incidence of SAE was noted in those naïve to IFX but exposed to another anti-TNF previously (group B). Importantly, participants in groups D and E (who were all IFX experienced) had low disease activity scores at baseline which suggested the timing of these swaps was at a point when their IBD was either in clinical remission or of low activity. The authors concluded that in those who were switched to SB2 treatment persistence was overall high. One of the main criticisms of this study, in particular related to biosimilar to biosimilar switching, is the small patient numbers. Furthermore, there was no data on endoscopic markers nor biomarkers such as FC of disease activity at any timepoints in the study. And finally, there is no data on IFX trough levels or anti-drug antibody (ADA) concentrations in this cohort to assess the risk of immunogenicity which remains one of the biggest concerns with switching between biosimilars.

Pagnini et al (2020) presented a case report of a 29-year-old patient with Crohn's disease and plaque psoriasis. The patient was started on CT-P13 due to extensive active ileal disease and was in complete remission after induction. He had a non-medical switch to SB2 after nine months of maintenance treatment which resulted in a severe flare of his plaque psoriasis which has previously been very well controlled. This occurred just a few days after his first dose of SB2 and completely resolved on switching back to CT-P13. The authors

concluded that caution must be advised in switching between biosimilars especially in those patients with co-existing comorbidities(77). This is discussed further in section 2.3.2 in the results of the paper by Gisondi et al who describe the implications of biosimilar to biosimilar switching in a cohort of patients with chronic plaque psoriasis(78).

In 2020, further work on immunogenicity was conducted by Lauret et al(79). They looked at two cohorts of patients with various chronic IMID – those on maintenance treatment with originator IFX and subsequently switched to CT-P13 (n=265) followed by SB2 (n=140) and those initiated on CT-P13 (n=44) who were then switched to SB2 (n=29). Twenty of 235 anti-drug antibody (ADA) free patients at baseline developed antibodies in cohort 1 (10 on CT-P13, 6 on SB2, 4 whilst back on originator) and 11 patients developed antibodies in cohort 2, within the three-year follow-up period. A meta-analysis of 16 studies (including these findings) showed a pooled incidence of immunogenicity of 4.7% after switching from originator to biosimilar and 21.1% for anti-TNF naïve patients being initiated on a biosimilar (8.5% and 25% retrospectively in the Lauret et al study findings). The conclusion from this study was that there was no predisposition to immunogenicity from multiple switches to biosimilars of IFX. However, again the major limitation of this study was the small numbers in the second cohort.

In 2021 further studies were reported focusing more on the clinical outcomes of switching from CT-P13 to SB2. Lovero et al conducted a retrospective analysis of 36 IBD patients switched from CT-P13 to SB2(80). The cohort included a proportion of patients who had experience of a previous switch from originator IFX as well (n=12). The primary objective was assessing safety and effectiveness after switching to SB2. The secondary objectives were assessing the rate of loss of response (LOR) and defining factors that predict the development of adverse events (AE) or LOR based on involvement in a single or double switch. Only two AE were reported during the entire study period with 181 infusions of SB2

being administered. Clinical remission was maintained in 69.4% of the cohort (n=25) based on disease activity scores and CRP levels. A clinical LOR was seen in 11 patients after the switch. Four of these patients were dose-optimised and the remainder were all switched to vedolizumab based on clinician decisions. One of the major limitations of this study is the lack of robust immunogenicity data in terms of IFX trough levels and ADA concentrations to substantiate the cause of LOR. The other weaknesses are the small sample size and the retrospective nature of data collection.

The next study reporting on biosimilar IFX switching was by Trystram et al. This French study reported the clinical outcomes and patient perspectives after single and double switching in stable, steroid-free IBD patients in clinical remission(81). This was a multi-centre, prospective study lasting 54 weeks and involving 158 patients on CT-P13 who were switched to SB2. The participants were further grouped based on previous exposure to originator IFX (double-switch group, n=115) or not (single-switch group, n=43). The main objectives were to assess effectiveness, safety, pharmacokinetics and the patient experience after double switching. A novel aspect of this study was evaluating the patients' perspectives by collecting survey data at baseline and 6-12 months post switch. These included the Beliefs about Medicines Questionnaire, the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) questionnaire and a non-validated questionnaire about biosimilars, generics and their delivery developed by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA)(82-84). The FACIT-F questionnaire is a 40-item measure to assess self-reported fatigue and the impact it has on daily activities and function.

There were no reported changes in disease activity scores, fatigue scores or biological activity in this study. Mean trough levels and ADA did not change either after switching from CT-P13 to SB2. These were taken at baseline (prior to the first dose of SB2) and 6-12 months after treatment. There was one fatal AE in this cohort (myocardial infarction with no

known history of ischaemic heart disease). Otherwise, AE were reported in 39.9% (n=66) of the cohort which was in keeping with current known evidence on IFX. The investigators concluded there were no major clinical or biological changes observed after the switch. There was also no appreciable difference in patients' beliefs from double switching. This study also concluded that switching to multiple biosimilars did not promote immunogenicity. Overall this study had many strengths providing good quality evidence which started to address the gap in knowledge on biosimilar to biosimilar switching. The main weakness was the lack of endoscopic assessment and FC monitoring throughout the duration of the study which would have provided objective markers of disease activity before and after the switch to SB2.

In June 2021, Mazza et al published their data from the Safety and clinical efficacy of the double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases (SCESICS) study(85). Fifty-two patients who had previously switched from originator IFX to CT-P13 went on to be switched to SB2. They concluded that double switching was safe and effective. However, this study too was limited by the small size of the cohort, the lack of biochemical markers of disease activity and the lack of data on immunogenicity.

Luber et al conducted a prospective observational study on 186 patients with IBD who were switched from CT-P13 to SB2 and followed up for one year. This included a cohort of patients who had been switched from the originator to CT-P13 prior to enrolling in the study. They assessed disease activity, biochemical markers and drug trough levels. They concluded that switching had no significant impact on disease activity or drug trough levels whether you were switching for the first or second time(86). Later in 2021, Tursi et al published a retrospective analysis of 380 patients with IBD who were switched from CT-P13

to SB2. They found no difference in terms of reaching and maintaining remission between the two biosimilars and concluded that the two biosimilars were effective and safe(87).

Hanzel et al conducted a prospective, multi-centre cohort study looking at three groups of adult patients with IBD – double switched patients from originator to CT-P13 and then SB2 (group 1, n=69) and single switched patients from CT-P13 to SB2 (group 2, n=80) and originator to CT-P13 (group 3, n=27)(88). The primary outcome was clinical remission based on the physician's assessment 12 months post switch. Secondary end-points for remission included CRP <5mg/L and faecal calprotectin <250ug/g. IFX drug levels and antibodies were measured at the discretion of the treating physician. 76.9%, 65.7% and 76.9% of patients in groups 1, 2 and 3 respectively were in clinical remission at one year. There was no significant difference in CRP and FC measurements at this time point. Treatment persistence was 85.0%, 87.0% and 70.1% for groups 1, 2 and 3 respectively at 12 months. There was nothing unexpected in terms of safety and immunogenicity in all of the groups. The study concluded that multiple switches are safe and effective and this is particularly true if patients are in remission at the time of the switch. This study adds valuable information to the evidence base on biosimilar to biosimilar switching. However, it did not have any evaluation of the patient experience.

The only study done on biosimilars in the paediatric IBD population was by Dispasquale et al in 2022. This was a multicentre, observational, retrospective study conducted in Sicily on 87 paediatric patients with IBD. The outcome measures included clinical remission, treatment persistence and safety. They reached similar conclusions to the studies in adult patients and concluded that biosimilar IFX was safe and effective. This study did not specifically evaluate a switch to biosimilar IFX but followed a cohort of children who were established on biosimilar IFX for a period of 52 weeks.

2.3.2 Biosimilar to biosimilar infliximab switching – in all IMID

The initial search was expanded by removing the terms restricting studies to IBD which enabled studies related to other IMIDs to also be included. With the search expanded to include all IMID a total of 28 studies were found (Figure 4).

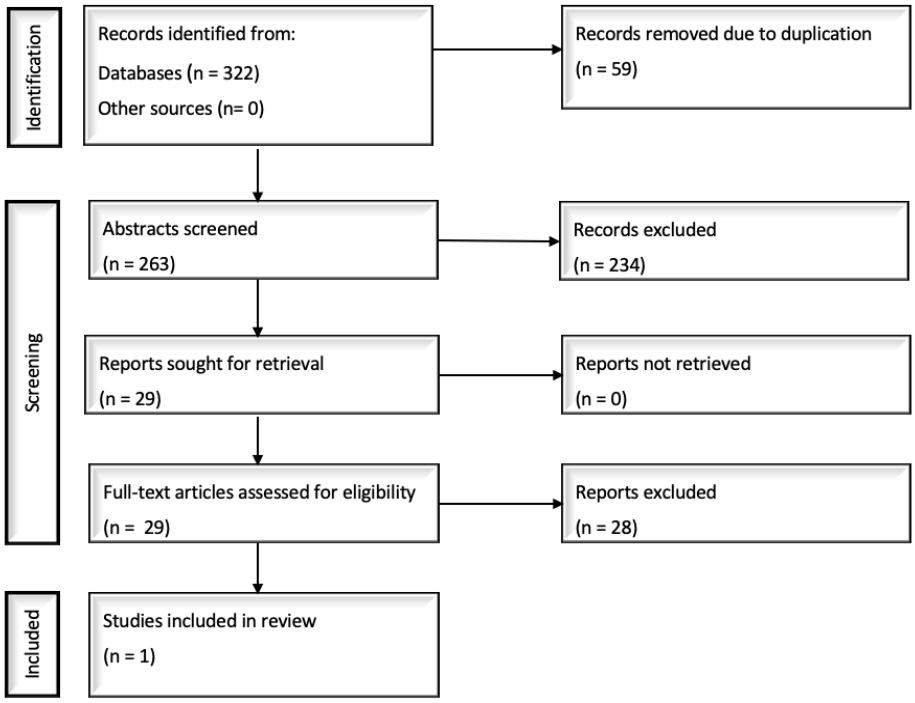


Figure 4: PRISMA flowchart – Biosimilar to biosimilar infliximab switching in all IMID

Twenty of those have already been discussed in the previous section. Seven were excluded (see

Authors	Year	Reason for exclusion
Jacobs et al	2016	Systematic review – no switch data between biosimilars. Only originator to biosimilar switching.
Jacobs et al	2016	Further systematic review – no switch data between biosimilars. Only originator to biosimilar switching.
Bellinvia et al	2017	Review article of SB2
Mahajan et al	2018	Review article
Strand et al	2020	No evidence of biosimilar to biosimilar switch
Neveu et al	2020	No evidence of biosimilar to biosimilar switch
Lee et al	2021	Systematic review – no switch data between biosimilars. Only

		originator to biosimilar switching.

Table 5). This left only one further study involving a biosimilar to biosimilar switch which is reviewed here (Table 6).

Authors	Year	Reason for exclusion
Jacobs et al	2016	Systematic review – no switch data between biosimilars. Only originator to biosimilar switching.
Jacobs et al	2016	Further systematic review – no switch data between biosimilars. Only originator to biosimilar switching.
Bellinvia et al	2017	Review article of SB2
Mahajan et al	2018	Review article
Strand et al	2020	No evidence of biosimilar to biosimilar switch
Neveu et al	2020	No evidence of biosimilar to biosimilar switch
Lee et al	2021	Systematic review – no switch data between biosimilars. Only originator to biosimilar switching.

Table 5: Articles excluded from analysis with reasons for exclusion - Biosimilar to biosimilar infliximab switching in all IMID.

Authors	Year	Study design	Population	Intervention	Outcome measures	Summary
Gisondi et al	2020	Prospective Observational	Psoriasis n=96	CTP13 to SB2 (single switch)	Disease activity Safety	No change in disease activity. However, 10% patient withdrawal rate due to loss of response or reactions.

Table 6: Summary of study characteristics of articles included in review - Biosimilar to biosimilar infliximab switching in all IMID.

Ninety-six patients with chronic plaque psoriasis were followed in this prospective observational study in Italy. The primary outcome measure was clinical effectiveness measured by changes in the Psoriasis Area and Severity Index (PASI) at baseline and 2, 4 and 6 months after. The main headline from this study was the 10% withdrawal rate of SB2 due to either loss of response or drug reactions.

2.3.3 Conclusion

At the time of submitting my first progression review in May 2021 the data on biosimilar to biosimilar switching was very limited. Over the last three years the pool of evidence has expanded as reviewed above. However, this is still in stark contrast to the abundance of evidence available on originator to biosimilar IFX switching in all chronic IMID. As mentioned, for IBD alone there is clear evidence to support switching to biosimilar IFX and this is supported by robust statements from major governing bodies(49, 73). The confidence in this type of switching is also reflected in the changes in attitude of physicians which have evolved since the inception of biosimilars. In 2013, ECCO conducted a survey amongst IBD specialists to evaluate their awareness of biosimilars and their readiness to use them. The two key concerns were regarding extrapolation of the evidence across indications and interchangeability. It was also noted that there was still a significant proportion of physicians who did not fully understand the concept(89). This survey was repeated in 2016 and revealed a complete reversal in attitudes towards the use of biosimilars. The results showed that physicians were better informed and educated on biosimilars and were much more confident in their use. This dramatic change was attributed to increased knowledge from postgraduate education and published evidence from clinical practice(90).

Overall, the studies reviewed here suggest that switching from CT-P13 to SB2 is safe with no major clinical concerns. However, as discussed each of these studies has their limitations

and it is clear that more data is needed to fill this gap and provide clinicians with the information they need to make these decisions confidently based on robust evidence.

2.4 The patient experience of switching to biosimilars

The other major area of concern in the biosimilar switching landscape is the patient's understanding of these molecules and their experience of switching medication. Shared decision making between patients and health care professionals has long been believed to be the best approach to determining an optimal IBD treatment plan (91-94). The EFCCA conducted an online survey of 1181 patients between November 2014 and October 2015 to explore their perspectives of biosimilars. The most common concerns were safety and efficacy in 47% and 40.3% of respondents respectively. It was evident that a significant proportion of patients were unfamiliar with the concept of biosimilars, even those who were on a biologic at the time. This suggested that biosimilars had not been discussed as a future option. The survey also highlighted the impact of the physician-patient relationship and the importance of patient involvement in developing a management plan that is acceptable to both parties and adhered to(84).The next part of this literature review looks at the available literature on the experiences of adult patients who are treated with biologic medication who have their medication switched to a biosimilar.

For this part of the literature review I used the SPIDER framework to develop the research question as below(95). This framework is used to formulate questions that explore experiences and perspectives and is used more in qualitative research and hence the reason for its use in this part of the literature review.

Sample	Adults treated with biologic medication
Phenomenon of **I**nterest	Switching to a biosimilars
Design	Interviews, surveys

Evaluation	Patient experience, perspectives of biosimilars and having biologic medication switched
Research type	Qualitative, mixed methods

Research question: What are the experiences of adult patients who are treated with a biological medicine having their medication switched to a biosimilar?

This literature review was performed using the Pubmed, Medline and Embase databases. Based on the above SPIDER framework a search was conducted with the MeSH terms (patient*) AND (experience*) AND (biosimilar*) to identify any studies that used qualitative interviewing techniques to gather data. The results of the search are shown below in Figure 5.

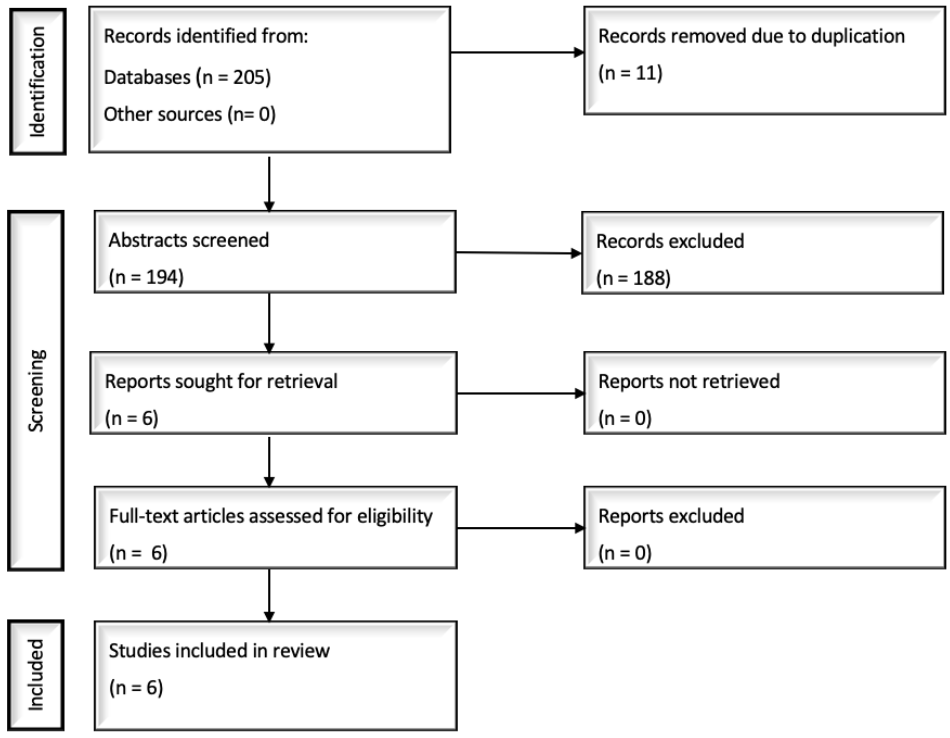


Figure 5: PRISMA flowchart – Patient experience of biosimilar switching.

Of the 194 abstracts screened, 188 were excluded as they did not explore the patient experience of having their biologic medication switched to a biosimilar. Six studies have

been included in this review and are discussed below. Only one study used qualitative data to describe the patient experience and was published in 2022. The studies have again been presented in chronological order to highlight the lack of data in this area when this study was first conceived (

Table 7).

Authors	Year	Population	Study design	Aim	Intervention	Summary
Vlijmen et al	2017	Patients switched to biosimilar growth hormone n=79	Questionnaire data	To survey patient experiences on switching from originator to biosimilar growth hormone	Novel questionnaire developed by study team	Overall, satisfied with switch and minimal side effects observed. Extensive counselling before switching was worthwhile.
Chau et al	2019	Rheumatological conditions n=52	Questionnaire data	To describe patient perspectives of switching from originator to biosimilar	Novel questionnaire developed by study team	Overall patients were satisfied with switching. Some concerns raised regarding safety and efficacy. Shared decision making can enhance successful biosimilar uptake.
Teeple et al	2019	Autoimmune conditions n=1696	Online survey	To evaluate attitudes on non-medical switching to biosimilars in patients with autoimmune conditions	Novel questionnaire developed by study team	Significant concerns about effectiveness and side effects raised.
Petitdidier et al	2019	IBD n=113	Questionnaire data	To assess patients' perspectives in a prospective manner after switching from originator to biosimilar	-Beliefs about medicine questionnaire -FACIT-F - IBD disability index	No difference observed in patients' perspectives after switching to biosimilar IFX
Gasteiger et al	2020	Rheumatological conditions n=196	Questionnaire data	To examine which demographic and psychological characteristics are associated with patients' safety perceptions and concerns about switching to biosimilars	-Brief illness perception questionnaire -Beliefs about medicine questionnaire -Perceived Sensitivity to Medicines Scale	More concerns about switching were associated with being female, illness beliefs, high perceived sensitivity to medicines, information seeking behavior and preference for originators.
Young et al	2022	IBD n=35	Semi-structured	To explore the patient experience of	Semi-structured interview guide designed by study	Overall patients felt comfortable with future transitions to biosimilars of adalimumab. Injection

			interviews	biosimilar adalimumab transition	team	experience was an important component to patient satisfaction.

Table 7: Summary of study characteristics of articles included in review – Patient experience of biosimilar switching.

The first study that described patient experience was in 2017 in a group of 79 patients who were switched from originator to biosimilar growth hormone. This study used a questionnaire designed by the study team to explore the difficulties experienced, the level of patient education, the effectiveness of the biosimilar, the side effect profile and the experience of the injecting device itself. Overall the patients rated the process of transition a 7.8 (out of 10) and were satisfied with the biosimilar. They also concluded that pre-switching counselling was highly valued(96).

Chau et al (2019) conducted a survey in 52 patients with rheumatological diseases to describe the patients' perspectives of switching from originator IFX to a biosimilar. Their results showed that overall 80% of patients were either satisfied or very satisfied with disease control on the biosimilar. However, there were major concerns about a lack of knowledge on the biosimilar (38%), developing side effects (35%) and lack of efficacy with loss of disease control (35%). They similarly reported that patient involvement with the decision making process could help to lessen those concerns and increase compliance(97). Further to this study, in 2019 Teeple et al conducted a large online survey in 1696 patients with autoimmune conditions to evaluate attitudes towards non-medical switching of biosimilars(98). This included patients with rheumatoid arthritis, IBD, psoriasis or psoriatic arthritis who were on a biological medication. They reported multiple concerns with switching including; concerns that the biosimilar would not treat their disease as well (85%), concerns about switching when they were stable on the originator (85%) and concerns about developing side effects (83%).

Petitdidier et al (2019) conducted a survey on 113 patients with IBD to investigate their perspectives after switching from originator IFX to a biosimilar. They concluded that although there were some concerns, mainly related to developing side effects and/or the loss of

disease control, there were no differences observed in the patients' perspectives post switching(99). Gasteiger et al (2020) conducted a slightly different study using a questionnaire to establish which demographic and psychological characteristics can be associated with patients' safety perceptions and concerns about switching to biosimilars. They used three validated questionnaires – the Brief Illness Perception questionnaire, Beliefs About Medicine questionnaire and the Perceived Sensitivity to Medicines questionnaire – to collect their data. They concluded that being female, illness beliefs, high perceived sensitivity to medicines, information seeking behavior and a preference for originators were associated with higher concerns about switching to biosimilars(100).

These studies were all solely based on questionnaire data using closed questions. There was no opportunity to collect qualitative data using open questioning which is arguably imperative to assess a patient experience. In a more recent study, Young et al (2022) conducted semi-structured interviews on 35 patients with CD who were transitioned from one biosimilar of adalimumab to another(101). They used open questions to gather qualitative data and then thematic analysis to present their findings. This study was also conducted at UHS with a protocol that was similar to ours but involved switching between biosimilars of adalimumab (where this study explored biosimilars of IFX). They identified five themes from their analysis; low level of knowledge related to biosimilars ahead of the switch despite being on one, an understanding of the motivation to switch being linked to financial implications and reducing drug expenditure, concerns about loss of disease control and the risk of side effects, trust in healthcare teams being crucial to acceptance of the transition and ultimately good experiences of the transition process with consistent efficacy and good tolerability.

There are instances where switching between biosimilars may not be considered beneficial. The nocebo effect is one of the main ones and is described in more detail in the next

section. Other challenges include the risk of immunogenicity and side effects associated with multiple switches and/or reverse switching between biosimilars. In these circumstances there is an increased risk of losing response, developing side effects or failing to regain response(102). Other situations where caution should be advised is in vulnerable groups such as the paediatric population, pregnant women or the elderly who can be more susceptible to poor outcomes(103).

2.4.1 Nocebo effect

The 'nocebo effect' has been identified as both a significant clinical challenge as well as an under recognised entity in the era of biosimilars(104). It has been shown to impact the number of adverse events experienced by a patient as well as a resultant perceived loss of efficacy(105-107). It is defined as a negative placebo effect in which a patient develops adverse side effects or symptoms that can occur with a drug or other therapy just because they believe they may occur. These effects are unrelated to the specific pharmacological action of the drug(108). Gaps in patients' understanding of biosimilars may trigger feelings of uncertainty and ungrounded negative attitudes towards the treatment which may then impact adherence and outcomes. There is a fine balance between providing patients with enough information to make an informed decision whilst minimising nocebo-related risks. In this study we also discuss and explore the presence of a nocebo effect to understand its impact on our cohort. This is described in more detail and discussed at length later in this thesis.

2.5 Conclusion

The main aim of this study was to evaluate the clinical outcomes of switching a cohort of IBD patients from one biosimilar of IFX to another in a real-world setting in terms of objective clinical markers, disease activity scores, patient reported outcome measures, safety and immunogenicity. By conducting semi-structured qualitative interviews with our patients, we

also aimed to explore the patient experience in more depth and identify the key factors that influence their decision making and adherence. Overall, the aim was to address all aspects of a managed switching programme in order to provide comprehensive data to support clinicians in their decision making about swapping from CT-P13 to SB2 in IBD. To my knowledge and based on this literature review, this is the first time that all these elements of a managed biosimilar switching programme have been incorporated in to one study.

Ethics, Approvals & Funding

Ethical approval for this research study was granted by the South-Central Hampshire B Research Ethics Committee (REC reference 18/SC/0254) and the Health Research Authority (HRA) in July 2018.

Local sponsor approval was granted by University Hospital Southampton under the reference MED1526.

The study is also registered on the European Union Clinical Trials Register with the EudraCT reference number 2018-001546-33.

This was an investigator-initiated study financially supported by Biogen Idec Limited. Biogen Idec Limited are the manufacturers of several biosimilars – Benepali™ (etanercept), BYOOVIZ™ (ranibizuman-nuna), Flixabi™ (infliximab), Imraldi™ (adalimumab) and TOFIDENCE™ (tocilizumab-bavi).

Written informed consent was obtained from all participants prior to any study activity.

Chapter 3 Methodology

Research methodology is the process of discussing and explaining the type of research that was conducted, how the data were collected and analysed, the tools used to conduct the research and the reasons for choosing those methods. It aims to answer the what, why and how of the research. There are three main types of methodology: quantitative, qualitative and mixed methods. Quantitative data is precise and uses numerical data collected from large groups of participants. Qualitative data is non-numerical and aims to capture human experience or behaviour by gathering data from interviews, observation or focus groups. Qualitative research generally presents data as words rather than numbers in order to discover reasons for observed patterns(109). Simply put, mixed methods research involves researchers collecting and analysing both quantitative and qualitative data within a single study(110). The aim of this type of research is to use the positives from both types of methodology in order to analyse data from different viewpoints and thus explore research questions in greater depth.

3.1 Mixed methods design

There are different ways in which mixed methods research can be conducted. Halcomb and Hickman (2015) describe four different types of mixed methods designs: *explanatory sequential, exploratory sequential, parallel and nested*(111). There are four characteristics which define each of these designs:

1. *How do the quantitative and qualitative data sets interact?*
2. *What sequence will the data be collected in?*
3. *What priority is given to each data set?*
4. *How do the two data sets integrate?*

Table 8 below is adapted from their work to summarise the four different types.

Explanatory sequential	Quantitative data collected and analysed first followed by collection and analysis of qualitative data. Quantitative data takes priority. Explanation of quantitative data is helped by qualitative data.
Exploratory sequential	Qualitative data collected and analysed first followed by quantitative data Qualitative data takes priority. Qualitative data informs the quantitative data collection and verifies it.
Parallel	Quantitative and qualitative data collected and analysed in parallel. Both data sets take equal priority. Different types of data obtained to answer a single research question.
Nested	Main design is either quantitative or qualitative dominant with an embedded study to answer a complementary question. One data set or the other takes priority. Different data obtained to answer a complementary research question.

Table 8: Summary of the different types of mixed methods designs. Adapted from Halcomb and Hickman (2015).

The procedures adopted for 'mixing' the data sets are important. Zhang and Creswell (2013) describe three methods: *integration* (qualitative and quantitative data collected separately and integrated at the interpretation stage), *connection* (one set of data builds upon the findings from the first data set) or *embedding* (the analysis of one data set is embedded within the other)(112).

I decided the best way to investigate the clinical outcomes of switching adult patients with IBD from one biosimilar of IFX to another was therefore to use mixed methods with a nested study design. Having identified my research question, which looked not only at clinical outcomes but also at the patient experience, I was clear that a mixed methods approach would be best. Quantitative measures would enable me to clearly show the outcome in terms of objective clinical and biochemical disease activity markers. However, this alone would not tell the whole story and so qualitative measures were incorporated to enrich this

data by allowing participants to have a voice and share their experiences in more depth. Ultimately, quantitative data was used for the main design of the research project with a nested qualitative project using thematic analysis embedded in to the study to explore a complementary part of the study which was the patient experience.

3.2 Study design

This was a prospective study set up at University Hospital Southampton NHS Foundation Trust following a single cohort of adult patients with IBD as they were transitioned from CT-P13 to SB2. The original concept was developed by Dr Fraser Cummings (Chief investigator) with an initial draft protocol outlining the proposed study design. The study was sponsored by University Hospital Southampton NHS Foundation Trust and funded by Biogen Idec. An external Contract Research Organisation (CRO) PHARMExcel managed the study in terms of regulatory approval, study management, data management and monitoring.

My role in this study was lead clinical research fellow. I was involved in further development of the initial draft protocol until it was finalised and liaised with the CRO to develop all the study procedures and materials. My role also included preparing the documents for local approval from University Hospital Southampton as well as the South-Central Hampshire B REC and the HRA. I attended the REC meeting alongside the CI to present our study for consideration of approval.

There were to be five study visits, as outlined below (Figure 6). IFX is usually given in six or eight weekly intervals and so the study was to run over a 54-56 week period depending on which infusion regime (six or eight weekly) the subjects were on.

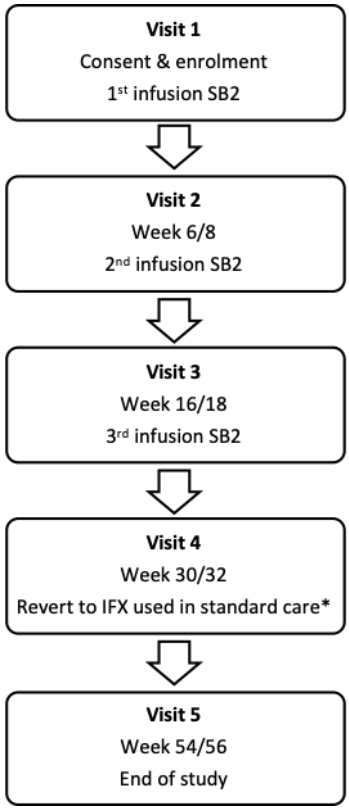


Figure 6: Visit schedule for iBiSS

*** Infliximab biosimilar used in standard of care at the time of visit 4 was SB2 and so participants continued on the same biosimilar**

Patients were provided with a letter of invitation with brief information about the study ahead of recruitment (Appendix B). We included any patient 18 years or older with CD or UC who had been treated with at least one dose of CT-P13 and who we anticipated would continue on treatment for at least the following three months. All participants who were recruited had to be able to provide written consent themselves. Exclusion criteria for this study included anyone who was pregnant or lactating at time of enrolment, anyone on a dosing regimen other than six or eight weekly or on doses higher than 5mg/kg and those with a diagnosis of IBD-unclassified (Table 9). All patients who fulfilled the inclusion criteria were sent information about the study in the post ahead of their next appointment to allow ample time to consider the study (Appendix C). This was a 12-page detailed patient information sheet (PIS) which was divided in to two parts. The first part explained the purpose of the study and what would happen if they agreed to take part. The second part provided a more detailed account of how the study would be conducted.

Inclusion criteria • Any patient 18 years or older with Crohn's disease or ulcerative colitis • Must have had at least one dose of CT-P13 with a plan to continue for ≥3 months • Able to provide written consent themselves
Exclusion criteria • Anyone who was pregnant or lactating at time of enrolment • Anyone on a dosing regimen other than six or eight weekly • Anyone on doses higher than 5mg/kg • Anyone with a diagnosis of IBD-unclassified.

Table 9: Inclusion and exclusion criteria

The electronic booking system for the Managed Care Infusion Centre was screened on a weekly basis by our Clinical Trials Assistant (CTA) to identify potential participants to recruit. I then formally approached these individuals face-to-face at their appointment where I would explain the study and review the PIS with them which had always been provided ahead of time. The participants were given ample time to consider the study and ask any questions before deciding about participating. I conducted all initial visits and recruited all participants in to this study obtaining written consent (Appendix D) myself over a four-month period from August to December 2018. At recruitment, patients were also provided with a patient identification (ID) card with details of the study and how to contact our team during and out of hours (Appendix E). Subsequent study visits were done by any member of the clinical research team including myself, the research nurses or the CTAs.

All eligible patients at UHS were approached for this study and the aim was to maximise recruitment to this single cohort to provide the most data. The number of patients who were ineligible or declined was small. We were therefore unable to use them as a comparator group due to the small sample size (n=25). At visit 1 the participants were switched to SB2 from CT-P13. At visit 4, they were then transferred back to routine care. During the study, SB2 became the biosimilar that was used in routine care at UHS and therefore the participants all ended up continuing on SB2 as they progressed to the final visit.

Each participant had their own individual folder which contained a paper copy of the case report form (CRF). There were two separate CRFs – one for those on a six-weekly regime and one for those on an eight-weekly regime. A copy of the paper CRF for those on a six-weekly regime is shown in Appendix F and the eight-weekly regime was similar but with the altered schedule. This was filled in at each study visit and the data was then entered in to an electronic case report (eCRF) form by the study team. These folders were all stored on site in the research office.

Once the participants were recruited they were entered in to an electronic tracker which alerted our study team each time they had any contact with the hospital. Given the 'real-world' nature of this study, the tracker was crucial. It prompted us if appointments were rescheduled or cancelled, as is often the case, and therefore avoided us missing any study visits and data collection. The general procedures at each study visit are outlined in Table 10. The two tables below this show a detailed overview of the trial procedure at each visit for those on a 6 weekly infusion regime (Table 11) and an 8 weekly infusion regime (Table 12).

Visit Number	Assessments undertaken
Visit 1 (Week 0)	Written informed consent Demographics and detailed medical history including drug history Disease activity scores Patient questionnaires

	Routine laboratory tests Anti-drug antibody and drug trough levels Faecal calprotectin
Visit 2 (Week 6/8)	Brief clinical history to assess progress and any changes in drug history Discuss any adverse events Disease activity scores Patient questionnaires Routine laboratory tests
Visit 3 (Week 16/18)	Brief clinical history to assess progress and any changes in drug history Discuss any adverse events Disease activity scores Patient questionnaires Routine laboratory tests Anti-drug antibody and drug trough levels Qualitative interviews on a sub-set of the cohort
Visit 4 (Week 30/32)	Brief clinical history to assess progress and any changes in drug history Discuss any adverse events Disease activity scores Patient questionnaires Routine laboratory tests Anti-drug antibody and drug trough levels Faecal calprotectin
Visit 5 (Week 54/56)	Brief clinical history to assess progress and any changes in drug history Disease activity scores Patient questionnaires Routine laboratory tests Anti-drug antibody and drug trough levels Faecal calprotectin
Early termination	Brief clinical history to assess progress and any changes in drug history Disease activity scores Patient questionnaires Routine laboratory tests Anti-drug antibody and drug trough levels Faecal calprotectin

Table 10: Schedule for each study visit in iBiSS

Infliximab infusion	**Week 0**	**Week 6**	**Week 12**	**Week 18**	**Week 24**	**Week 30**	**Week 36, 42, 48**	**Week 54**	**Early discontinuation**
Study visit number	**1 Consent & enrolment**	**2**	**No study visit**	**3**	**No study visit**	**4**	**No study visit**	**5**	
Study information provided to patient	X								
Informed consent obtained	X								
Patient identification card provided	X								
Past medical history	X								
Active and inactive tuberculosis tests	X								
Hepatitis B & C virus and varicella tests	X								
Review of entry criteria	X								
Prior/concomitant medication history	X	X		X		X		X	X
Partial Mayo Score or modified Harvey Bradshaw Index	X	X		X		X		X	X
History and physical examination (as indicated by routine clinical care)	X	X		X		X		X	X
Health-related quality of life (IBD Control-PROM)	X	X		X		X		X	X
TSQM	X			X					
Adverse events	X	X		X		X		X	X
Routine laboratory measurements (as per routine care)	X	X		X		X		X	X
Anti-drug antibody and drug trough levels	X			X		X		X	X
Faecal calprotectin	X					X		X	X
Qualitative interviews				X					
Administer trial medication	X	X	X	X	X				

Investigational Product accountability	X	X	X	X	X				

Table 11: Schedule of assessments – 6 weekly regime

Infliximab infusion	**Week 0**	**Week 8**	**Week 16**	**Week 24**	**Week 32**	**Week 40, 48**	**Week 56**	**Early discontinuation**
Study visit number	**1 Consent & enrolment**	**2**	**3**	**No study visit**	**4**	**No study visit**	**5**	
Study information provided to patient	X							
Informed consent obtained	X							
Patient identification card provided	X							
Past medical history	X							
Active and inactive tuberculosis tests	X							
Hepatitis B & C virus and varicella tests	X							
Review of entry criteria	X							
Prior/concomitant medication history	X	X	X		X		X	X
Partial Mayo Score or modified Harvey Bradshaw Index	X	X	X		X		X	X
History and physical examination (as indicated by routine clinical care)	X	X	X		X		X	X
Health-related quality of life (IBD Control-PROM)	X	X	X		X		X	X
TSQM	X		X					
Adverse events	X	X	X		X		X	X
Routine laboratory measurements (as per routine care)	X	X	X		X		X	X

Anti-drug antibody and drug trough levels	X		X		X		X	X
Faecal calprotectin	X				X		X	X
Qualitative interviews			X					
Administer trial medication	X	X	X	X				
Investigational Product accountability	X	X	X	X				

Table 12: Schedule of assessments – 8 weekly regime

3.3 Disease activity scores

This study used the pMCS to assess disease activity in UC and the mHBI for CD which were discussed in Chapter 1 and are shown in full detail in Appendix G. Remission was defined as a mHBI <5 and a pMCS of $\leq$1. Worsening of clinical status was defined as a $\geq$3-point increase in mHBI or pMCS.

3.4 Laboratory measurements

Blood tests were done at each study visit as per routine standard of care. These samples were processed and handled by the main hospital laboratory at UHS in accordance with Trust policy. The samples collected included a full blood count, renal profile, liver profile and a C-reactive protein. At enrolment all patients' results were reviewed to ensure they had been screened for any opportunistic infections prior to their original initiation with IFX. These included tuberculosis, hepatitis B, hepatitis C, HIV and varicella zoster.

3.5 Faecal calprotectin

FC is a small calcium-binding protein of the S-100 protein family. It is released in to the intestinal lumen at sites of inflammation from activated neutrophils with higher levels indicative of active inflammation(113). It is measured in stool samples and is stable at room temperature and does not degrade. It is used widely, in both primary and secondary care, and is recommended by NICE in the differential diagnosis of IBD and irritable bowel syndrome (IBS) and to guide referral for further investigation(114). It is simple, non-invasive and less expensive - all of which make it an ideal test and surrogate marker for disease activity in IBD patients. Its use has also reduced the need for endoscopic assessment which is disliked by patients and is often not feasible in stretched healthcare systems. We monitored FC at visit 1, 4 and 5. A FC was also collected at early termination if possible.

3.6 Patient questionnaires

3.6.1 Quality of life

Health related quality of life was assessed using the IBD Control PROM questionnaire which assesses disease control from a patient's perspective (Appendix H). Achieving and maintaining disease control is one of the main goals of IBD treatment and this correlates with improved quality of life. The IBD Control PROM is a validated tool comprising 13 items and a visual analogue scale (VAS)(53). It is rapid, reliable and sensitive and can be used to measure disease control from the patient's perspective. The IBD Control 8 sub score and the IBD Control VAS score are intended to represent a summary measure of perceived disease control by the patient. The two scores show a strong positive correlation, with higher scores in both indicating better disease control. The IBD Control PROM was conducted at each study visit including end of study (or early termination).

3.6.2 Illness perception

IBD is an unpredictable illness which often results in severe symptomatology which can be disabling. This can have a negative impact on both a patient's physical and psychological wellbeing as well as their performance in their day to day life(115). Almost half of all patients with IBD report some form of psychological effect from living with this chronic and invasive condition(116). Perception of illness has been described as a patient's cognitive appraisal and personal understanding of a medical condition and its potential consequences(117). These perceptions influence multiple factors including self-management, adherence to treatment and decisions to seek healthcare(118). Patients' beliefs about their illness clearly influence their overall health and importantly their treatment outcomes. It is therefore important that we understand their perceptions to enable decisions, such as those under investigation in this study, to be undertaken well with good uptake and clear understanding.

The revised illness perception questionnaire (IPQ-R) is an 84-item questionnaire developed to provide a quantitative measurement of illness representations (patient's beliefs about their chronic disease) and has been used extensively across various different health conditions(119). We used the IPQ-R at baseline to help us understand our cohort of patients and their perceptions prior to this treatment change (Appendix I). The IPQ-R consists of three sections. The first two explore a patient's views about their illness and the last section looks at their views on the cause of their illness. The final question in the IPQ-R asks the participants to list the three most important causes of their IBD. This can be based on the suggested factors in the questionnaire or written as a free hand answer.

Identity

The first section of the IPQ-R (*identity*) lists a number of symptoms and asks the participant to state if they have experienced that symptom (yes or no) since being diagnosed with IBD and if they have, to determine if they relate that symptom to their underlying illness (yes or no). Only the second part of this question is scored where the answer 'yes' scores 1 and 'no' scores 0. The responses are summed to give an overall score.

Opinions

The second section (*opinions*) looks at the participants' personal opinion of their current illness and the personal meaning they give to their IBD. They are asked to rank 38 statements on a 5-point Likert scale from 'strongly disagree' to 'strongly agree'. The statements are grouped in to seven sub-scales: timeline (acute/chronic), consequences, personal control, treatment control, illness coherence, timeline (cyclical) and emotional representation. Items for each subscale are summed and divided by the number of items to give an overall score. Higher scores in the identity section as well as in the subscales of timeline (acute/chronic), consequences and timeline (cyclical) are thought to represent the negative attributes and consequences of illness. Conversely, high scores in the personal control, treatment control and illness coherence subscales reflect positive beliefs of illness (119).

Causes

The third section (*causes*) lists fourteen possible causes of their illness which are ranked on a 5-point Likert scale from 'strongly disagree' to 'strongly agree' and participants are to indicate how strongly they feel the cause relates to their illness. These statements are also grouped in to four subsections: psychological attributes, risk factors, immunity and accident/chance and are detailed in the table below (Table 13).

Psychological attributes	Stress or worry Mental attitude Family problems/worries Overwork Emotional state Personality
Risk factors	Hereditary Diet Poor previous medical care Behaviour Ageing Alcohol Smoking
Immunity	Germ/virus Pollution Altered immunity
Accident or chance	Chance/bad luck Accident/injury

Table 13: Subsections of causes – grouped in to psychological attributes, risk factors, immunity and accident/chance.

3.6.3 Treatment satisfaction

The treatment satisfaction questionnaire for medication (TSQM) was used to assess patients' satisfaction with their medicine and was conducted at baseline and then at week 16/18 after the switch (Appendix J). This timepoint was chosen as patients would have had sufficient experience of their new infusion (SB2), but not be too far from their previous experiences with CT-P13. The 14 items of the TSQM are scored on 2-, 5- or 7-point Likert scales and cover four domains – effectiveness, side effects, convenience and global satisfaction(120). Higher scores reflect greater perceived effectiveness, lower burden of side effects, greater convenience and greater satisfaction. The minimal clinically important

difference (MCID) was estimated as one half of the standard deviation of the baseline values(121).

3.7 Safety

All adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and documented clearly in the AE log sheet (Appendix K). AE were reported from the point of enrolment up until eight weeks after the last trial dose of SB2 (visit 4) to assess safety during the study. We recorded any AE, serious AE (SAE), AE of special interest (AESI) and suspected unexpected serious adverse reaction (SUSAR). The AESI are shown in Table 14.

Acute hypersensitivity reaction (including anaphylactic shock)
Hepatitis B reactivation
Congestive heart failure
Opportunistic infections
Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
Tuberculosis
Serum sickness (delayed hypersensitivity reactions)
Haematological reactions
SLE/lupus like syndrome
Demyelinating disorders
Melanoma and Merkel cell carcinoma
Lymphoma (excluding Hepato-splenic T-Cell Lymphoma)
Hepato-splenic T-Cell Lymphoma (HSTCL)
Hepatobiliary events
Intestinal or perianal abscess (in CD)
Serious infusion reactions during a reinduction regimen following disease flare
Sarcoidosis/sarcoid like reactions
Leukaemia
Malignancy (excluding lymphoma, HSTCL, leukaemia, melanoma, merkel cell carcinoma)
Colon carcinoma/dysplasia (in UC)
Skin cancer
Exposure during pregnancy
Use of infliximab during lactation

Table 14: List of adverse events of special interest (AESI)

Adverse events were also actively sought out if the patient tracker alerted the research team that a participant had visited the hospital outside of their scheduled visits for their infusions.

Reporting included:

- the symptoms or diagnosis of the AE
- onset
- duration
- severity
- action taken with SB2
- any medical intervention
- whether the AE was expected or not.

A causality assessment with regards to SB2 was undertaken for each AE where the relation was assessed as either *possible*, *probable* or *definite*. SAE were reported in more detail using a separate reporting form which included a follow-up report (Appendix L). All SAEs were reviewed and signed off by the CI and were then reviewed promptly by the sponsor at the time of the event.

3.8 Drug levels, immunogenicity and cytokine profiles

Blood samples were also taken to measure IFX drug trough levels and anti-drug antibody levels at visit 1 (baseline), 3, 4 and 5. Further work was then undertaken to look at cytokine profiles in our cohort. Samples were collected from the patients and stored securely in the NIHR Southampton Clinical Research Facility. I was not involved in this part of the study as analysis of these samples was undertaken at the University of Lisbon by Professor Gonçalves and his team. Details of the processes involved are in Appendix M.

3.9 Nocebo effect

I explored the presence of a nocebo effect in this study by reviewing biochemical markers of inflammation, quality of life measures and disease activity scores in those who discontinued from the study. We split this group in to two and compared these parameters in those who discontinued early due to *their own choice* versus those who discontinued due to *objective secondary loss of response*. This was based on objective evidence of disease activity (i.e. a rise in markers of inflammation and/or endoscopic evidence of disease activity). The cytokine profiles that were chosen and analysed by Professor Gonçalves and his team in Portugal were also reviewed with regards to the presence of a nocebo effect. I also reviewed the transcripts of the interview participants who discontinued early due to their own choice to assess for any specific evidence to suggest and support the presence of this effect.

3.10 Statistical analysis

The statistical analysis for the majority of the quantitative results of iBiSS was conducted by an external statistician, Justin Harvey, who was based at the University of Capetown, South Africa. The statistical analysis plan (SAP) described the methods used during the analysis for the reporting of demographic, efficacy and safety data. He designed the SAP which was then reviewed by myself and the study team at UHS before being finalised.

3.11 Patient experience

The primary aim of this nested qualitative study was to explore the experience of having biological medication switched in patients with IBD. Qualitative research has long been criticised for being researcher biased, for lacking reproducibility and generalisability(122, 123). However, rigor has been described as a way that trust and/or confidence can be established in the findings of a piece of qualitative research. Ritchie describes three central

principles to qualitative research as described below, of which rigor is one of the key components(124).

1. Research must have an explicit methodological base and conducted in a rigorous way to ensure precise design and execution.
2. There is a 'reality' to be captured to inform social policy and theories.
3. The data from small-scale qualitative studies can be used to draw conclusions based on evidence and reasoning about the 'social world'.

3.11.1 Philosophical stance

In medicine there is a strong tradition of research and evidence-based practice being centred on conventional, quantitative studies. This has indeed been my experience working mostly as a Specialist Registrar in Gastroenterology during my period of research and latterly as a Consultant. There is an integral role of qualitative research to understand social phenomena by recording experiences and collecting rich data. This was apparent in trying to answer our complementary research question which integrates the social and clinical entities. In order to conduct qualitative research, there were certain principles that had to be understood ahead of designing the study.

The first was understanding the role of the researcher themselves. It is essential to appreciate that the position and views of the researcher has a huge impact on the project(125). This is often referred to as their '*world view*'. Researchers must first fully reflect and articulate their position in relation to the research. Addressing questions such as - *Why does this interest me? What do I perceive the answer to be? What do others think of me and my expertise on this subject? What will I achieve from doing this research?* – can help to start the reflective process. Ontology is our understanding of what we call reality and what there is to know about the world(124). Epistemology is the theory of knowledge and seeks to

discover what is known and how we know it. An in-depth understanding and transparency of your own ontological and epistemological views is crucial to conducting rigorous qualitative research.

My philosophical stance on this aspect of the project came from two different perspectives. One was as a clinician with fairly extensive experience of patients with IBD and the second was as a research student with no previous experience of qualitative data and analysis. As a trainee in Gastroenterology I developed a passion for IBD quite early on and therefore have had a lot of exposure to the medical aspects of this condition. Having this experience shaped my personal views and beliefs on the research. On the other hand, as a research student, acquiring and handling qualitative data was entirely new to me. As such I had minimal preconceived thoughts or notions affecting how I approached this part of the study. Critical realism evolved from the work of English philosopher Roy Bhaskar. It is a branch of philosophy which looks at the 'real' world and the 'observable' world. It states the 'real' world cannot be truly observed as it is independent of external perception and knowledge. The 'observable' world is therefore created based on our own knowledge and perspectives. This philosophy applied to me and is the approach I used for this part of the study.

In this next section I will outline the processes involved in conducting the nested qualitative part of the research study including the deliberate planning and steps taken to ensure rigor was achieved. I have also completed the Standards for Reporting Qualitative Research (SRQR) checklist to show transparency of my reporting (**Table 15**). The SRQR consists of 21 items which are recommended as key elements that must be reported in qualitative research(126) (Appendix N).

Title and abstract		
1	Title	For journal publication: Clinical Outcomes and Patient Experience of Biosimilar to Biosimilar Infliximab Switching in Patients with Inflammatory Bowel Disease: A Prospective, Single-Centre, Phase IV Interventional Study with a Nested Qualitative Study.
2	Abstract	See Abstract
Introduction		
3	Problem formulation	See Section 2.4 The patient experience of switching to biosimilars
4	Purpose or research question	See Section 2.4 The patient experience of switching to biosimilars
Methods		
5	Qualitative approach & research paradigm	See Section 3.1 Mixed methods design
6	Research characteristics and reflexivity	See Section 3.11.1 Philosophical stance
7	Context	See Section 3.11.2 Sample and recruitment
8	Sampling strategy	See Section 3.11.2 Sample and recruitment
9	Ethical issues pertaining to human subjects	See Ethics, Approvals & Funding
10	Data collection methods	See Section 3.11.3 Data collection method
11	Data collection instruments and technologies	See Section 3.11.3 Data collection method and Appendix O
12	Units of study	See Section 5.1 Study participants
13	Data processing	See Section 3.11.3 Data collection method
14	Data analysis	See Section 3.11.4 Qualitative analysis
15	Techniques to enhance trustworthiness	See Section 3.11.3 Data collection method
Findings		
16	Synthesis and interpretation	See Chapter 5 Qualitative findings
17	Links to empirical data	See Chapter 5 Qualitative findings
Discussion		
18	Integration with prior work, implications, transferability, and contribution to the field	See Abstract, Chapter 6 Discussion and Section 6.3 Qualitative analysis
19	Limitations	Chapter 6 Discussion and Section 6.3 Qualitative analysis
Other		
20	Conflicts of interest	None declared
21	Funding	See Ethics, Approvals & Funding

Table 15: Standards for Reporting Qualitative Research checklist

3.11.2 Sample and recruitment

Purposive sampling is a well-used method in qualitative research. Creswell and Plano Clark (2011) describe it as identifying and selecting individuals or groups of individuals that are especially knowledgeable about or experienced with a phenomena of interest(127). I purposively sampled participants with the aim of including a range of patients with characteristics representative of the factors identified in the literature that were thought to affect decision making namely age, education level, severity of disease at the time of switch and experience of a previous switch(91, 128). This type of purposive sampling is known as *maximum variation* or *heterogenous* sampling(129). The aim being to identify a diverse range of cases relevant to a particular event or experience. This is important as it ensures a broad representation of perspectives and a comprehensive range of experiences of the targeted population. The participants all specifically consented to take part in qualitative interviews during the consent process and only those who agreed were approached for this part of the study. In order to identify this sample, demographic data were collected at baseline including age, sex and highest education level. This was incorporated with disease activity scores at enrolment and whether participants had experience of a switch before, to identify a range of participants to provide insight to the research question.

There are various approaches to undertaking qualitative assessments and for this study I chose to use semi-structured interviews. Other methods include focus groups, participant observation, content analysis and case studies. The reason for choosing interviews for this study was to gain a depth of insight in to their experiences and to enable the data collection to be entirely participant-centred. The pros and cons to each type of approach are shown in the table below (Table 16)(109).

	Pros	**Cons**
Interviews	Depth of insight	Time-intensive

	Flexibility Particpant-centred	Interviewer bias
Focus groups	Allows group dynamics and participants to build on each other's ideas Time-efficient Natural interactions	Dominance in discussions can skew views Sensitive topics may not be discussed in an open setting Requires a facilitator with experience
Observation	Captures experiences in real-life setting Moves beyond self-report Useful to study interactions or systems	Observer bias Behaviour may be altered due to presence of the observer Ethical issues with covert observation
Content analysis	Cost-effective Uses existing data	Dependent on material being available Relies on accurate documentation of the event or experience at the time Risk of ambiguity
Case studies	Provides a holistic view Allows multiple data sources to be utilised and incorporated	Resouce-intensive

Table 16: Strengths and weaknesses of qualitative assessments

Interviews were conducted soon after week 16/18. This was selected as a timepoint at which interviewees would have had ample experience of the new infusion but not be so far from the initial switch to be able to compare and describe their experience of the process accurately. Our aim was to continue sampling until data saturation had been reached with no new data emerging. This originates from Glaser and Strauss' (1967) grounded theory but is now widely used in various approaches in qualitative research(130). Data saturation is the point at which there is enough data to draw conclusions and new data is redundant (131, 132).

We identified three groups in our cohort to interview. The main group comprised;

- those who agreed to switch from CT-P13 to SB2

The two subgroups included;

- those who discontinued early from the trial due to their own choice and

- those who declined to take part in the switching study from the outset and chose to remain on CT-P13.

I felt it was important to include the two sub-groups as they had very different experiences to the main group and provided a very different narrative to the research question.

3.11.3 Data collection method

A topic guide was developed to outline the key issues and areas of questioning required based on the existing literature and the study team's combined clinical experience. All interviews were semi-structured and conducted by myself, either face-to-face on the hospital site or over the telephone, based on interviewee preference. Interviews were conducted at a convenient time to the participant.

The main purpose of semi-structured interviewing is to gather information systematically whilst also allowing new topics or issues to be explored as they emerge during the interview. The topic guide was created based on this premise and was used to provide a framework to the interview so that all relevant themes were covered. At the same time I was also able to be flexible to enable the conversation to flow naturally and allow the participants to expand on any points without being interrupted.

I designed the topic guide using a series of open questions which were neutral, clear and void of jargon(133). The interviews were started with a clear introduction of the process and my role in the interview. This introduction was adapted slightly based on the specific group that was being interviewed at the time. The full topic guide is available in Appendix O. The interviews were recorded using an audio-recorder and transcribed verbatim by myself. These transcripts were then read and re-read to see what emerged from the data. There are several computer programmes available to help organise qualitative data including, but not

limited to, NVivo, ATLAS.ti, MAXQDA and Quirkos(134). However, I chose to look at the data 'by hand' which was my personal preference. An inductive process as described above was then used to produce a coding framework. Once the initial codes and themes were derived I went through a process of verification with one of my supervisors. They acted as a 'second checker' and were trained in qualitative research. They performed their coding independently initially before then reviewing results together. Verification by a third-party is a process of rigor to reduce bias in the analysis. Checking can either be by the respondent (member check) or by independent peer review (inter-rater reliability) by another qualitative interviewer(122, 135, 136).

3.11.4 Qualitative analysis

Inductive versus deductive approaches

These are the two fundamental approaches to analysing qualitative data(124). An inductive approach works from the ground up with the data with no prior assumptions or theories. The idea is that the data itself will derive the structure of the analysis. In a deductive approach the researcher already has a pre-conceived theory and uses that basis to explore if the theory is supported or not.

Methods of qualitative analysis

Analysing qualitative data is not a simple or quick task. There are different approaches to analyse qualitative data. Five common approaches include: content analysis, narrative analysis, discourse analysis, grounded theory and thematic analysis(133). I have discussed four of these briefly below. Thematic analysis is discussed separately in more depth afterwards as it is the analysis that I carried out.

Content analysis: Systematically and objectively analysing data by categorising, coding and quantifying specific words, themes or concepts within a text to identify patterns and themes.

Narrative analysis: Interpretation of stories and personal narratives to understand participants feelings and behaviours and how they make sense of their experiences and communicate their perspectives.

Discourse analysis: A process that goes beyond analysing words and sentences. It tries to establish a deeper context of how language is used in social context to create meaning.

Grounded theory: Aims to develop theories and concepts grounded in data. It uses iterative data collection and analysis to develop an inductive theory from the unstructured data.

In some respects, data analysis occurs alongside data collection as the researcher is being constantly exposed to the data during the interviews(137). It is difficult to ignore and set aside and therefore becomes part of the process. This was evident in part in this study. Initially interviews were only conducted with the participants who agreed to the biosimilar switch (Group 1). It was clear after several interviews that there was a large void in our understanding of this experience as I was only being presented with one side of the experience. I was unable to gain any insight in to the participants who had a negative experience of the switch. Nor did I gather data on the experiences of those who were not inclined to switch at all. This led me to include and interview those who withdrew their consent part way, as well as those who declined to take part from the outset. By having an appreciation of the data that I was gathering initially I was able to realise this gap existed and therefore refine the study and develop new avenues of inquiry to enrich the data.

Thematic analysis

Thematic analysis is a method described by Braun and Clarke for identifying, analysing and reporting patterns within a qualitative data set(138).

There are six phases of thematic analysis:

1. *Familiarising yourself with the data and identifying items of interest*

   This process is said to be easier if data collection and transcription is done by the same researcher doing the analysis.

2. *Generating codes: finding labels that capture what is interesting about the data.*

   These codes are determined at the start but can evolve throughout the process. Codes are either *semantic* (capturing obvious or surface meanings) or *latent* (capturing an underlying meaning or assumptions that underpin the surface meaning).

3. *Generating themes: codes cluster together to build themes which have a central organising concept.*

   At this stage the researcher starts to think about the relationship between themes and can use the data collection questions to structure the analysis.

4. *Reviewing potential themes*

   It is important to not have too many themes and to be flexible and discard themes if appropriate.

   The quality of each theme needs to be assessed. Questions that can help this process include: *Is there enough meaningful data to support this theme? What are the boundaries of this theme? Is the theme too diverse or wide-ranging?*

5. *Defining and naming your themes*

   Important to use clear descriptions at this stage for the reader to have an explicit understanding of the theme.

6. *Producing the report*

   A report must be produced by using analytic commentary, data extracts and agreed themes following the above processes. The order of presenting the themes must be finalised with vivid and compelling examples to support them taken from across the

participants. Ultimately the analysis must link back to the research question and the existing literature to show how it builds on and contributes to this in the wider context.

The amount of textual data generated from transcripts is vast. This data is descriptive and needs to be analysed using a structured approach in order to provide a comprehensive description of the phenomenon being explored. Using thematic analysis, I was able to provide an in-depth understanding of the human behavior around switching medication in this cohort and the factors that govern those behaviours.

3.12 Summary

In this chapter I described the processes involved in this study and clearly explained the rationale for a mixed method design to evaluate the research questions posed. In the next chapter I will describe the quantitative results from the main body of the study.

Chapter 4 Quantitative results

4.1 Study population

A total of 158 eligible subjects were approached for the study (125 CD, 33 UC) and of these 133 consented to take part. Ninety-eight subjects completed the study and 35 discontinued. Figure 7 shows the CONSORT flow diagram through this process in more detail. This figure also shows the reasons for early termination from the study.

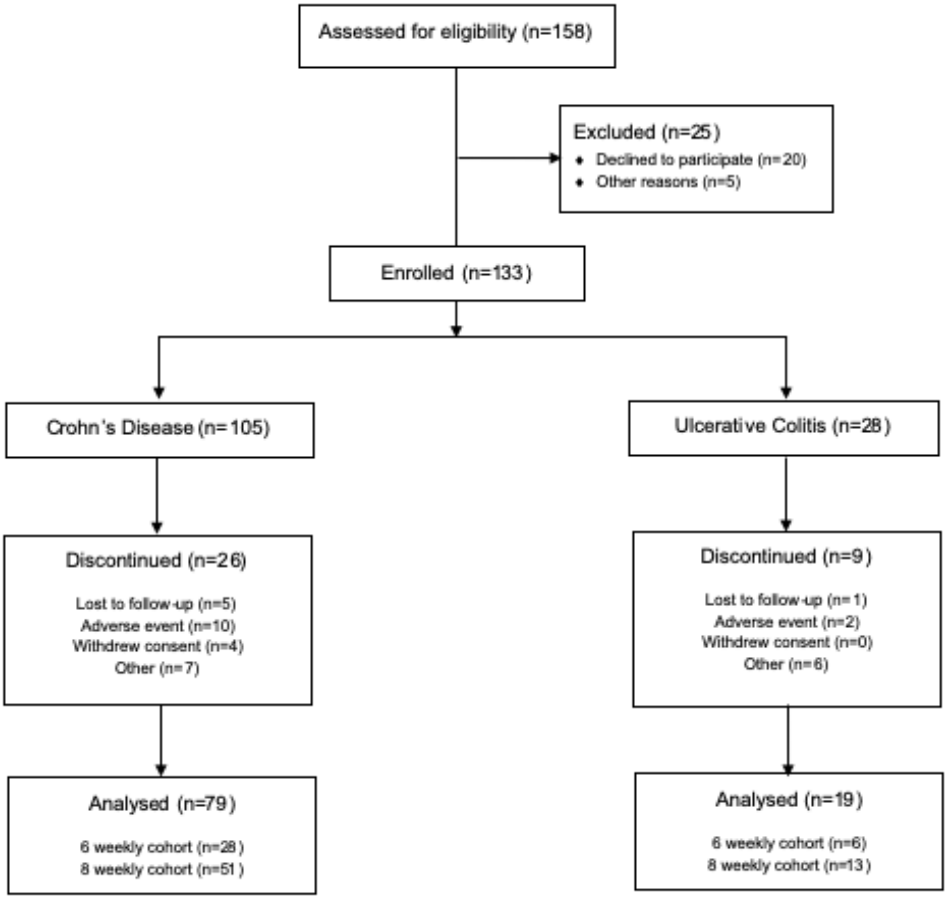


Figure 7: CONSORT diagram for iBiSS

The demographics and baseline characteristics of the cohort are shown in Table 17. Male subjects comprised 55.6% of the cohort. The median age was 39 years [range 18 – 90 years]. The median disease duration was seven years [range 0 – 38 years]. Of the 133 subjects, 105 [78.9%] had CD and 28 [21.1%] had UC. 113 subjects [84.9%] were biologic

naïve and 20 subjects [15.1%] were biologic exposed prior to starting IFX. Eighty-three [62.4%] subjects were on concomitant immunomodulator therapy at baseline.

	UC cohort	CD cohort	Complete cohort
Total number	28	105	133
Age – median [range] years	43 [19-74]	38 [18-90]	38 [18-90]
Male/Female – no [%]	16[57.1]/12[42.9]	58 [55.2]/47 [44.8]	74 [55.6]/59 [44.4]
Race – no [%] - White - Mixed - Asian or Asian background - Black or Black British - Chinese - Other	 24 [85.7] 0 [0] 1 [3.6] 3 [10.7] 0 [0] 0 [0]	 99 [94.3] 0 [0] 4 [3.8] 2 [1.9] 0 [0] 0 [0]	 123 [92.5] 0 [0] 5 [3.8] 5 [3.8] 0 [0] 0 [0]
BMI – median [range]	26.5 [19.7–40.2]	25.4 [16.6-48.4]	25.9 [16.6-48.4]
Smoking status – no [%] - Never - Current - Previous	 21 [75.0] 0 [0] 7 [25]	 52 [49.5] 22 [21.0] 31 [29.5]	 73 [54.9] 22 [16.5] 38 [28.6]
Vaping status – no [%] - Never - Current - Previous	 26 [92.9] 2 [7.1] 0 [0]	 97 [92.4] 7 [6.7] 1 [1.0]	 123 [92.5] 9 [6.8] 1 [0.8]
Duration of disease – median [range] years	3 [0-38]	8 [0-36]	7 [0-38]
Age at onset – no [%] - A1: < 16 - A2: 17-40 - A3: >40		 8 [7.6] 78 [74.3] 19 [18.1]	
Site of Crohn's disease – no [%] - L1: Ileal - L2: Colonic - L3: Ileocolonic - L4: Upper GI tract		 25 [23.8] 30 [28.6] 50 [47.6] 4 [3.8]	
Crohn's disease behaviour – no [%] - B1: Non-stricturing/non-penetrating - B2: Stricturing - B3: Penetrating - p: Perianal disease		 65 [61.9] 16 [15.2] 24 [22.9] 17 [16.2]	
Site of Ulcerative Colitis – no [%] - E1: Proctitis - E2: Left sided - E3: Extensive	 0 [0] 14 [50.0] 14 [50.0]		
Concomitant medications at baseline – no [%] - Azathioprine/Mercaptopurine - Methotrexate	 11 [39.3] 6 [21.4]	 56 [53.3] 14 [13.3]	 67 [50.4] 20 [15.0]

Previous biologic history – no [%] - Remicade - Adalimumab	 7 [25.0] 3 [10.7]	 45 [42.9] 16 [15.2]	 52 [39.1] 19 [14.3]
Disease activity at enrolment – no [%] - Remission - Mild - Moderate - Severe - Unknown	 15 [55.6] 9 [33.3] 3 [11.1] 0 [0] 1 [3.7]	 79 [76.7] 14 [13.6] 9 [8.7] 1 [1.0] 2 [2.0]	 94 [72.3] 23 [17.7] 12 [9.2] 1 [0] 3 [2.3]

Table 17: Patient demographics and clinical characteristics

4.2 Clinical outcomes

The primary outcome of the study was clinical status at week 30/32 using disease activity scores and laboratory measurements. The results are presented for the cohort as a whole except for the disease activity scores which are disease-specific and presented as such. The results from week 30/32 excluded all those who had discontinued at that point as we were unable to collect complete data after discontinuation. This is discussed further later in this chapter.

4.2.1 Disease activity

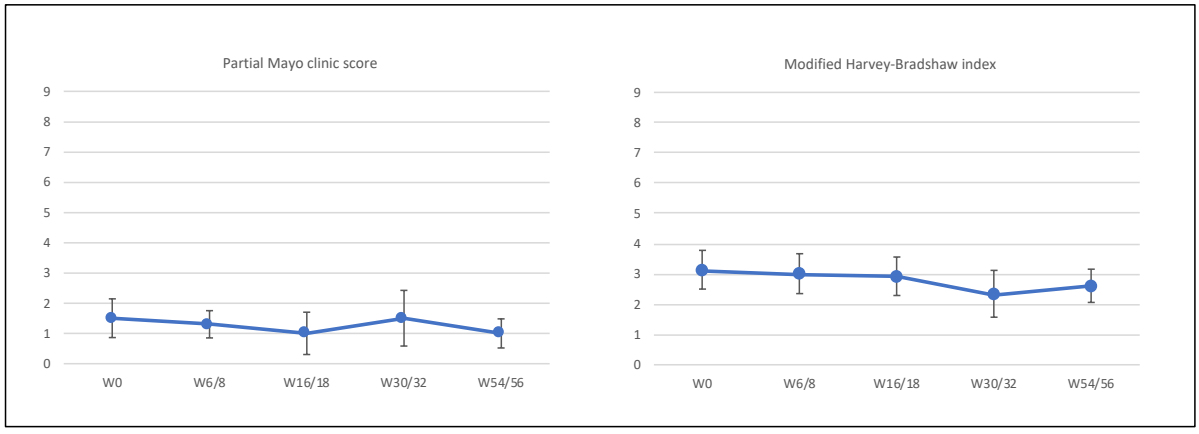


Figure 8: Disease activity scores for UC and CD cohorts with error bars representing one standard deviation from the mean.
Remission defined as mHBI <5 and pMCS of <1. Worsening of clinical status defined as >3-point increase in mHBI or pMCS.

4.2.2 Laboratory measurements

All 133 subjects had mean haemoglobin, platelet count, albumin and CRP collected at baseline and 107 subjects had samples collected at week 30/32. Overall, there was no difference in mean haemoglobin, platelet count, albumin and CRP before and after switching to SB2. This is shown in

Figure 9 along with normal ranges at UHS for the measurements shown.

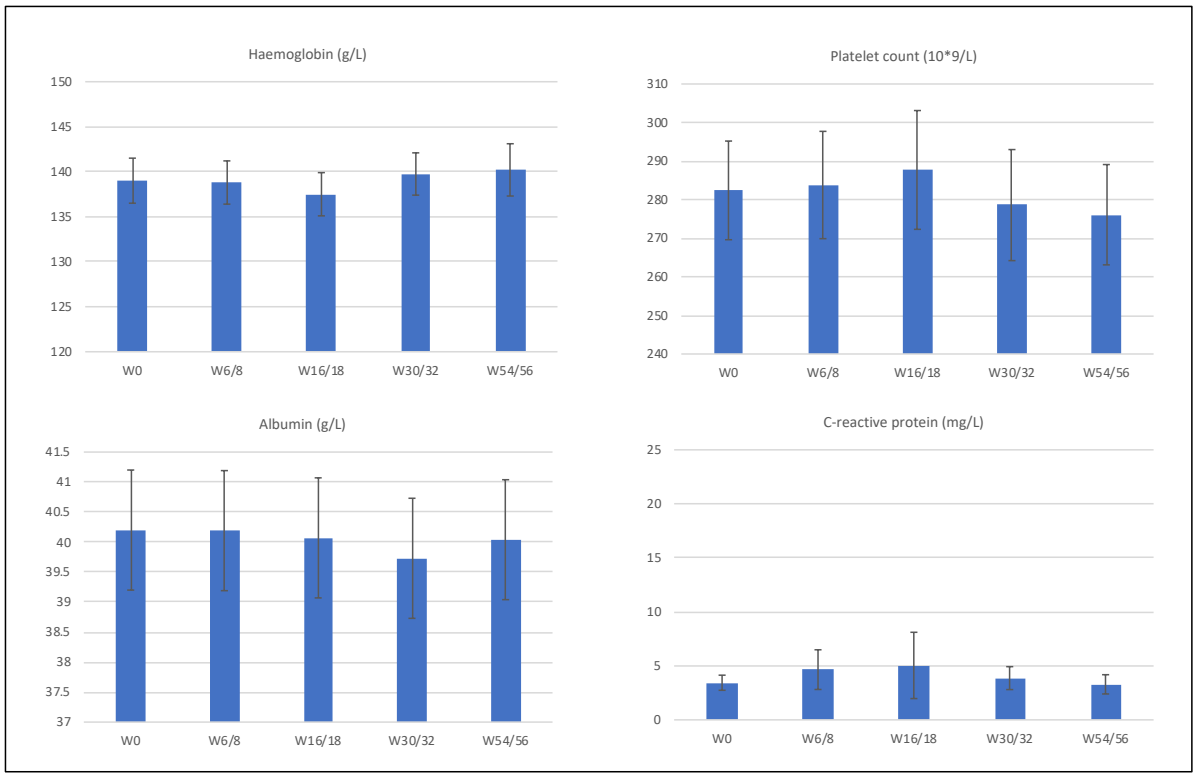


Figure 9: Laboratory results at weeks 0, 6/8, 16/18, 30/32 and 54/56 with error bars representing one standard deviation from the mean.
Reference ranges: Haemoglobin 130-170g/L (for males) 120-150g/L (for females), platelet count 150-400 10*9/L, albumin 35-50g/L, C-reactive protein 0-7.5mg/L

4.2.3 Faecal calprotectin

The mean FC results at baseline (n=119) and at week 30/32 (n=84) were 306ug/g versus 210ug/g (Figure 10). The reference range for FC at UHS is 0-50ug/g but in our participants with known IBD a value <250ug/g was considered acceptable and indicative of clinical remission.

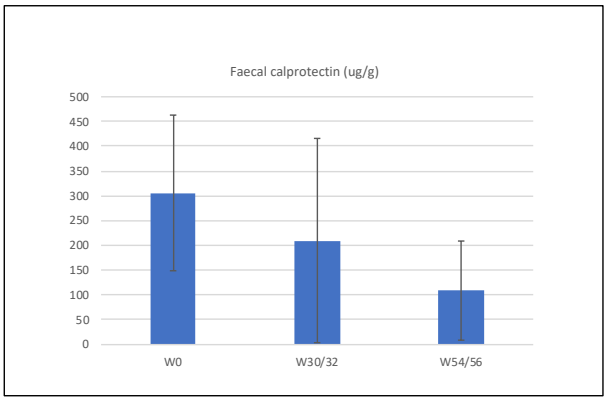


Figure 10: Faecal calprotectin results at weeks 0, 30/32 and 54/56 with error bars representing one standard deviation from the mean.

4.2.4 Patient reported outcomes

4.2.4.1 Quality of Life

Patient-reported outcomes were collected before and after the switch to SB2. The mean IBD Control 8 score was 11.75 at baseline and 13.19 at week 30/32 (p=0.005). The mean IBD Control VAS was 75.24 versus 79.59 at week 30/32 (p=0.57).

4.2.4.2 Illness Perception Questionnaire - Revised

132 out of 133 participants completed the IPQ-R at baseline.

4.2.4.2.1 Identity

Only two participants reported none of the listed symptoms since being diagnosed with IBD. The remaining 130 all reported at least one symptom with the mean reported number of symptoms being 7.6 (range 0-14, SD 3.5). The top three reported symptoms were fatigue (86.3%), abdominal pain (83.3%) and upset stomach (81.1%) with the vast majority believing these were related to their IBD (96.5%, 91.9% and 90.7% respectively). Overall, the cohort attributed a mean of 5.9 (SD 3.2) of the symptoms to IBD. Figure 11 shows these results in full detail.

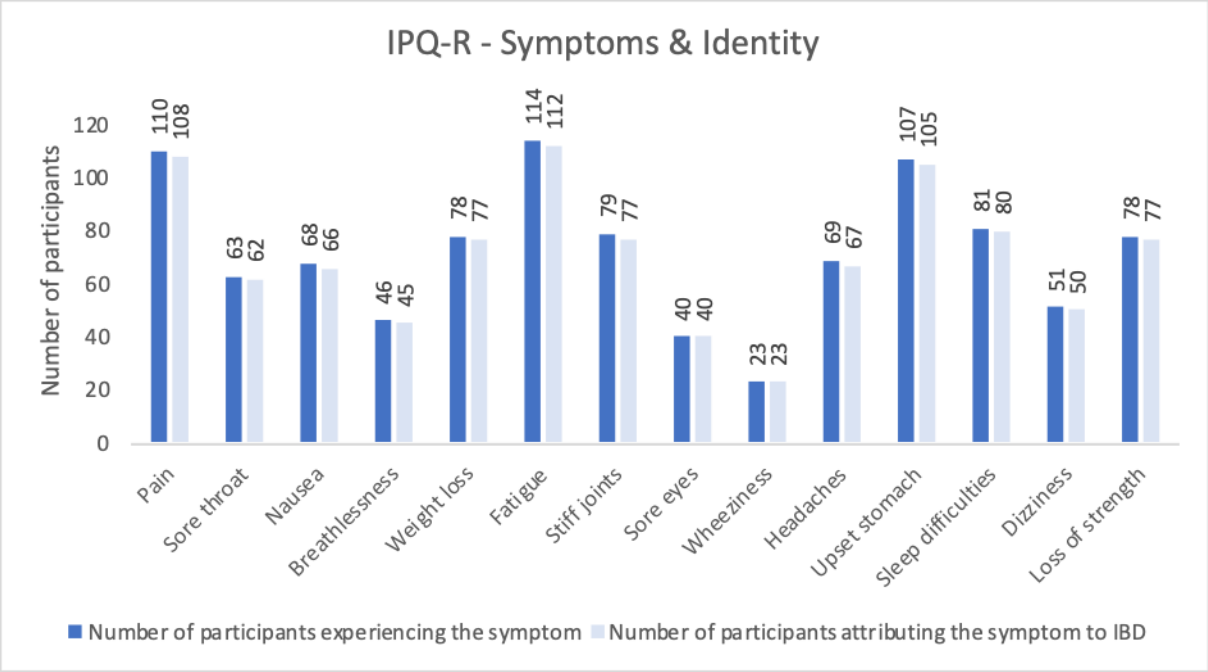


Figure 11: Illness Perception Questionnaire–Revised: Section 1 Identity.

4.2.4.2.2 Opinions

The cohort gave the highest overall score to the statements contributing to the subscale of perceiving the disease as being chronic. Although this is accurate with IBD being a long-term condition this was seen as a negative attribute. The mean scores of each subscale are shown in Figure 12.

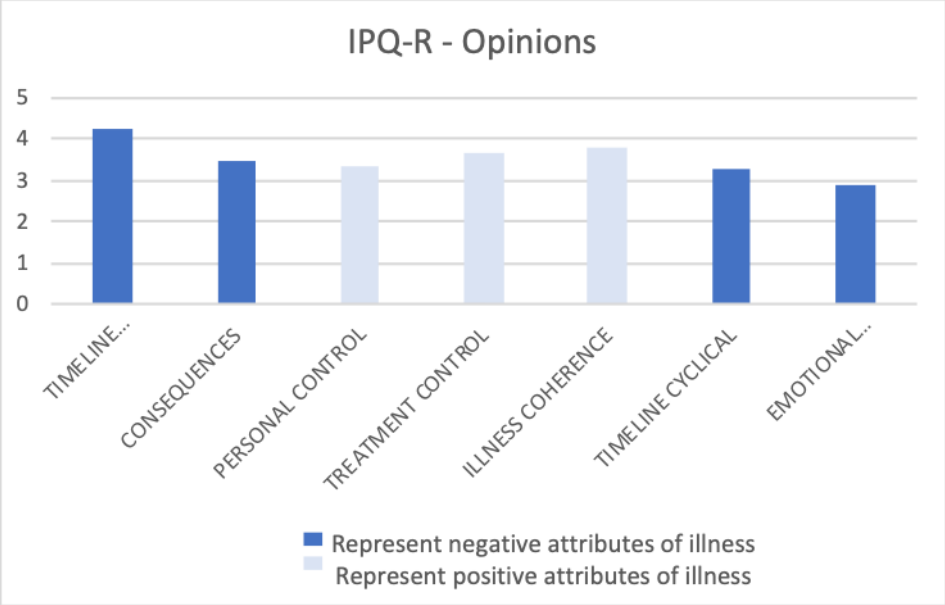


Figure 12: Illness Perception Questionnaire–Revised: Section 2 Opinions.

4.2.4.2.3 Causes

The most weight was given to stress in the list of causes of IBD followed by diet/eating habits and being hereditary. The full results are shown below in Figure 13.

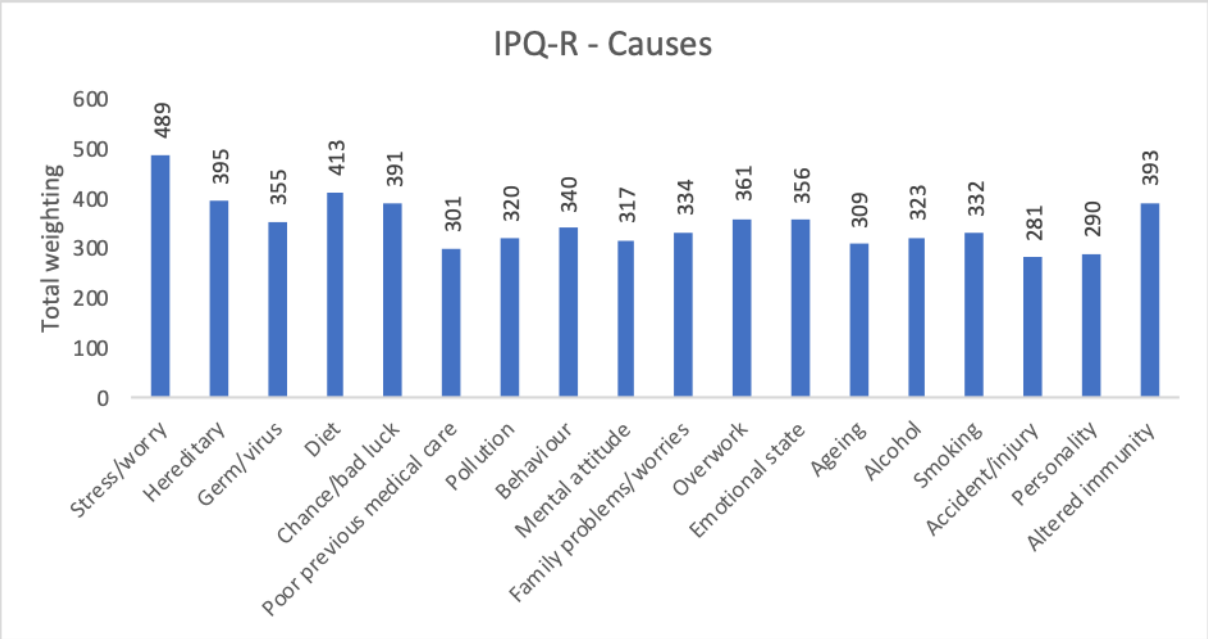


Figure 13: Illness Perception Questionnaire–Revised: Section 3 Causes.

This was closely reflected in the final question of the IPQ-R which is shown in the word cloud below (Figure 14). This is a visual representation of our cohort's views on the causes of their IBD based on the final question in the questionnaire, with the larger and bolder words being the causes most mentioned.

Figure 14: Word cloud showing all causes for IBD from final question in the IPQ-R.

4.2.4.3 Treatment Satisfaction Questionnaire for Medication

The TSQM results are shown in Figure 15. Overall, the mean scores in all four domains of the TSQM remained similar from baseline to week 16/18. These included: effectiveness 76.22 vs 79.79 (p=0.12), side effects 74.69 vs 79.80 (p=0.06), convenience 71.00 vs 74.73 (p=0.12) and global satisfaction 75.49 vs 78.13 (p=0.27) with all domains scored out of 100. The differences between the two groups was not found to be statistically significant in each domain. The MCID were estimated as 9.4 for effectiveness, 11.6 for side effects, 9.5 for consequences and 9.3 for global satisfaction. The mean change from baseline to week 16/18 was less than the MCID in all four domains, therefore suggesting there was no clinically significant difference.

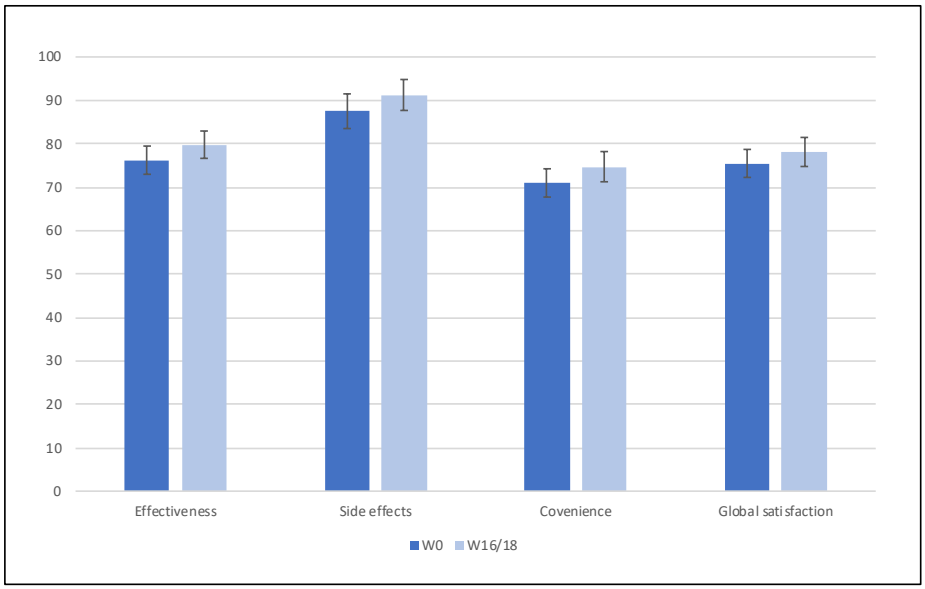


Figure 15: Mean change from baseline to week 16/18 in the four domains of the TSQM with error bars representing one standard deviation from the mean.

4.2.5 Safety

A total of 193 AE were recorded throughout the study period. With regards to causality, nine [4.7%] AE were deemed possibly and 38 [19.7%] were probably related to SB2 by the investigators. Further details are presented in Table 18. Of these, 16 were deemed to be SAE which were all reviewed in detail with the sponsor (5 possibly related and 1 probably related to SB2). There were no fatal AEs, AESIs or SUSARs. The most common AE was viral upper respiratory tract infection (9% of all AEs).

	UC cohort n (%)	CD cohort n (%)	Whole cohort n (%)
Any adverse event	27	166	193
Severity of adverse event Mild Moderate Severe	 19 [70.4] 8 [29.6] 0 [0]	 105 [63.3] 43 [25.9] 18 [10.8]	 124 [64.3] 51 [26.4] 18 [9.3]
Serious adverse events	0 [0]	16 [9.6]	16 [8.3]
Fatal adverse events	0 [0]	0 [0]	0 [0]
Adverse event leading to discontinuation of SB2	5 [18.5]	12 [7.2]	17 [8.8]
Adverse event associated with infusion reaction	2 [7.4]	0 [0]	2 [1.0]

Relationship to SB2			
Not related	4 [14.8]	31 [18.7]	35 [18.1]
Unlikely	16 [59.3]	95 [57.2]	111 [57.5]
Possibly	0 [0]	9 [5.4]	9 [4.7]
Probably	7 [26.0]	31 [18.7]	38 [19.7]

Table 18: Summary of all adverse events

4.2.6 Drug levels and immunogenicity

Figure 16 shows the analysis of pharmacokinetics (PK), anti-drug antibodies (ADA) and neutralising antibodies (NAb) along the course of the study. The analyses showed a stable concentration of IFX up to the primary end-point in those who completed the study (week 30/32). A decline in IFX concentration was noted from baseline to week 30/32 in those who terminated early compared to those who completed. Development of immunogenicity was comparable between patients that completed the study and those who terminated early. The ADA response was predominantly IgG1 followed by IgG4, IgG2 and IgG3.

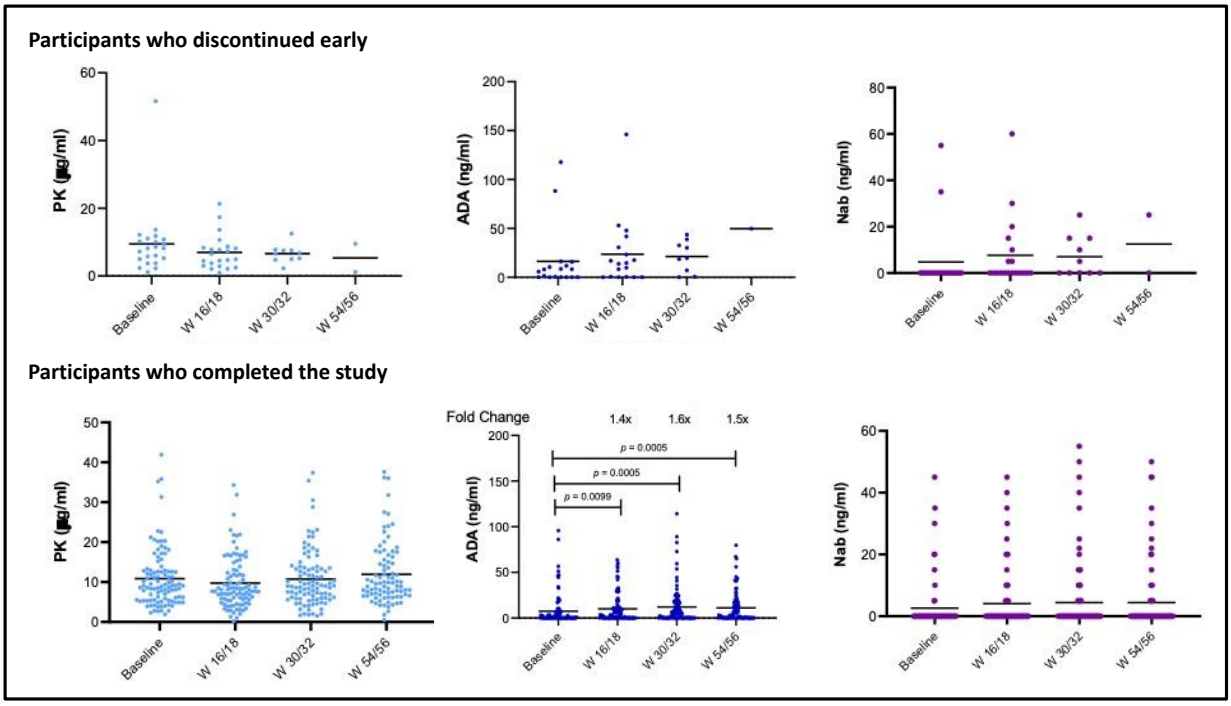


Figure 16: Drug levels and immunogenicity
Analysis of PK (light blue), ADA (dark blue) and neutralising antibodies (purple) along the course of the study

4.2.7 Nocebo effect

Thirty-five participants discontinued early from this study. Fifteen required a change to a different medication due to a loss of response (two to adalimumab, nine to ustekinumab and four to vedolizumab), six stopped treatment completely, two moved out of area, one required re-loading with SB2 due to a gap in treatment and one was lost to follow-up.

The remaining ten participants (7 CD, 3 UC) discontinued due to perceived side effects and loss of efficacy to SB2. They all asked to be switched back to CT-P13. All but one of these was before week 30/32. This sub-set of participants were of particular interest to us in terms of the nocebo effect. Unfortunately, the dataset for this sub-set is not complete as not all samples were handed in by participants. However, of the data available, objectively the mean CRP at termination was 9.4 (n=9) and the mean FC was 18.6 (n=5) which did not suggest active disease. Subjectively, IBD Control VAS changed from 73 at baseline (n=10) to 50 (n=9) at the point of discontinuation. The mHBI changed from 3.8 to 5 (n=6) suggesting subjects were still classed as being in clinical remission and the pMCS from 1 to 1.3 (n=3) which suggests a slight worsening of clinical status. Table 19 shows these results in more detail.

CD/UC	Duration in study (days)	CRP		FC		IBD Control VAS		Disease activity score	
		W0	ET	W0	ET	W0	ET	W0	ET
CD	37	2	2	1640	NA	95	50	1	3
CD	43	23	9	295	NA	75	50	4	5
CD	98	1	40	1	26	35	35	6	9
CD	119	1	15	4.5	NA	75	40	NA	3
CD	154	4	9	11	3.8	97	93	2	2
CD	155	6	5	299	11	30	10	4	8
CD	NA	1	NA	22	NA	50	NA	6	NA
UC	63	1	1	67	NA	100	95	0	0
UC	112	1	1	13	8.2	97	50	0	1
UC	138	4	3	59	44	77	32	3	3

Table 19: Data from the sub-set who discontinued due to patient choice
CD = Crohn's Disease UC = Ulcerative Colitis NA = not available W0 = Week 0 ET = early termination CRP = C-reactive protein FC = faecal calprotectin

4.2.7.1 Cytokine profiles

As discussed, serum samples were sent to Portugal for analysis of cytokine profiles by Professor Gonçalves and his team. The method is described in Appendix M. Particular interest was paid to the group of subjects who discontinued from the study. The aim was to investigate whether the concentration of pro-inflammatory cytokines was altered during the study in order to distinguish any potential differences in immune system responses. When analysed, the cytokine concentrations in patients that terminated early due to their own choice versus those who did so due to objective secondary loss of response, a statistical difference in some Th1, Th2, Th9 and Th22 cytokines was observed. Patients who discontinued due to their own choice showed lower concentration of IL-2, TNF-alpha, IL-5, IL-13 and IL-9 versus sera from the second group who maintained higher concentration of these cytokines suggesting disease activity (Figure 17). Although the number of patients included in this comparison is low, these results might indicate that these cytokines can be used to distinguish different causes for stopping treatment and hence the presence of the nocebo effect. Most of the other cytokines showed relatively consistent frequencies of detection across the two groups (Figure 18).

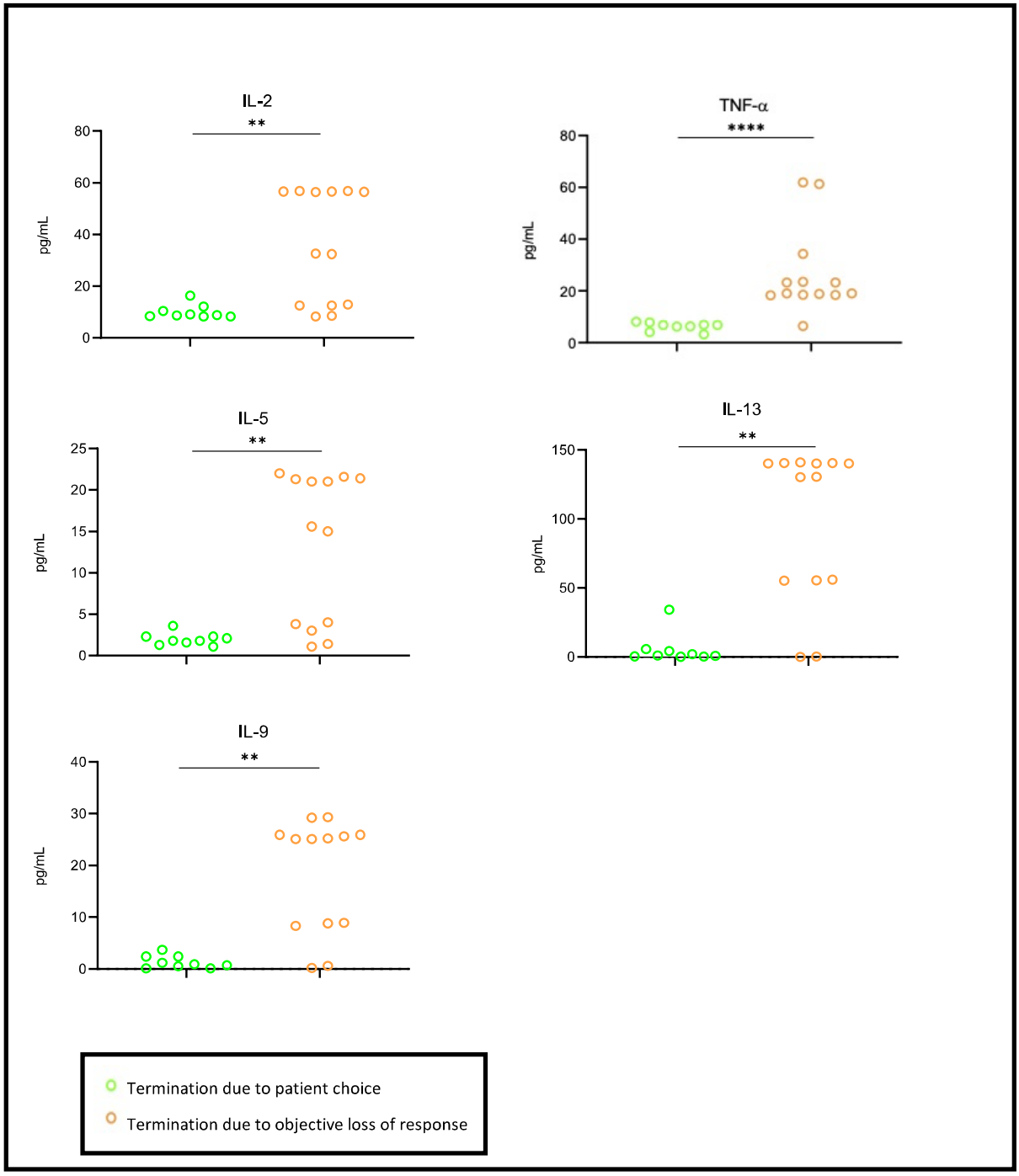


Figure 17: Cytokine profiles – IL2, TNF-alpha, IL5, IL13, IL9

Comparison between those who terminated due to patient choice (green circles) versus objective loss of response (orange circles).
*, **, ***, **** denotes a p<0.05, p<0.01, p<0.001, p<0.0001 and ns denotes not significant

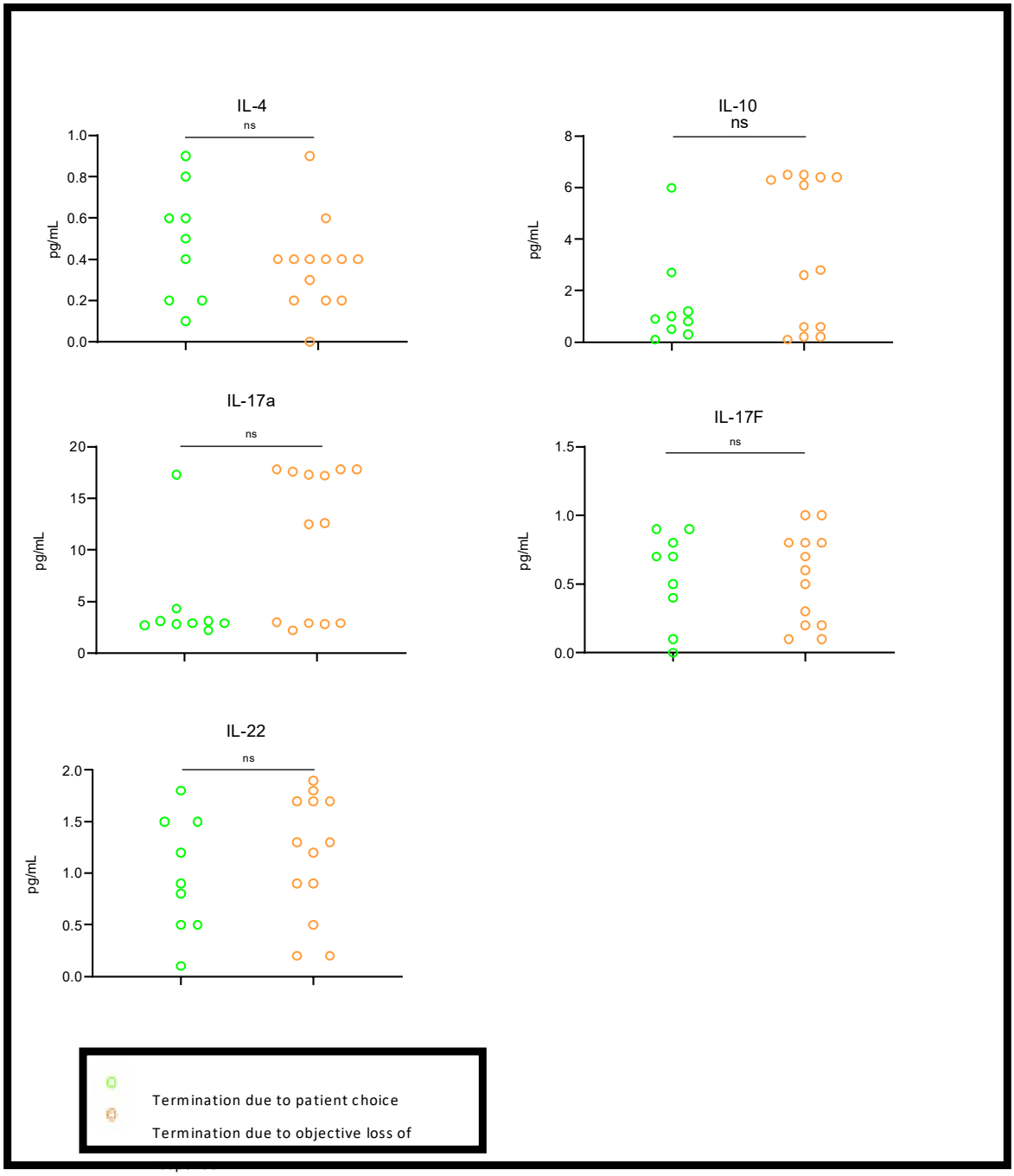


Figure 18: Cytokine profiles – IL4, IL10, IL17, IL22

Comparison between those who terminated due to patient choice (green circles) versus objective loss of response (orange circles).
*, **, ***, **** denotes a p<0.05, p<0.01, p<0.001, p<0.0001 and ns denotes not significant

Summary

In this chapter I presented the results from the main body of the study looking at the clinical outcomes of the participants in iBiSS who were switched from one biosimilar of IFX (CT-P13) to another (SB2). Overall, the results show that making this switch is effective from a clinical perspective in terms of disease activity, biochemical markers, immunogenicity and safety. Furthermore, these results show that patient satisfaction with their treatment after the switch is maintained. In Chapter 5 I will discuss the findings from the nested qualitative study exploring the patient experience of having their medication switched. Finally, in Chapter 6 I will discuss the study as a whole looking at the strengths and limitations of both the quantitative results and the qualitative findings and drawing all pertinent conclusions from this work as a whole.

Chapter 5 Qualitative findings

There were three separate groups in the qualitative study as previously discussed;

Group 1: those who agreed to take part in the switch

Group 2: those who discontinued early from the study due to their own choice

Group 3: those who declined to take part in the study from the time they were first approached.

5.1 Study participants

At the point that I started to sample participants for the interviews in December 2018, there were 85 participants already enrolled to the main iBiSS study. Of those, 70 had consented to being interviewed at enrolment. The 15 participants who had not given consent were not considered in the purposive sampling nor approached again for consent. I approached 34 participants regarding the Group 1 interviews, and of those 16 were ultimately interviewed for this cohort. Eight participants were unable to help with this part of the study when they were approached. This was mainly due to time constraints. The remaining ten participants were not required for the interviews in the end as I had reached data saturation.

All ten participants who exited the study due to their own choice were approached for a Group 2 interview. Of those only five were willing to take part and were interviewed. Finally, of the 25 IBD patients at UHS who were eligible to take part but declined to do so I was able to interview five for the Group 3 cohort. Twenty of those patients were not willing to be interviewed. I did not question them at the time as to their reasons for declining. The two subgroups (group 2 and group 3) therefore consisted of five interviewees in each.

The total number of interviews was 26 which included 21 participants with CD and 5 UC participants. Eleven of the 26 interviewees had previous experience of an originator to biosimilar switch. All the interviews lasted approximately twenty minutes. Nineteen interviews were face-to-face and seven were telephone interviews. Detailed characteristics of the sample are shown in Table 20.

ID	Age	Sex	Education level	IBD subtype	Active disease at switch	Prev switch experience
Group 1 – those who agreed to switch from CT-P13 to SB2 (n=16)						
Group 1:003	37	M	PG	CD	Yes	No
Group 1:012	40	F	UG	CD	No	Yes
Group 1:013	44	M	UG	CD	No	Yes
Group 1:014	29	M	AL	CD	No	Yes
Group 1:015	73	M	None	UC	No	No
Group 1:016	64	F	None	CD	No	No
Group 1:017	21	F	AL	UC	No	No
Group 1:018	33	F	UG	CD	No	No
Group 1:021	28	M	PG	CD	No	Yes
Group 1:030	21	F	UG	CD	No	Yes
Group 1:037	49	M	GCSE	CD	No	Yes
Group 1:051	32	M	GCSE	CD	No	No
Group 1:055	73	M	None	CD	No	No
Group 1:057	45	M	GCSE	CD	No	Yes
Group 1:071	24	F	AL	UC	Yes	No
Group 1:082	45	F	GCSE	CD	No	Yes
Group 2 – those who discontinued early from the trial due to their own choice (n=5)						
Group 2:026	23	F	AL	UC	No	Yes
Group 2:038	43	F	UG	CD	No	Yes
Group 2:039	55	M	GCSE	CD	No	Yes
Group 2:079	65	F	GCSE	CD	No	No
Group 2:105	25	M	AL	CD	No	No
Group 3 – those who declined to switch from the outset (n=5)						
Group 3:BR	21	F	-	UC	-	No
Group 3:HW	48	F	-	CD	-	No
Group 3:KS	34	M	-	CD	-	No
Group 3:SM	35	F	-	CD	-	No
Group 3:SW	69	F	-	CD	-	No

Table 20: Demographics of qualitative interviewees.
PG: Postgraduate, UG: Undergraduate, AL: Advanced Level, GCSE: General Certificate of Secondary Education

5.2 Thematic analysis

Thematic analysis, as described in chapter 3, was undertaken with the transcribed data from the interviews. Data from the three groups were initially analysed separately. However, as the analysis progressed it was apparent that the themes across the groups were similar and so have been presented together and this will be discussed in more depth in Chapter 6. The six themes identified were:

- Trust
- Clinical status at the point of switching
- Past experience of switching
- General disposition
- Information provision
- Concerns and anxieties

These are described here in narrative form with representative quotes. The code in parentheses after the quotes refers to the exact participant who made the comment. This is their group followed by their three-digit iBiSS participant ID. As group 3 participants were not formally part of the iBiSS study they are represented by their group number followed by a three-digit code in the order of their recruitment in to the qualitative study.

5.2.1 Trust in the multidisciplinary team

Trust in the IBD multidisciplinary team (MDT) was a clear theme that emerged. Participants across all three groups identified this as a significant contributing factor to a successful (or unsuccessful if lacking in trust) transition. There appeared to be widespread inherent trust in the staff with several commenting that even if they themselves did not understand the switch the clinical team would protect them.

"I trust you guys to do your job basically. It sounds quite blunt but I do. I don't want to go into reading everything about it and trying to learn everything about it. I see you guys know everything that is going on so, it wouldn't bother me. I trust you. I'm pretty sure you're not going to give me something that might poison me." (Group 1:051)

Comments covered issues such as the staff's clinical and research knowledge as well as the value of a good rapport between staff and patients that had developed over many years.

"It comes from a history of dealing with medical professional people… which I have had a good relationship with in that way throughout my life. So, I suppose that has given me the confidence to say you know best." (Group 1:015)

"My experiences here at the General have been many and have always been good. Everybody's fantastic! You all do a marvelous job." (Group 2: 039)

One of the more tangible benefits of this trust was the expectation that they would receive support if they needed it and also be able to switch back if they felt it wasn't working.

"And I think in general, we get to see doctors who then explain to us on the day what is happening and check if we have any questions and things like that.. It's just nice to have a human person come and speak to you so you know there is someone on the other side who knows what is happening and responding to any letters or emails I send." (Group 1:017)

"And having that point of contact that if you are slightly concerned or have any queries that there's someone there that you can ask." (Group 3:002)

"So no because you gave me a phone number and everything so I was able to call that and that was reassuring. And I was able to get straight through and speak to somebody. So yeah that was good." (Group 2:038)

"Not worried, no because you've answered the question…when I said to you, 'if it doesn't do it properly – cant I go back?'…then the worry is taken out." (Group 1:055)

5.2.2 Clinical status at point of switching

Another over-arching theme, with significant importance on the decision-making process to switch, was the impact the participant's disease state had at the time of switching. Being in *either* a stable *or* an active disease state was a major consideration prior to agreeing to switch or not. For some, being stable was a deterrent to switching in an attempt to maintain their much-valued stability.

"It kind of felt like I was relatively stable and I was managing the condition quite well and then changing – it kind of went back to the old adage 'if it ain't broke, don't fix it'!" (Group 1:003)

"If you've got something that works very well the question in your head is why would you change it? We've taken so long to get where we are you know? If it's working why change it?" (Group 2:039)

"I was just unsure about switching because I didn't want to rock the boat if you like. I didn't want it to go back to how it was…" (Group 3:005)

"...for once things were actually going well. After everything I've been through…I think I was a bit reticent to change anything, you know…kinda better the devil you know!" (Group 3:002)

Whereas others felt that if they were stable they would be willing and happy to try something new. This seemed to work either way and was different for individual patients.

"I was really easy going and happy about it because my Crohn's is well controlled so I felt reassured I was still staying on a very similar drug. Umm…and so I was perfectly happy." (Group 1:018)

"…I found myself flaring more in the last week or two. Not sure if it was due to the change or it was my Crohn's. I think I was on infliximab only for about 3-4 months before the trial so I didn't really find my feet properly…" (Group 1:003)

5.2.3 Past experience of switching

Unsurprisingly, a participant's past experiences of switching medication weighed heavily on their decision to participate this time, as demonstrated by those who had a bad experience in the past being more reluctant to switch despite reassurance.

"Because of the experience I had from it, it has made me more cautious and I would worry. And the problem with that is then that you've got it in your head…you start thinking and worrying you've got symptoms and you become more aware. In your mind it all becomes more psychological and you're thinking you feel like this because you've changed drugs but maybe that's not the case at all." (G2:038)

"I said I was not going on it because of my previous experiences. As soon as I saw it was about the biosimilar I was like no. That was it. I don't think so." (Group 3:004)

Conversely, those who had a good experience were reassured by this and happy to go ahead.

"All a very smooth transition. I suppose going through it before helped." (Group 1:013)

However, a few unique stories showed us that even those who had a bad experience in the past were able to make the decision to switch again with the right information and support.

"My past experience wasn't good..it was a bit upsetting at the time. But this time, there were more people around to speak to, more availability of information." (Group 1:012)

5.2.4 General disposition

Individual differences in how participants think, feel, and behave in different situations also influenced the decision and emerged as a theme. At one end of the spectrum were those who wanted to be helpful and were grateful for their treatment so far and portrayed a degree of altruism towards the research being conducted.

"I thought, 'Well, why not?' - as long as it didn't make me any worse someone could gain from it." (Group 1:016)

"For the patient - benefits health wise, that nothing is going to change but that the hospital could benefit from this and save money elsewhere." (Group 1:012)

There were other participants who described themselves as "easy-going" and "laid back" and this was their driver for participating in the study.

"I just go with the flow. I'm optimistic. I'm not a worrier in that respect." (Group 1:015)

"As I said I'm pretty laid back and it is what it is. Let's get on with it!" (Group 1:057)

At the other end were those who appreciated the rationale for making this change but did not want to change what they were familiar and comfortable with.

"I was a little bit nervous just because I always am…" (Group 2:026)

"It was all down to me really, just being a bit of a pain really." (Group 3:001)

5.2.5 The importance of blended modes of information

The role of information provision at the time of the switch was a clear theme from the interviews with sub-themes emerging related to preferences for *how much information was given*, *in what format* and *by whom*. In relation to how much information was provided; thorough and understandable information was important to the majority of participants in the study.

"You can never have too much information in my opinion. It may have been a bit heavy going for some people but not for me." (Group 1:057)

With regards to the format of information, in general written information was very well received, and participants appreciated having the time to consider this and also have it for future reference.

"I do think that pack was nice because it didn't hide anything. Not that you would hide anything! (laughs) I did appreciate the fact

that it was all there so if I wanted to 'Google it' I could. I found that quite useful." (Group 1:017)

Having said that, there was an overwhelming preference for a face-to-face discussion and for some was actually a prerequisite to deciding about going ahead one way or the other.

"I felt reassured rather than if someone had just given me a sheet and said we're going to do this. Having someone speak to me about it was definitely better for me." (Group 2:038)

"I do think having a face-to-face discussion is really important…well for me it was." (Group 1:018)

"I think they'd be better off coming and speaking to you. Like I say, it's pretty complicated to try and work it out for yourself." (Group 3:004)

A blend of information with written information being sent out first followed by a face-to-face discussion was identified as some of the cohort as their preference.

"I thought it was good how you could have a read at home and then speak to someone in person if you had any questions." (Group 2:026)

Whilst a few participants preferred their face to face interaction to be with a doctor, the majority expressed no specific preference as to the type of healthcare professional as long as they were well informed.

"As long as it's someone who is able to answer the questions and give their confident opinion on what I'd be likely to experience and things related to it…it wouldn't matter who did it as long as they had the information." (Group 1:021)

An alternative, though less recurrent view, was that too much information could cause worry or be too complex and lead to "over-thinking" the decision to switch.

"It was very medically gravitated for some of the documentation you gave me especially the manufacturer's sheet and things like that" (Group 1: 003)

"I think when I saw the pack I was slightly overwhelmed…it seemed like a very big deal with lots of information and seemed a bit daunting…" (Group 1:017)

No one complained of insufficient information or the need for more detail. Choosing not to read any of the information and go ahead regardless was another observation from some participants which seemed to link in with emphasis being placed on other themes such as their past experiences and trust in the team.

"To be honest – I didn't really read it! As the last one worked I didn't see the problem in changing."

5.2.6 Concerns and anxiety

The final theme identified was the role a participant's concerns and anxieties played in the decision-making process. This theme does tie in with those above (general disposition and clinical status at the point of switching). Yet, in its own right, was distinct and had a clear impact. Interestingly, this theme seemed to relate more to the overall process of switching rather than the initial decision to switch. Again, there appeared to be a spectrum. There were those who had no concerns about quality, efficacy, side effects, safety or the fact that the new biosimilar was less expensive ("the optimists").

"I don't notice any difference whatsoever. That is the nice part. I feel absolutely fine and no different." (Group 1:037)

"Nothing major seems to have changed. I'm just as happy on this drug as the previous" (Group 1:018)

On the other hand, there were those who were quite concerned about most of these aspects ("the sceptics"). However, this did not always ultimately preclude them from switching as with the first quote from a participant in group 1.

"If it was again considering changing just purely for the price of it I would maybe be a bit concerned about why we are getting it cheaper and cheaper and cheaper. Is it going to be cost effective or is it going to be a health effective thing? I do look at quality and finance and worry that if you're going cheaper, cheaper, cheaper - would the quality still be there?" (Group 1:012)

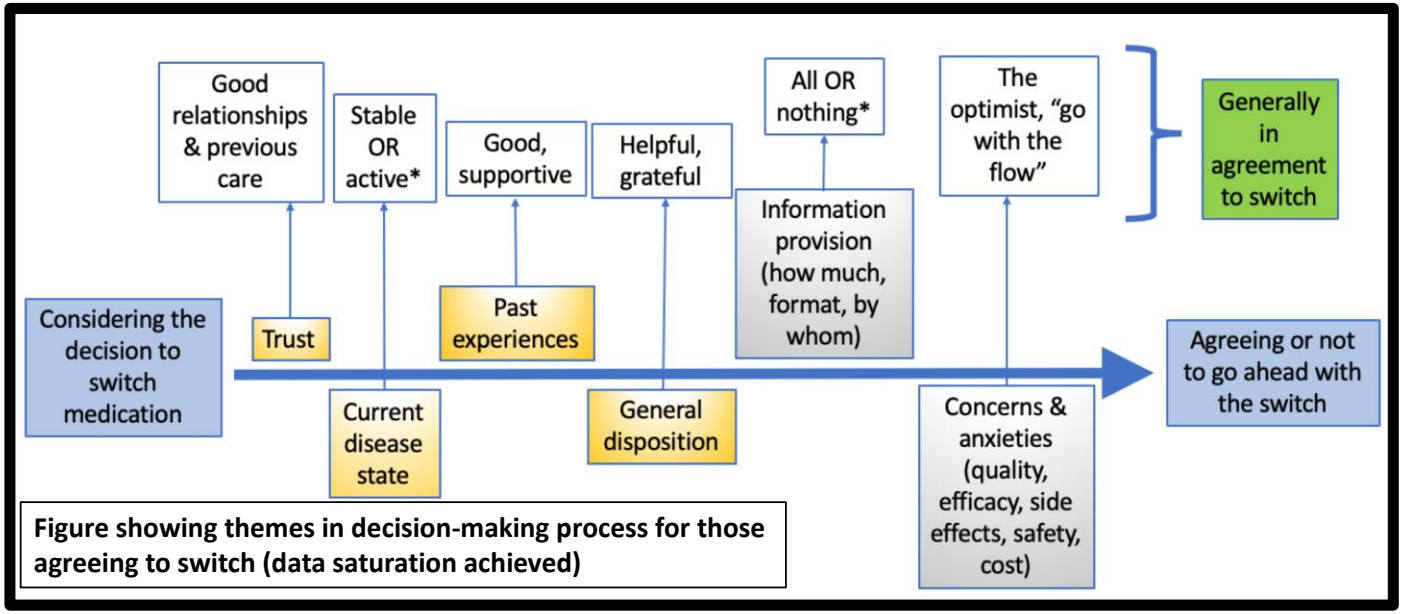
"As it's cheaper they are obviously going to use inferior medication…that's what I think!" (Group 3:005)

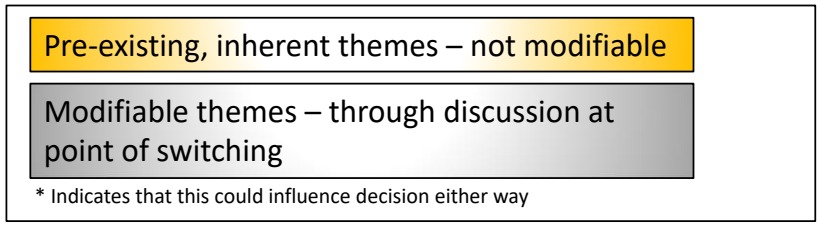
"I didn't really worry that it wasn't safe. I did worry that it might not be as effective…" (Group 3:002)

5.2.7 Conclusion

In this analysis, six themes were identified. There was no clear hierarchy to the themes. It was very individualistic with each participant placing varying degrees of importance on each theme to reach their ultimate decision. Of note, it was clear that some themes could be off-set by other themes depending on the importance it held to the participant in order to come to a final decision. For example, concerns and anxieties could be overcome by trust and information provision and lead to a participant still agreeing to switch.

Figure 19 is a visual representation of this thematic analysis. It shows the factors that were identified and impact on participants from the point they start to consider the decision to switch to the point that they then make that decision. In this diagram I have also introduced the concept of 'modifiable' and 'non-modifiable' themes. Of the six themes, some were inherent and likely to be unchangeable at the *point of switching* (trust, disease state, past experience, general disposition) whilst others (information provision, concerns and anxieties) were potentially modifiable. It is vital to appreciate that this distinction between a theme being 'modifiable' or 'non-modifiable' is at the point of deciding to switch. This is discussed in more detail in Chapter 6.





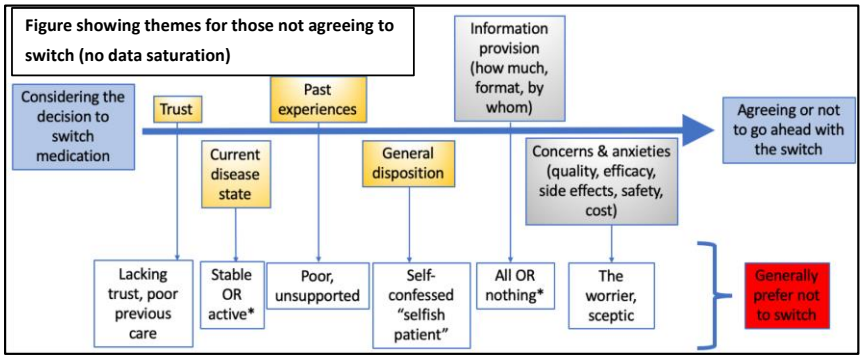


Figure 19: Visual representation of thematic analysis showing the main themes identified.

5.3 Nocebo effect

As discussed, of the ten patients in the group who discontinued due to their own choice, five were interviewed at the point of discontinuation. The transcripts from these five participants were analysed again separately to establish if there were any other themes that emerged specifically illustrating the presence of a nocebo effect. Overall, the group felt well informed about the process and were happy with all the information that was given to them.

"It was discussed really well." (Group 2:026)

"The letter was good - it explained it pretty well and then clarification in person just before kickstarting everything." (Group 2:105)

There were no clear character traits that were evident to suggest they would be more nervous about the switch nor were there any overwhelming negative preconceptions.

"I felt quite relaxed about it all…" (Group 2:038)

"I had obvious sorts of worries because you don't know but I wasn't expecting a problem…no." (Group 2:079)

Interestingly, all five participants maintained that their IBD symptoms remained stable with no major flares. It was the intolerance of the side effects they developed that were the main factor in deciding to switch back. These were many and varied.

"The next day - sore throat, runny nose, joint pain. Following day - heavy head, sore throat, tightness, joint pain particularly in the right leg." (Group 2:039)

"But I did really struggle with the nausea." (Group 2:026)

"I do get tired anyway, but this was very tired. I became very hot, I had a stomach ache, heavy head, my eyes have become heavy.. I tried to eat something but I did not even get to the first mouthful. I was just laying on the floor and I stayed there for a while." (Group 2:079)

"Yeah I just felt I had had six weeks of feeling really rough and I just wanted to go back on what I'd already been on." (Group 2:038)

Given the small sample size (n=5) it is difficult to draw any significant conclusions. However, there were some pertinent quotes that I have picked out that do suggest the presence of a nocebo effect to an extent in this cohort.

"Having said that even after going back on the other one I've been the same. So it's hard to know really what the cause is." (Group 2:038)

"In your mind it all becomes more psychological and you're thinking you feel like this because you've changed drugs but maybe that's not the case at all. I mean having switched back and still having problems there is a part of me that thinks is it worth going back to it, but then at the same time it scares me as well." (Group 2:038)

"It seems a lot for just a change in drug but it might be the drug as well as the stress…a bit of a combination maybe." (Group 2:039)

Despite their experiences on iBiSS and needing to switch back to CT-P13 all five participants volunteered that they would still consider switches in the future if they were deemed necessary but would be likely to question the rationale more.

"I wouldn't want to rule it out but I would be more apprehensive about it. I mean I wouldn't rule it out but I would probably ask more questions…" (Group 2:038)

"Yeah I'd probably give it a go. But not for another year or couple of years or so I think. But I probably would think about it though." (Group 2:105)

Summary

In this chapter I have presented the qualitative findings using a narrative with quotes from the interview transcripts to highlight the themes described. Overall, the implications from this analysis are that individualised discussions surrounding medication changes are likely to be highly valued and preferred by patients. These discussions must take in to account multiple factors including a patient's previous experiences, their current well-being as well as their general disposition. This will all be discussed in more detail in the final chapter of this thesis.

Chapter 6 Discussion

6.1 Introduction

In this thesis I have presented the IBD Biosimilar to Biosimilar Switching Study which prospectively followed a large cohort of patients with IBD as they switched from CT-P13 to SB2. I was brought on to this study at its inception. I was involved in all stages, from developing the protocol and obtaining ethics, to recruiting each participant and conducting qualitative interviews and finally analysing the data and publishing the results. This study primarily investigated the clinical outcomes of the patients in terms of disease activity, clinical biomarkers, drug levels and safety. Importantly, it also explored the patient experience of this process and having their medication switched using qualitative research methods. This study came about in 2018, at a time when there was no data on biosimilar to biosimilar IFX switching. Over the years, as my thesis has progressed the available data on this type of switching has admittedly grown. However, to my knowledge and based on my review of the literature this is the first time that both these elements of a managed biosimilar IFX switching programme have been incorporated into one piece of research using a mixed methods design.

6.2 Overview of thesis

Chapter 1: This chapter provides the background to IBD by providing an in depth understanding of the two main conditions, UC and CD. In this chapter I discuss pathogenesis, how the conditions present and are diagnosed, the tools used in disease classification and measuring disease activity and management of IBD with the main emphasis on medical options. I have also clearly laid out the objectives and hypothesis of the study.

Chapter 2: Chapter 2 is a comprehensive literature review which is based on two separate research questions;

Is there a difference in clinical outcomes for adult patients with immune mediated inflammatory disorders who are switched from one biosimilar of infliximab (CT-P13) to another (SB2)?

And;

What are the experiences of adult patients who are treated with a biological medicine having their medication switched to a biosimilar?

This chapter also clearly describes the role of IFX in the management of IBD and provides a deep dive in to biosimilars.

Chapter 3: In Chapter 3 I present the methodology of the study. I have shown what a mixed-methods design entails and why this was the chosen method to answer the specific research questions posed.

Chapter 4: A detailed analysis of the results from the main body of iBiSS which includes clinical outcome measures, patient reported outcomes, safety data and IFX drug levels and immunogenicity. This chapter also provides data on the nocebo effect.

Chapter 5: This chapter provides the findings from the thematic analysis of the nested qualitative study of iBiSS.

Chapter 6: In this final chapter I will discuss the results of both the quantitative and qualitative aspects in depth and summarise the main findings. I will also discuss how this piece of research links back to the wider literature and how it might inform future care.

6.3 Strengths and limitations

One of the major strengths of this piece of research is that the data were collected from a large, unselected group of IFX treated IBD patients in as close to a real-world setting as possible. This therefore allows these results to be applied to wider clinical practice. The aim was that iBiSS would mimic a real-world managed switching programme as far as possible

in terms of information provision, patient support, monitoring and the ability to switch back if not tolerated. I do acknowledge that there were aspects that resembled the stricter discipline of a phase IV study with clinical trial framework compared to routine care. The full details of all these aspects were discussed in Chapter 3.

Another strength of this study was the survey data that was collected from the participants at baseline and during the study. This included the IBD Control PROM, the IPQ-R and the TSQM. This provided valuable information from the participants about their perspective of their illness as well as the change. The IBD Control and TSQM questionnaires in particular which were measured before and after the switch to SB2 objectively showed that participants felt their disease control was maintained as was their satisfaction with the medication. The impact illness perception has on treatment compliance is widely documented in many chronic conditions(139-141). Given the focus of the patient experience in this thesis, the data from the IPQ-R at baseline was incredibly valuable. It highlighted that symptoms such as fatigue, which are not necessarily directly related to the gastrointestinal tract, were the most highly reported affecting patients. This is well known in the wider literature and is a significant unmet need in IBD(142, 143). Having an understanding and appreciation of such perceptions is therefore crucial and if this is lacking there is often a disconnect between the patient and the clinician(144). Tailoring discussions such as a switch in medication based on a patient's individual perspectives and perceptions, which can be gleaned from surveys like the IPQ-R, could enable optimal care. However, in time and resource constrained systems such as the National Health System (NHS) this is clearly a challenge.

This study did not use endoscopic assessments routinely. This is the current gold standard for assessment of disease activity and histological remission. However, patient acceptance of colonoscopy in real-world routine clinical practice, as well as in the context of research is

poor. Whilst there are challenges with sample handling and logistics to overcome in the use of faecal calprotectin, it is widely accepted as a surrogate marker of inflammation in IBD in clinical practice and correlates well with endoscopic disease(145). The lack of endoscopic and histological assessments at baseline and week 30/32 was therefore not felt to be a major limitation.

Overall, the quantitative results from Chapter 4 showed no appreciable difference before and after the switch in terms of the clinical and biochemical disease activity markers. This type of biosimilar to biosimilar switching is deemed safe and effective. Showing that was crucial as this was the main hypothesis of the study and was what was expected to be the outcome. There were no clear preconceptions about the thematic analysis as this has not been explored before. This nested qualitative study was therefore another major strength of the study. The implications from the thematic analysis are that individualised discussions and care surrounding medication changes are likely to be highly valued and preferred by patients. An awareness of the importance of the six main themes should enable insightful and more constructive discussions around switching medication, especially when switches are non-clinically driven and based on funding or availability.

There are however limitations to this study. The main limitation is the dataset for those who terminated early, and in particular the sub-set of participants who discontinued due to perceived side effects to SB2, is not complete. Unfortunately, it was more difficult to acquire samples from this set of participants as they were not available to have them collected or were unable to send them in. This has implications for the analysis and in particular determining if there was a definite nocebo effect. This is discussed in more detail later in this chapter. Similarly, the dataset for faecal calprotectin results is not complete with 119 samples at baseline but only 84 at week 30/32 which was the primary end-point. Although these results were encouraging in the analysis, the interpretation of these results could be

falsely reassuring as a proportion of the participants whose data was lacking are likely to have been the sub-group of participants who had active disease.

Another limitation of this study was the exclusion of those who were not on a six- or eight-weekly regime and those who were on a dose other than 5mg/kg. It could be argued that these patients required more intensive schedules and were more prone to treatment failure hence causing selection bias to the results. Another criticism is that almost 75% of the cohort at baseline were in remission. Having said that, non-medical switching between biosimilars, based on cost or availability, generally happens irrespective of disease activity state and patients are usually stable. So, although this could cause bias, this cohort does represent the real-world experience. Regardless, this therefore means that the views and outcomes of those with active disease are not clear.

Another limitation of this study was the lack of a comparator arm. Our goal was to recruit as many patients as possible in to the main study. Of the 158 eligible participants, 133 were successfully recruited. This therefore left too few patients to be used as a comparator group as they continued on CT-P13. A comparator arm establishes a baseline for comparison and allows researchers to compare the effects of the intervention and determine if there is a true effect of that intervention. However, it was felt more important to have as large a cohort as possible to enhance the results of the study and therefore not use a comparator group.

Finally, of the three groups that we conducted qualitative interviews with data saturation was achieved in group 1 only. This is primarily because the other two groups were harder to recruit to given their nature. Hence, the results of groups 2 and 3 must be interpreted with caution and further research is required with those who declined or discontinued a switch to achieve data saturation.

6.3 Qualitative analysis

There is a paucity of data on switching between biosimilars of infliximab and certainly there are no randomised controlled trials that evaluate this. In clinical settings physicians therefore need to use real-world data such as the data presented in this study and combine this with what they know about their individual patient. In the qualitative analysis I described patient related themes that would be pertinent to understand ahead of discussing a biosimilar to biosimilar switch. In this next section I will discuss these findings in more detail and show how they link to the existing literature.

Trust in the clinical team was one of the most prevalent themes which corroborates previous research that emphasises the importance of the relationship between healthcare professionals and patients in order to develop an optimal and adhered to IBD management plan(84, 91, 101, 108, 128). It has implications for practices such as drug substitution which are done at a pharmacy level with minimal patient interaction(146). There is an expectation from NHS England that Integrated Care Boards (ICB) will work with clinicians and prescribers and support them to work with their patients to ensure the most cost-effective biosimilars are used wherever possible in a timely fashion(147). The rationale being that the money saved could be channeled in to additional services and benefit the patients in other ways(148-150). The trust that patients' have in their teams and the role of continuity of care has implications for the success of such policy and is critical.

A full appreciation of a patient's clinical status at the point of switching along with any concerns they may have regarding this, and therefore their appropriateness to switch, should be fundamental prior to designing targeted information and suggesting a switch in treatment. This was evident in my analysis. Interestingly this was true of both stable and

active disease at the point of making the decision to switch. Some valued disease stability and this was one of the most cited barriers to accepting a switch in medication but this was not true for all. It is well documented that prolonged and stable periods of remission positively impact patients(144). Further research is now needed to understand the interplay between disease stability and the decision to switch as this is clearly a very important consideration when asking patients to change their medication.

Information provision was discussed extensively. Most patients clearly valued being well informed by both written information and face-to-face interactions. A less common finding was that too much information could be overwhelming and complicate the decision-making process. This study was not entirely akin to standard clinical practice as the information provided was more detailed due to being given as part of a fully consented clinical trial. Further research should focus on the optimal amount of information provision and the format this should take. This should aim to include an evaluation of those who don't agree to switch and achieve data saturation to assess reasons why as this will provide very valuable insight.

Figure 19 in Chapter 5 is a visual representation of the thematic analysis and illustrates the six themes identified. The main diagram shows the factors identified in Group 1 that tended towards them making the decision to switch from the point they first learnt about the study to the day that consent was obtained. The box inset shows the flip-side to this. The diagram is laid out as it is (versus being presented as one merged diagram) because data saturation was not achieved in this group. Hence more research is needed here as this was based on the views of a smaller sub-group. Nonetheless, we speculate that these may still be the main factors to be considered by teams before asking patients to switch their biosimilar medication.

The concept of being modifiable or non-modifiable also has important implications for future practice in terms of where to target time and resources to enable participants to feel more comfortable in committing to a switch. Past experiences, disease stability and general disposition certainly seemed unchangeable at the point of switching and did have bearings on a participant's preconception of the trial. However, as previously discussed, some themes could off-set others. There were several participants who had poor experiences of a past switch in their medication but were able to overcome this with good information provision and from the trust they had developed in the team subsequently. Trust was deemed to be non-modifiable. However, it was clear that trust was more complex than this. Trust can and must be developed continually as it can be easily broken down and so must not be assumed or ignored. In particular, for some patients who had never met me personally before this had to be gained during our discussion before an agreement was made.

Overall, the findings from this part of the study suggest that assessing past experiences and any other concerns or anxieties (related to safety or efficacy) in conjunction with understanding a patient's general disposition and providing individualised information based on all these factors is key(98, 151-154). This is in keeping with the wider literature on adherence which supports the importance of shared decision-making(92, 128).

6.4 Nocebo effect

One of the subgroups that we paid particular attention to was the group of patients who discontinued of their own choice due to perceived side effects. As mentioned, the dataset for this group was not complete. However, of the data available objectively the mean CRP at termination was 9.4 (n=9) and the mean FCP was 18.6 (n=5). Both these markers do not suggest objective evidence of active disease. This is corroborated in the transcripts from the five participants who were interviewed and confirmed that there was no subjective worsening

of disease control. The main concern was the side effects from SB2. In Section 5.3 I have highlighted more excerpts from the transcripts which suggest some insight in to the presence of the nocebo effect. The cytokine profile data also showed interesting results to suggest that pro-inflammatory cytokine levels are higher in those who discontinue due to objective loss of response versus those who did so due to side effects and in whom disease activity was maintained.

Clearly, this is a *very* small number of participants and interpretation of these findings must be done with caution but it is certainly of interest that there was no clear marked change in both clinical and biochemical markers. The true burden of the nocebo effects in patients on biosimilars is difficult to estimate(104). In previous studies on originator to biosimilar switching rates were >10%(155). Confirming this was the nocebo effect and not a true worsening of IBD due to a loss of response from switching to SB2 is difficult. However, it does pique interest and could suggest the presence of the nocebo effect which has been identified as a significant problem in the era of biosimilars.

6.5 Future work

There are opportunities for this data to be developed further. The data on the nocebo effect is one of the most interesting parts of this research project. Further research with larger samples is now necessary to explore this in more depth and identify clinical, or even perceptual markers, at baseline that could predict which patients might be prone to the nocebo effect and thus tailor discussions around switching accordingly. This could lend itself to the development of targeted patient education sessions and initiatives to discuss treatment plans. Research should focus on how to deliver the optimum amount of information to those identified as being at risk to prevent the nocebo effect from occurring. In

line with this, further work could also look at correlating biochemical markers with survey data and qualitative data.

This research could also provide the basis to develop a clear patient information leaflet for biosimilar switching in the future. It is highly likely that non-medical switching will become common practice and a succinct but comprehensive information sheet highlighting the positive real-world data could help compliance with these changes by providing patients with examples of how this has worked in practice. There would also be the opportunity to design a clinician information leaflet sheet and disseminate to different specialties who use biologics and biosimilars. This information could help guide clinicians during their consultations about biosimilar switching and understand the different themes that have been identified and how they impact a patient's decision to switch. Furthermore, the information gleaned in the qualitative analysis could be used to develop an information sheet for patients and clinicians for organisations such as CCUK.

The cytokine profile work could also be developed further with a possible role in diagnostics and predicting treatment failure and/or susceptibility to the nocebo effect. In disease process like IBD,where cytokines are crucial mediators in the inflammatory pathway, specific cytokine expression could predict disease activity and pathophysiology. However, there is lack of specificity to disease processes which can make interpretation difficult. Cytokine profiling is also expensive and unlikely to be feasible in routine care due to the cost implications. Overall, these results are important but much more work will be needed to fully understand which exact markers could be used in diagnostic assays and how they can be clinically useful. In the future there may be a role for integrating cytokine profiles with disease activity scores and biochemical markers to create multimodal scores to use in specific disease processes.

6.6 Conclusion

Biosimilars have provided a less expensive treatment option for patients with immune-mediated conditions. Remaining competitive, by being able to switch between biosimilars based on cost, is imperative to health systems such as the NHS with significant financial constraints. It allows more access to wider populations whilst controlling expenditure. During the course of their illness, patients with IBD are likely to experience many different changes to their treatment plans and switching between biosimilars is an example of one such decision. Involving patients and understanding their thought processes in making these decisions when they occur is key. This is due to both the increasing complexity of the choices available as well as when there is equipoise in the treatment decision with no clear 'right answer'. Having patient involvement and sharing decision making between patients and the clinical teams has also shown to improve adherence with treatment plans and be the best approach(91-94, 156). Foundations such as the Crohn's and Colitis United Kingdom (CCUK) charity, which is the leading charity for IBD in the UK, place great emphasis on shared-decision making and purport that when patients participate in decision making with all aspects of their care, they are more likely to follow through and have better outcomes(157). However, the degree to which these discussions do actually take place varies significantly. Although exact reasons are not declared, one UK based study of patients with ankylosing spondylitis showed that the majority of patients who were switched to biosimilar adalimumab were never actually asked for consent, showing that this is an issue(158). As a general rule, clinicians rely on robust evidence-based data to guide clinical decisions and come to the best option for their patients. In biosimilar to biosimilar switching this will always be lacking as providing this type of data is not a priority for regulatory bodies(159). Hence, the emergence of real-world data such as the data shown here is of major value to provide that confidence to clinicians.

This study has shown that in a population of IFX treated patients, switching from CT-P13 to SB2 is safe and effective. Overall, the data showed there did not appear to be any significant issues switching from one biosimilar molecule to another. Participants completed the study without major clinical concern beyond what is experienced in routine clinical practice. The safety profile of SB2 was similar to the current evidence for IFX(160, 161). The study also gained insight into the factors that may need to be considered in supporting patient decision-making which is crucial. The aim is that the results from this study will support clinical teams in the development of clear and stream-lined processes between pharmacy, physicians, nurses and patients to confidently deliver a well-monitored biosimilar switching programme. This is of particular relevance now with the development of multiple biosimilars, not just of IFX but of other biologics as well.

Appendix

Appendix A Critical Appraisal Skills Programme (CASP) Checklist

CASP
Critical Appraisal Skills Programme

Paper for appraisal and reference:.....

Section A: Are the results of the study valid?

1. Did the study address a clearly focused issue?

Yes ☐
Can't Tell ☐
No ☐

HINT: A question can be 'focused' in terms of
- the population studied
- the risk factors studied
- is it clear whether the study tried to detect a beneficial or harmful effect
- the outcomes considered

Comments:

2. Was the cohort recruited in an acceptable way?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for selection bias which might compromise the generalisability of the findings:
- was the cohort representative of a defined population
- was there something special about the cohort
- was everybody included who should have been

Comments:

Is it worth continuing?

CASP
Critical Appraisal Skills Programme

3. Was the exposure accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- were all the subjects classified into exposure groups using the same procedure

Comments:

4. Was the outcome accurately measured to minimise bias?

Yes ☐
Can't Tell ☐
No ☐

HINT: Look for measurement or classification bias:

- did they use subjective or objective measurements
- do the measurements truly reflect what you want them to (have they been validated)
- has a reliable system been established for detecting all the cases (for measuring disease occurrence)
- were the measurement methods similar in the different groups
- were the subjects and/or the outcome assessor blinded to exposure (does this matter)

Comments:

CASP
Critical Appraisal Skills Programme

5. (a) Have the authors identified all important confounding factors?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- list the ones you think might be important, and ones the author missed

Comments:

5. (b) Have they taken account of the confounding factors in the design and/or analysis?

Yes ☐
Can't Tell ☐
No ☐

HINT:
- look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

Comments:

6. (a) Was the follow up of subjects complete enough?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- the good or bad effects should have had long enough to reveal themselves
- the persons that are lost to follow-up may have different outcomes than those available for assessment
- in an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort

6. (b) Was the follow up of subjects long enough?

Yes ☐
Can't Tell ☐
No ☐

Comments:

Section B: What are the results?

7. What are the results of this study?

HINT: Consider
- what are the bottom line results
- have they reported the rate or the proportion between the exposed/unexposed, the ratio/rate difference
- how strong is the association between exposure and outcome (RR)
- what is the absolute risk reduction (ARR)

Comments:

8. How precise are the results?

HINT:
- look for the range of the confidence intervals, if given

Comments:

CASP
Critical Appraisal Skills Programme

9. Do you believe the results?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- big effect is hard to ignore
- can it be due to bias, chance or confounding
- are the design and methods of this study sufficiently flawed to make the results unreliable
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

Comments:

Section C: Will the results help locally?

10. Can the results be applied to the local population?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider whether
- a cohort study was the appropriate method to answer this question
- the subjects covered in this study could be sufficiently different from your population to cause concern
- your local setting is likely to differ much from that of the study
- you can quantify the local benefits and harms

Comments:

11. Do the results of this study fit with other available evidence?

Yes ☐
Can't Tell ☐
No ☐

Comments:

CASP
Critical Appraisal Skills Programme

12. What are the implications of this study for practice?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- one observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- for certain questions, observational studies provide the only evidence
- recommendations from observational studies are always stronger when supported by other evidence

Comments:

Appendix B Patient Letter of Invitation

Date 25th July 2018

Patient Letter of Invitation

STUDY TITLE: IBD Biosimilar to Biosimilar Infliximab Switching Study

SHORT TITLE: iBiSS

Dear Sir or Madam

You have been given this letter as you are currently being treated with a drug called Infliximab for adults with Ulcerative Colitis or Crohn's disease and we would like to invite you to consider participating in our research study

Infliximab was originally marketed by a single pharmaceutical company and was given the brand name Remicade. Remicade belongs to a group of drugs called "biologics". After an agreed number of years other companies are now allowed to produce their own copies of the medicine. Simple medicines, like paracetamol, are relatively easy to produce and copy *exactly*. The production of biologics, like Remicade, is much more complicated. The resulting molecule is similar but it won't be an exact copy. These are known as "biosimilars". Biosimilars have been extensively tested and analysed by the authorities that regulate medication in the UK and have been deemed just as safe and effective as Remicade (the original Infliximab).

You are currently being treated with a biosimilar called CT-P13 or Remsima for your IBD. There have been many studies that compare switching from the originator Infliximab (Remicade) to biosimilar CT-P13 (Remsima) including some that were run here at UHS. However, there are currently no studies that compare switching from one biosimilar to another biosimilar. This is what we aim to do in ~~this~~ our study.

We would like to give you the option to participate in this study, which includes switching you from your current medication (CT-P13) to an alternative biosimilar (SB2). Despite the fact that we do not expect any patients to experience problems as a result of switching to this biosimilar, you will be monitored very closely as part of this in terms of your progress and any side effects. We believe this alternative medication is as safe and effective as your current medication.

If you would like any more information regarding this new biosimilar Infliximab or if you have any questions regarding any of the issues raised in this letter please feel free to discuss them with us.

Appendix C Patient Information Sheet (PIS)

University of Southampton | NHS University Hospital Southampton NHS Foundation Trust

Trial ID	M E D 1 5 2 6
Site:	0 1
Patient ID No	

PATIENT INFORMATION SHEET

PART 1

STUDY TITLE: **IBD Biosimilar to Biosimilar Infliximab Switching Study**

SHORT TITLE: **iBiSS**

INTRODUCTION

We would like to invite you to take part in our research study as you either have Ulcerative Colitis (UC) or Crohn's disease (CD) and are currently being treated with a drug called CT-P13 (known commercially as Remsima).

Before you decide, it is important for you to understand why the research is being done and what it will involve for you.

A member of our team will go through this information sheet with you and answer any questions you may have. We recommend you take about 10 minutes to read it. We would encourage you to talk to others about the study if you wish and ask us if there is anything that is not clear.

Part 1 tells you the purpose of the study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

This is an important document. Please read it carefully as it contains information you need to know about this study. If you agree to participate, you will be asked to sign a consent form. This will ensure that you are aware of the study features, the risks that you may be exposed to whilst participating and confirm your agreement to participate.

We are willing to provide any further clarification if required.

WHY ARE WE DOING THIS STUDY?

This study is looking at the effects of switching from one type of Infliximab used to treat UC or CD to another type of Infliximab. Currently, you will be receiving CT-P13 which is commercially known as Remsima. CT-P13 is a biosimilar drug which we will explain more about shortly. In this study, we would like to switch you from CT-P13 to another biosimilar drug, SB2 (commercially known as Flixabi).

This study aims to explore a number of things including;

- How your condition is maintained after switching
- How safe it is to switch from one biosimilar drug to another
- To assess your quality of life after switching from CT-P13 to SB2.
- To assess your views and experience of being asked to switch from CT-P13 to SB2.

We will now provide a brief explanation of this medication and how the study will work if you decide to take part in this study.

What is the current treatment for IBD?

The aim of treatment in patients with IBD is to control the inflammation which causes the symptoms. Current treatments can be medical, surgical or a combination of both. One example of medical treatment is biologic drugs.

When your body is fighting infection or inflammation it naturally produces a protein called TNF-alpha (tumor necrosis factor) as part of its immune response. Over-production of this protein is thought to be partly responsible for the chronic inflammation found in IBD. Biologic drugs are a group of drugs known as anti-TNFs. One of these is Infliximab and it acts by binding to TNF-alpha and helping to prevent inflammation and thereby relieve symptoms.

What is a biosimilar product?

Infliximab was originally marketed by a single pharmaceutical company and given the brand name Remicade. After a number of years, it was agreed that other companies would be allowed to produce their own copies of Remicade. These are known as biosimilars.

Simple medicines, like paracetamol, are relatively easy to produce and copy exactly. These copies are known as 'generic' medicines. The production of biologics, like Remicade, is more complicated. Biosimilars have been extensively tested and analysed by the authorities that regulate medication in the UK and have been deemed just as safe and effective as Remicade (the original Infliximab).

CT-P13 (branded as Remsima) and SB2 (branded as Flixabi) are two different 'biosimilars' of Remicade. You are currently being treated with CT-P13 and in this study you will be switched to SB2.

What will this study do differently?

This study aims to evaluate the outcome of switching patients currently on CT-P13 to SB2 as there are currently no comparisons in terms of efficacy (how well the drug works) and outcomes between biosimilars. There have been many comparisons made between switching from **the originator Infliximab (Remicade) to a biosimilar** and you yourself may have been involved in such programmes here at Southampton General Hospital in the past. This study is novel in that we are switching from **one biosimilar to another biosimilar**.

WHAT WOULD TAKING PART INVOLVE?

If you decide to take part in this study you will be required to attend a number of visits at University Hospital Southampton NHS Trust (UHS) for trial assessments and study drug infusión which will mirror exactly your normal clinical care.

The total duration of your time in the study will be up to 56 weeks.

Consent & enrolment including initial switch from CT-P13 to SB2 (Study Visit 1-Week 0)

At this visit you will have already received this information sheet to read. You will have been given time to take all this information away and discuss it with relatives and friends before deciding if you would like to take part.

If you chose to do so we will reconfirm you are eligible and you will be asked to sign a consent form.

We will then do a number of baseline evaluations (many of which would have been undertaken as part of your routine care) to ensure you meet the inclusion criteria for the study. These baseline assessments will be carried out at UHS.

The baseline assessments include the following tests/assessments:

- Checking prior and current medication
- Taking your blood pressure, temperature, respiration rate, height and weight
- Undertaking a physical examination if clinically indicated
- If not done previously as part of your standard care we will take a blood test to check for Tuberculosis, Hepatitis B, Hepatitis C virus and Varicella virus – this is to rule out any underlying infection before starting your treatment.
- Collecting a stool sample to test for active inflammation in the intestine (faecal calprotectin)
- Taking routine blood tests and urine samples as per your normal standard of care
- Taking a blood test for measuring drug antibody levels
- Completing a questionnaire regarding the status of your condition

- Completing a questionnaire regarding your satisfaction with your medication
- Completing quality of life questions regarding your condition
- If you become pregnant during this study your doctor must be informed as soon as possible so this can be reviewed and your treatment discussed.
- Taking specific blood tests to look at inflammatory markers

Switch from CT-P13 to SB2 and SB2 Administration

If your baseline assessments are satisfactory and your eligibility in the study confirmed, you will then have your current CT-P13 treatment switched to SB2 and your 1st SB2 infusion given.

You will be given SB2 intravenously (in a vein), which will be administered at the same rate as your previous dose of CT-P13 was given. During the infusion, you will be monitored and have your routine observations (blood pressure, pulse rate, respiration rate, temperature and oxygen saturation) taken. All of this is standard practice for these infusions. Once completed you will be observed and monitored for 1 hour.

Your observations will be taken every 30 minutes for up to 1 hour after the infusion has finished. You will also be monitored for acute infusion-related reactions. After this observation period you will be allowed to go home.

As reactions can still occur a few hours after the infusion, you will be advised to seek immediate medical advice if you experience any delayed adverse effects.

WHAT WILL HAPPEN AT EACH INFUSION?

At each visit during this study we will try to mimic, as much as possible, what would happen if you were still in standard NHS care.

- You will have a number of assessments and tests as part of your normal standard of care including a brief history and a physical examination if indicated.
- We will take your blood samples for the study
- Whilst your infusion is running, we will ask you to complete a series of questionnaires to assess your progress. During the questionnaire process, if at any time you feel any level of distress, you will be given the option to either take a break or to discontinue completion of the questionnaire. A member of the research team will always be available to discuss any issues you may have about any of the questions you are presented with.
- You may be selected for an interview regarding your experience of switching from CT-P13 to SB2. You will have provided your consent to participate in such interview. This is

a novel aspect of this study and we would like to get your views and experience of having your medication switched. We would use these patient perspectives to guide our future practice to ensure the best experience for patients.

- We anticipate that there will be some patients who do not respond, or lose response, to SB2 during the study. If this is evident, we will discuss it with you and if clinically indicated consider discontinuing this medication early. This would mirror exactly what would happen in routine care if a similar situation were to arise.
- At week 32, considered as the end of treatment, patients will revert to whichever infliximab is currently being used as standard of care at UHS. This may include continuing on SB2, switching back to the originator Infliximab Remicade or switching back to the previous biosimilar CT-P13.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

It is not known if you will personally benefit from this research, however, we hope that this research will show that it is safe to switch from biosimlar to another biosimilar (ie CT-P13 to SB2).

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form of which you will also receive a copy. If you decide to take part, you are still free to withdraw at any time and without giving a reason. If you decide to stop treatment with SB2, you will be invited to participate in an interview for us to understand a little more about your experiences. You are under no obligation to participate in the interviews. We will seek your consent for the option to approach you about such interviews.

Stopping this medication will not affect the standard of care that you will receive.

EXPENSES AND PAYMENTS

Patients will not be given any payments for taking part in this research as the infusion visits and schedules follow standard of care.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

Most of the treatments and assessments you will receive/undergo will be standard of care (i.e. you will have received this anyway even if you weren't in the study).

It has been shown that the risks associated with SB2 infusion are no greater than those associated with its reference drug, Remicade.

The most common risks associated with SB2 are exactly the same as other biosimilars of Infliximab i.e. CT-P13. These include viral infections (such as flu or cold sores), headache, upper-respiratory-tract infection (colds), sinusitis (inflammation of the sinuses), nausea (feeling sick), abdominal pain (stomach ache), infusion-related reactions and pain which is comparable to the originator molecule.

With any Infliximab infusion there is a risk of developing an allergic reaction. This is no different with SB2. If a serious reaction occurs, treatment will be given to alleviate the symptoms and further treatment with SB2 will be reviewed.

In previous clinical trials, delayed hypersensitivity reactions have been reported so you will be advised to seek immediate medical advice if you experience any delayed adverse effects.

If you were to become pregnant whilst on the trial and receiving SB2 then it is important that you are aware that your baby will not be allowed to have any 'live' vaccinations until they are six months old.

Your GP will also be notified of this.

WHAT HAPPENS IF I ~~OR MY PARTNER~~ BECOME PREGNANT?

If you were to become pregnant we would ask that you let your study doctor know as soon as possible. Current practice would be to continue your treatment until you reach the 3rd trimester. At this point, after discussion with your doctor and the obstetric/midwifery team, I may be advised to stop treatment at 32 weeks or continue treatment until my delivery date. The sponsor will be notified of your pregnancy and its outcome in an anonymized format. This data will be captured on the study database and held in Cape Town, South Africa. If you do become pregnant the local research team would like to follow your pregnancy specific data up until delivery and we will seek separate consent to do this. This data will not be transferred outside of the hospital or provided to the sponsor

WHAT HAPPENS IF MY PARTNER GETS PREGNANT DURING THE STUDY?

There will be no requirement for us to monitor your partner's pregnancy specific data through their pregnancy but if you have any questions or concerns we would be happy to review these with you

WHAT HAPPENS WHEN RESEARCH STOPS?

When you finish taking part in the research your treatment and subsequent follow-up will continue as it would have had you not taken part in the study.

WHAT IF THERE IS A PROBLEM?

Any complaint about the way with which you have been dealt with during the study or any possible harm you might have suffered will be addressed. The detailed information relating to this is given in part 2 of this information sheet.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes. All the information about your participation in this study will be kept confidential. More details are included in Part 2 of this information sheet.

This completes Part 1

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Trial ID | M | E | D | 1 | 5 | 2 | 6 |

Site: | 0 | 1 |

Patient ID No | | | |

PATIENT INFORMATION SHEET

PART 2

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes during a study, new information becomes available about the treatment that is being studied. If this happens, your doctor will tell you about it. You can then discuss if you want to continue the study or not. Your doctor can also decide to withdraw you from the study if it is felt this is in your best interests.

WHAT WILL HAPPEN IF I DO NOT WANT TO CARRY ON WITH THE STUDY?

Taking part in this study is your choice. You can choose to participate in this study and then you can change your mind. Your choice will not influence the medical care that you receive.
The study doctor may decide to remove you from this study without your permission for different reasons:

- If you do not follow the procedures required by the study.
- If the study procedures are found to be unsafe.
- If the study procedures are found to be ineffective.
- If the study is closed.

It is important that you tell the study doctor if you want to withdraw from the study, so that they can plan an appropriate visit to discuss withdrawal and follow up.

WHAT IF THERE IS A PROBLEM?

Complaints

If you have a concern about any aspect of this study, you should ask to speak with the research staff who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your local hospital. If you are harmed due to someone's negligence, then you may have grounds for legal action. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Involvement of the General Practioner/Family Doctor/Other Healthcare Practitioner

If you agree and sign a consent form to participate in the study a letter will be sent to your GP/family doctor/health practitioner informing them of your participation. Please discuss this with your research doctor if you have any objections to this being undertaken.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

University Hospital Southampton NHS Trust (UHS R&D) is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means we are responsible for looking after your information and using it properly. The sponsor will retain non-identifiable study data for 5 years after study conclusion

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting Dr Fraser Cummings.

University Hospital Southampton NHS Trust (the site) will keep your name, NHS number and contact details confidential and will not pass this information to the sponsor. The site will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the sponsor organisation and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The sponsor will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details.

The site will keep identifiable information about you from this study for 5 years after the study has finished.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

The anonymised data collected for the purposes of this research will be sent to a data management company (located in Cape Town, South Africa) so that we can analyse the results. You cannot be identified but we will ask for your consent to this.

Following the study, the researchers may share results of the study with other researchers which may be used to support other research in the future. You will not be identified in any of the published data.

We will ask for you to consent to your GP being informed of your taking part in the study.

WHAT WILL HAPPEN TO ANY SAMPLES I GIVE?

The blood and stool samples you provide will be stored at The Wellcome Trust Clinical Research Facility Prep Lab storage facility at UHS, analysed locally and the results maintained within the normal hospital systems. These will remain at this facility throughout the duration of the study.

Once the study is closed, we would like to retain certain samples at an HTA licensed Biobank facility (University of Southampton Faculty of Medicine) at UHS. These samples may be used for further research in the field of biosimilars and will be stored for up to five years. This may involve samples being analysed by another researcher who may potentially be in the European Union. . All samples will be fully anonmised. We will seek your consent for this. Should you choose not to have your samples retained, this will not preclude you from the research project.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

The results of the study will be published in relevant medical and scientific journals once the data has been reviewed by the researchers. The results will also be made available to you via your study team (upon request) and through accessing the European Clinical Trial Database. The results will also be reviewed by the Ethics Committee and the Medicines and Healthcare product Regulatory Agency (MHRA) at the end of the study. We will also share the results with patients, for example, at the IBD patient open day at UHS.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

The study is Investigator driven and sponsored by University Hospital Southampton NHS Trust. The funding for the research has come from Biogen Idec Ltd who produce SB2.

WHO HAS REVIEWED THE STUDY?

The study has been reviewed by Biogen Idec Ltd as part of the process for obtaining funding and the internal Southampton trial committees.

The study will also be reviewed and approval obtained by the Research Ethics Committee and the Medicines and Healthcare product Regulatory Agency (MHRA) before the study can commence.

FURTHER INFORMATION AND CONTACT DETAILS

If you have any questions about the study or if you have an injury – please contact the following persons:

Study Physician: Dr Clare Harris Telephone: 0238 120 3713

Study Physician: Dr Fraser Cummings Telephone: 0238 120 3713

Appendix D Informed Consent Form (ICF)

University Hospital Southampton NHS
NHS Foundation Trust

Trial ID: | M | E | D | 1 | 5 | 2 | 6 |

Site Number: | 0 | 1 |

Enrolment Identification Number for this trial | | | |

CONSENT FORM

Title of Project: IBD Biosimilar to Biosimilar Infliximab Switching Study

Short Title: **iBiSS**

Name of Principal Investigator: Dr Fraser Cummings

	Please initial box
1. I confirm that I have read the information sheet V4.0 dated 18th September 2018 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals involved in the trial, from regulatory authorities or from the 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.	☐
4. I am also aware anonymised data collected from the trial will be sent to a data management company based in Cape Town, South Africa to allow the data to be prepared ready for analysis.	☐
5. I understand that certain blood samples collected will be sent for analysis as part of the study. I agree to my samples being sent for the purposes of the study.	☐
6. I understand that certain blood samples will be collected and stored in a Biobank for	

use in future projects. This may involve samples being analysed by another researcher who will potentially be within the European Union. All samples will be fully anonymised. I agree/do not agree *(delete as appropriate)* to my samples being held in a biobank for use in future projects. (You may still participate in the study if you do not agree to retention of samples) ☐

7. I understand that I may be selected to take part in an interview and answer questions regarding my experience of switching from one biosimilar of infliximab to another. I also understand the interview will be conducted at a setting of my choice, last for up to 1 hour and will be audio recorded using a digital recorder and fully transcribed. I agree/do not agree *(delete as appropriate)* to participate in such interviews ☐

8. I understand that if I stop treatment I will be invited to participate in an interview to understand a little more about my experiences in the study. There is no obligation to take part in this interview. I agree/do not agree *(delete as appropriate)* to be approached about such interviews ☐

9. I understand that if I become pregnant during the study separate consent will be sought from me to allow follow up from the research team (add N/A if not applicable) ☐

10. I understand that if my partner becomes pregnant during my participation in the study, I will have any questions/concerns regarding treatment answered by the research team (add N/A if not applicable) ☐

11. I understand that the results of the study may be used to support other ethically approved research in the future, and may be shared anonymously with other researchers ☐

12. I agree to my General Practitioner being informed of my participation in the study. ☐

13. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix E Patient identification (ID) card

PATIENT IDENTIFICATION CARD University Hospital Southampton NHS NHS Foundation Trust

SUBJECT ID: iBiSS01-XXX

This patient is taking part in a clinical trial at University Hospital Southampton NHS Trust with Flixabi – a biosimilar used in the treatment of Inflammatory Bowel Disease (iBiSS).

Please carry this card with you at all times and show it to any doctor you visit

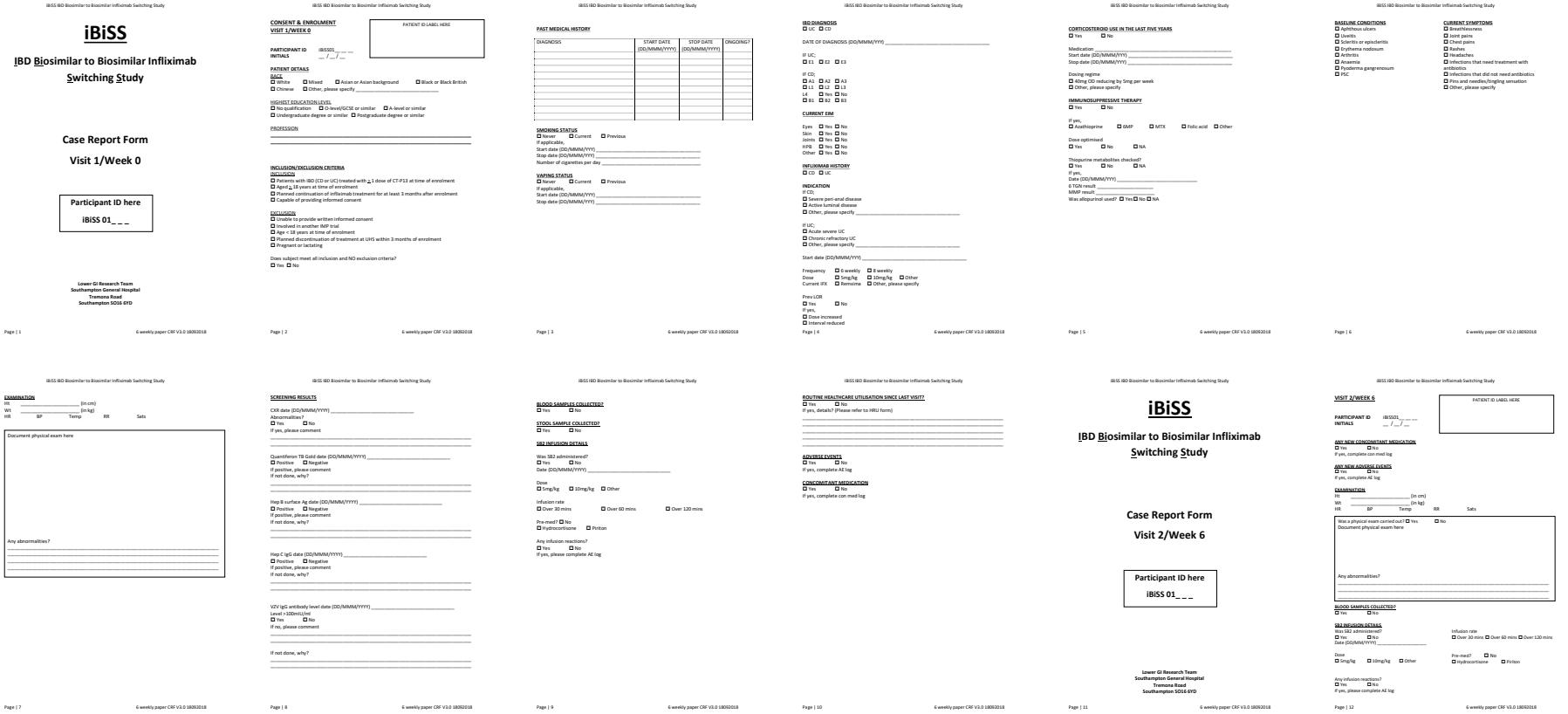
Patient identification card V1.0 18 Jul 2018

CONTACT DETAILS

Lower GI Research Team
Southampton General Hospital
☎ 0238 120 3713
07769 234251
ibdresearch@uhs.nhs.uk
In case of emergency:
Contact Dr Fraser Cummings via UHS switchboard on 02380 777 222.

Please carry this card with you at all times and show it to any doctor you visit

Appendix F Case Report Form



iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

iBiSS

IBD Biosimilar to Biosimilar Infliximab Switching Study

Case Report Form

Visit 1/Week 0

Participant ID here

iBiSS 01_ _ _

Lower GI Research Team
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Page | 1 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

CONSENT & ENROLMENT VISIT 1/WEEK 0

PATIENT ID LABEL HERE

PARTICIPANT ID INITIALS iBiSS01_ _ _ _ _ /_ _/_ _

PATIENT DETAILS

RACE
☐ White ☐ Mixed ☐ Asian or Asian background ☐ Black or Black British
☐ Chinese ☐ Other, please specify _____

HIGHEST EDUCATION LEVEL
☐ No qualification ☐ O-level/GCSE or similar ☐ A-level or similar
☐ Undergraduate degree or similar ☐ Postgraduate degree or similar

PROFESSION
_____
_____

INCLUSION/EXCLUSION CRITERIA

INCLUSION
☐ Patients with IBD (CD or UC) treated with ≥ 1 dose of CT-P13 at time of enrolment
☐ Aged ≥ 18 years at time of enrolment
☐ Planned continuation of infliximab treatment for at least 3 months after enrolment
☐ Capable of providing informed consent

EXCLUSION
☐ Unable to provide written informed consent
☐ Involved in another IMP trial
☐ Age < 18 years at time of enrolment
☐ Planned discontinuation of treatment at UHS within 3 months of enrolment
☐ Pregnant or lactating

Does subject meet all inclusion and NO exclusion criteria?
☐ Yes ☐ No

Page | 2 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

PAST MEDICAL HISTORY

DIAGNOSIS	START DATE (DD/MMM/YYYY)	STOP DATE (DD/MMM/YYYY)	ONGOING?

SMOKING STATUS
☐ Never ☐ Current ☐ Previous
If applicable,
Start date (DD/MMM/YYYY) _____
Stop date (DD/MMM/YYYY) _____
Number of cigarettes per day _____

VAPING STATUS
☐ Never ☐ Current ☐ Previous
If applicable,
Start date (DD/MMM/YYYY) _____
Stop date (DD/MMM/YYYY) _____

Page | 3 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

IBD DIAGNOSIS
☐ UC ☐ CD

DATE OF DIAGNOSIS (DD/MMM/YYY) _____

IF UC;
☐ E1 ☐ E2 ☐ E3

IF CD;
☐ A1 ☐ A2 ☐ A3
☐ L1 ☐ L2 ☐ L3
L4 ☐ Yes ☐ No
☐ B1 ☐ B2 ☐ B3

CURRENT EIM

Eyes ☐ Yes ☐ No
Skin ☐ Yes ☐ No
Joints ☐ Yes ☐ No
HPB ☐ Yes ☐ No
Other ☐ Yes ☐ No

INFLIXIMAB HISTORY
☐ CD ☐ UC

INDICATION
If CD;
☐ Severe peri-anal disease
☐ Active luminal disease
☐ Other, please specify _____

If UC;
☐ Acute severe UC
☐ Chronic refractory UC
☐ Other, please specify _____

Start date (DD/MMM/YYY) _____

Frequency ☐ 6 weekly ☐ 8 weekly
Dose ☐ 5mg/kg ☐ 10mg/kg ☐ Other
Current IFX ☐ Remsima ☐ Other, please specify

Prev LOR
☐ Yes ☐ No
If yes,
☐ Dose increased
☐ Interval reduced

Page | 4 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

CORTICOSTEROID USE IN THE LAST FIVE YEARS
☐ Yes ☐ No

Medication _____
Start date (DD/MMM/YYY) _____
Stop date (DD/MMM/YYY) _____

Dosing regime
☐ 40mg OD reducing by 5mg per week
☐ Other, please specify

IMMUNOSUPPRESSIVE THERAPY
☐ Yes ☐ No

If yes,
☐ Azathioprine ☐ 6MP ☐ MTX ☐ Folic acid ☐ Other

Dose optimised
☐ Yes ☐ No ☐ NA

Thiopurine metabolites checked?
☐ Yes ☐ No ☐ NA
If yes,
Date (DD/MMM/YYY) _____
6 TGN result _____
MMP result _____
Was allopurinol used? ☐ Yes ☐ No ☐ NA

Page | 5 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

BASELINE CONDITIONS
☐ Aphthous ulcers
☐ Uveitis
☐ Scleritis or episcleritis
☐ Erythema nodosum
☐ Arthritis
☐ Anaemia
☐ Pyoderma gangrenosum
☐ PSC

CURRENT SYMPTOMS
☐ Breathlessness
☐ Joint pains
☐ Chest pains
☐ Rashes
☐ Headaches
☐ Infections that need treatment with antibiotics
☐ Infections that did not need antibiotics
☐ Pins and needles/tingling sensation
☐ Other, please specify

Page | 6 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

EXAMINATION
Ht _____ (in cm)
Wt _____ (in kg)
HR _____ BP _____ Temp _____ RR _____ Sats _____

Document physical exam here

Any abnormalities?
_____
_____
_____
_____

Page | 7 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

SCREENING RESULTS

CXR date (DD/MMM/YYYY) _____
Abnormalities?
☐ Yes ☐ No
If yes, please comment
_____
_____

Quantiferon TB Gold date (DD/MMM/YYYY) _____
☐ Positive ☐ Negative
If positive, please comment
If not done, why?
_____
_____

Hep B surface Ag date (DD/MMM/YYYY) _____
☐ Positive ☐ Negative
If positive, please comment
If not done, why?
_____
_____

Hep C IgG date (DD/MMM/YYYY) _____
☐ Positive ☐ Negative
If positive, please comment
If not done, why?
_____
_____

VZV IgG antibody level date (DD/MMM/YYYY) _____
Level >100mIU/ml
☐ Yes ☐ No
If no, please comment
_____
_____

If not done, why?
_____
_____

Page | 8 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

BLOOD SAMPLES COLLECTED?
☐ Yes ☐ No

STOOL SAMPLE COLLECTED?
☐ Yes ☐ No

SB2 INFUSION DETAILS

Was SB2 administered?
☐ Yes ☐ No
Date (DD/MMM/YYYY) _____

Dose
☐ 5mg/kg ☐ 10mg/kg ☐ Other

Infusion rate
☐ Over 30 mins ☐ Over 60 mins ☐ Over 120 mins

Pre-med? ☐ No
☐ Hydrocortisone ☐ Piriton

Any infusion reactions?
☐ Yes ☐ No
If yes, please complete AE log

Page | 9 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

ROUTINE HEALTHCARE UTILISATION SINCE LAST VISIT?
☐ Yes ☐ No
If yes, details? (Please refer to HRU form)
_____
_____
_____
_____
_____

ADVERSE EVENTS
☐ Yes ☐ No
If yes, complete AE log

CONCOMITANT MEDICATION
☐ Yes ☐ No
If yes, complete con med log

Page | 10 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

iBiSS

IBD Biosimilar to Biosimilar Infliximab Switching Study

Case Report Form

Visit 2/Week 6

Participant ID here

iBiSS 01_ _ _

Lower GI Research Team
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

Page | 11 6 weekly paper CRF V3.0 18092018

iBiSS IBD Biosimilar to Biosimilar Infliximab Switching Study

VISIT 2/WEEK 6
_____

PATIENT ID LABEL HERE

PARTICIPANT ID INITIALS iBiSS01_ _ _ _ _ /_ _/_ _

ANY NEW CONCOMITANT MEDICATION
☐ Yes ☐ No
If yes, complete con med log

ANY NEW ADVERSE EVENTS
☐ Yes ☐ No
If yes, complete AE log

EXAMINATION
Ht _____ (in cm)
Wt _____ (in kg)
HR _____ BP _____ Temp _____ RR _____ Sats _____

Was a physical exam carried out? ☐ Yes ☐ No
Document physical exam here

Any abnormalities?
_____
_____
_____
_____

BLOOD SAMPLES COLLECTED?
☐ Yes ☐ No

SB2 INFUSION DETAILS

Was SB2 administered?
☐ Yes ☐ No
Date (DD/MMM/YYYY) _____

Dose
☐ 5mg/kg ☐ 10mg/kg ☐ Other

Infusion rate
☐ Over 30 mins ☐ Over 60 mins ☐ Over 120 mins

Pre-med? ☐ No
☐ Hydrocortisone ☐ Piriton

Any infusion reactions?
☐ Yes ☐ No
If yes, please complete AE log

Page | 12 6 weekly paper CRF V3.0 18092018

iBiSS

IBD Biosimilar to Biosimilar Infliximab Switching Study

Case Report Form

Visit 3/Week 18

Participant ID here

iBiSS 01_ _ _

Lower GI Research Team
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

VISIT 3/WEEK 18

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01_ _ _
INITIALS _ /_ /_ _

ANY NEW CONCOMITANT MEDICATION
☐ Yes ☐ No
If yes, complete con med log

ANY NEW ADVERSE EVENTS
☐ Yes ☐ No
If yes, complete AE log

EXAMINATION
Ht _____ (in cm)
Wt _____ (in kg)
HR BP Temp RR Sats

Was a physical exam carried out? ☐ Yes ☐ No
Document physical exam here

Any abnormalities?
_____
_____
_____

BLOOD SAMPLES COLLECTED?
☐ Yes ☐ No

SB2 INFUSION DETAILS
Was SB2 administered?
☐ Yes ☐ No
Date (DD/MM/YYYY) _____

Infusion rate
☐ Over 30 mins ☐ Over 60 mins ☐ Over 120 mins

Dose
☐ 5mg/kg ☐ 10mg/kg ☐ Other

Pre-med? ☐ NA
☐ Hydrocortisone ☐ Piriton

Any infusion reactions?
☐ Yes ☐ No
If yes, plea se complete AE log

iBiSS

IBD Biosimilar to Biosimilar Infliximab Switching Study

Case Report Form

Visit 4/Week 30

Participant ID here

iBiSS 01_ _ _

Lower GI Research Team
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

VISIT 4/WEEK 30

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01_ _ _
INITIALS _ /_ /_ _

ANY NEW CONCOMITANT MEDICATION
☐ Yes ☐ No
If yes, complete con med log

ANY NEW ADVERSE EVENTS
☐ Yes ☐ No
If yes, complete AE log

EXAMINATION
Ht _____ (in cm)
Wt _____ (in kg)
HR BP Temp RR Sats

Was a physical exam carried out? ☐ Yes ☐ No
Document physical exam here

Any abnormalities?
_____
_____
_____

BLOOD SAMPLES COLLECTED?
☐ Yes ☐ No

STOOL SAMPLE COLLECTED?
☐ Yes ☐ No

INFLIXIMAB INFUSION DETAILS

Was Infliximab administered?
☐ Yes ☐ No
Date

Which brand of Infliximab was used?
☐ Remicade ☐ CT-P13 ☐ SB2

Infusion rate
☐ Over 30 mins ☐ Over 60 mins ☐ Over 120 mins

(intentionally blank)

iBiSS

IBD Biosimilar to Biosimilar Infliximab Switching Study

Case Report Form

Visit 5/Week 54

Participant ID here

iBiSS 01_ _ _

Lower GI Research Team
Southampton General Hospital
Tremona Road
Southampton SO16 6YD

VISIT 5/WEEK 54

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01_ _ _
INITIALS _ /_ /_ _

ANY NEW CONCOMITANT MEDICATION
☐ Yes ☐ No
If yes, complete con med log

EXAMINATION
Ht _____ (in cm)
Wt _____ (in kg)
HR BP Temp RR Sats

Was a physical exam carried out? ☐ Yes ☐ No
Document physical exam here

Any abnormalities?
_____
_____
_____

BLOOD SAMPLES COLLECTED?
☐ Yes ☐ No

STOOL SAMPLE COLLECTED?
☐ Yes ☐ No

INFLIXIMAB INFUSION DETAILS

Was Infliximab administered?
☐ Yes ☐ No
Date

Which brand of Infliximab was used?
☐ Remicade ☐ CT-P13 ☐ SB2

Infusion rate
☐ Over 30 mins ☐ Over 60 mins ☐ Over 120 mins

Appendix G Disease Activity Scores

Partial Mayo Clinic Score (pMCS)

Partial Mayo Score – for patients with UC

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01__ __ __
INITIALS __ / __ / __
DATE __ / __ / __

Dear patient,
Please enter the number of daily bowel motions you would have when in remission or before your diagnosis or symptoms of ulcerative colitis began.
This number will be your **normal**.

Then please complete questions 1 & 2 only.

1. Stool frequency (based on the past 3 days)

Normal number of stools	0
1-2 stools more than normal	1
3-4 stools more than normal	2
5 or more stools more than normal	3

2. Rectal bleeding (based on the past 3 days)

No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood with stool most of the time	2
Blood alone passed	3

****To be completed by medical team****

3. Physician's Global Assessment (PGA)

Normal (sub-scores are mostly 0)	0
Mild disease (sub-scores are mostly 1)	1
Moderate disease (sub-scores are mostly 1 to 2)	2
Severe disease (sub-scores are mostly 2 to 3)	3

TOTAL SCORE | |

Modified Harvey Bradshaw Index

Modified Harvey-Bradshaw Index
For patients with Crohn's Disease

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01__ __ __
INITIALS __ / __ / __
DATE __ / __ / __

Dear Patient,
Please complete questions 1, 2 & 3 and base your answers on how you felt yesterday.

1. **General well-being**

Very well	0	
Slightly below par		1
Poor	2	
Very poor	3	
Terrible		4

2. **Abdominal Pain**

None	0
Mild	1
Moderate	2
Severe	3

3. **Number of liquid or soft stools per day (yesterda** ☐

****To be completed by medical team****

4. **Additional manifestations**

None	0	
Arthralgia	1	
Uveitis	1	
Erythema nodosum	1	
Aphthous ulcer		1
Pyoderma gangrenosum		1
Anal fissure	1	
New fistula	1	
Abscess		1

TOTAL SCORE ☐

General Well-being Descriptors

General well being includes fatigue in the overall rating and how you feel today.
Record the worst you have felt today.
Compare yourself to someone else of your age, how would they rank their general wellbeing?

Below are some descriptors to help you rank your category of general well being.

- Very Well: General health is not generally a problem. You're feeling very good or great and under control.
- Slightly Below Par: You're getting through things but feeling below par and not normal. Something overall is preventing you from saying "I feel wonderful". You're feeling good but not great. You can work, socialize, and function on a day to day basis.
- Poor: Your symptoms bother you. You occasionally miss work, school, or social activities. You have some embarrassing moments with faecal incontinence. You have diarrhoea, abdominal pain, fatigue, and basically just feeling unwell, but you are still able to function. You're getting through the day, doing all your normal stuff but it is a struggle.
- Very Poor: You're getting through a part of the day, but can't do your normal stuff. You can't attend social events in evening. You sometime leave home from work early. You feel pretty bad and are not doing much activity – only those absolutely necessary. Your symptoms interfere with life considerably, you don't go out or are fearful when out, you miss a lot of school or work. Faecal incontinence happens several times per week.
- Terrible: You're unable to function. You can't manage the basics and you're almost bedridden. This is the worse you have ever been. You're not working.

Abdominal Pain Descriptors

Abdominal pain may include cramping and discomfort.
It does not have to be just "pain" as we know it.

Below are some descriptors to help you rank your category of abdominal pain.

- Mild: You're aware that the abdominal pain is there but it does not interfere with your life and you continue with activities such as work and pleasure. You feel and hear rumbles, gurgles and cramps.
- Moderate: You're aware of your abdominal pain and must alter your activities to manage the pain (i.e. lie down to rest, postpone shopping trips until later, and take pain killers).
The pain interferes with your life and daily activities.
You may have to miss work or pleasure activities on occasion.
- Severe: Your abdominal pain causes you to stop all activity. You are frequently in bed because of the pain, you call in sick to work and cancel all activities.

Appendix H IBD Control PROM

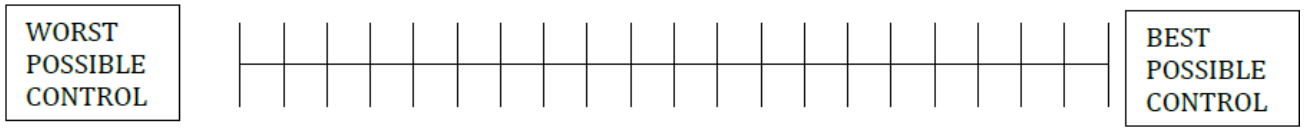
IBD Control PROM – for all patients
Inflammatory Bowel Disease Control Questionnaire

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01__ __ __
INITIALS __ / __ / __
DATE __ / __ / __

	Yes	No	Not sure
1. Do you believe that: **a.** Your IBD has been well controlled in the past two weeks? **b.** Your current treatment is useful in controlling your IBD? (if you are not taking any treatment, please tick this box)			
	Better	**No change**	**Worse**
2. Over the past two weeks, have your bowel symptoms been getting worse, getting betters or not changed?			
	Yes	**No**	**Not sure**
3. In the past two weeks, did you: **a.** Miss any planned activities because of IBD? (e.g. attending school/college, going to work or a social event **b.** Wake up at night because of symptoms of IBD? **c.** Suffer from significant pain or discomfort? **d.** Often feel lacking in energy (fatigued)? (by 'often' we mean more than half the time) **e.** Feel anxious or depressed because of your IBD? **f.** Think you needed in a change in your treatment?			
	Yes	**No**	**Not sure**
4. At your next clinic visit, would you like to discuss: **a.** Alternative types of drug for controlling IBD **b.** Ways to adjust your own treatment **c.** Side effects or difficulties with using your medicines **d.** New symptoms that have developed since your last visit			

5. How would you rate the OVERALL control of your IBD in the past two weeks?
(Please draw a vertical line on the scale below)



Appendix I Illness Perception Questionnaire-Revised (IPQ-R)

Illness Perception Questionnaire (IPQ-R)

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01__ __ __
INITIALS __ / __ / __
DATE __ / __ / __

Your views about your illness

Listed below are a number of symptoms that you may or may not have experienced since your illness. Please indicate by circling *yes* or *no* whether you have experienced any of these symptoms since your illness and whether you believe that these symptoms are related to your illness.

	I have experienced this symptom ***since*** my illness		This symptom is ***related to my illness***	
Pain	Yes	No	Yes	No
Sore throat	Yes	No	Yes	No
Nausea	Yes	No	Yes	No
Breathlessness	Yes	No	Yes	No
Weight loss	Yes	No	Yes	No
Fatigue	Yes	No	Yes	No
Stiff joints	Yes	No	Yes	No
Sore eyes	Yes	No	Yes	No
Wheeziness	Yes	No	Yes	No
Headaches	Yes	No	Yes	No
Upset stomach	Yes	No	Yes	No
Sleep difficulties	Yes	No	Yes	No
Dizziness	Yes	No	Yes	No
Loss of strength	Yes	No	Yes	No

We are interested in your own personal views of how you now see your current illness.

Please indicate how much you agree or disagree with the following statements about your illness by ticking the appropriate box

Views about your illness	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1.My illness will last a short time					
2.My illness is likely to be permanent rather than temporary					
3.My illness will last a long time					
4.This illness will past quickly					
5.I expect to have this illness for the rest of my life					

6.My illness is a serious condition					
7.My illness has major consequences on my life					
8.My illness does not have much effect on my life					
9.My illness strongly affects the way others see me					
10.My illness has serious financial consequences					
11.My illness causes difficulties for those who are close to me					
12.There is a lot which I can do to control my symptoms					
13.What I do can determine whether my illness gets better or worse					
14.The course of my illness depends on me					
15.Nothing I do will affect my illness					
16.I have the power to influence my illness					
17.My actions will have no affect on the outcome of my illness					
18.My illness will improve with time					
19. There is very little that can be done to improve my illness					
20.My treatment will be effective in curing my illness					
21.The negative effects of my illness can be prevented (avoided) by my treatment					
22.My treatment can control my illness					
23.There is nothing which can help my condition					
24.The symptoms of my condition are puzzling to me					
25.My illness is a mystery to me					
26.I don’t understand my illness					
27.My illness doesn’t make any sense to me					
28.I have a clear picture or understanding of my condition					
29.The symptoms of my illness change a great deal from day to day					
30.My symptoms come and go in cycles					
31.My illness is very unpredictable					
32.I go through cycles in which my illness gets better and worse					
33.I get depressed when I think about my illness					
34.When I think about my illness I get upset					
35.My illness makes me feel angry					
36.My illness does not worry me					
37.Having this illness makes me feel					

anxious					
38.My illness makes me feels afraid					

Your views on the causes of your illness

We are interested in what ***you*** consider may have been the cause of your illness. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your illness rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your illness. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

Possible causes	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1.Stress or worry					
2.Hereditary – it runs in my family					
3.A germ or virus					
4.Diet or eating habits					
5.Chance or bad luck					
6.Poor medical care in my past					
7.Pollution in the environment					
8.My own behaviour					
9.My mental attitude e.g. thinking about life negatively					
10.Family problems or worries caused my illness					
11.Overwork					
12.My emotional state e.g. feeling down, lonely, anxious, empty					
13.Ageing					
14.Alcohol					
15.Smoking					
16. Accident or injury					
17.My personality					
18.Altered immunity					

In the table below, please list in rank-order the three most important factors that you now believe caused your illness. You may use any of the items from the box above or you may have additional ideas of your own.

The most important causes for me:

1. _____

2. _____

_____

Appendix J Treatment Satisfaction Questionnaire for Medication

Treatment Satisfaction Questionnaire for Medication (TSQM)

PATIENT ID LABEL HERE

PARTICIPANT ID iBiSS01__ __ __
INITIALS __ / __ / __
DATE __ / __ / __

Instructions:
Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking. We are interested in your evaluation of the effectiveness, side effects and convenience of the medication over the last two to three weeks, or since you last used it. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
   - Extremely dissatisfied
   - Very dissatisfied
   - Dissatisfied
   - Somewhat satisfied
   - Satisfied
   - Very satisfied
   - Extremely satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
   - Extremely dissatisfied
   - Very dissatisfied
   - Dissatisfied
   - Somewhat satisfied
   - Satisfied
   - Very satisfied
   - Extremely satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
   - Extremely dissatisfied
   - Very dissatisfied
   - Dissatisfied
   - Somewhat satisfied
   - Satisfied
   - Very satisfied
   - Extremely satisfied

4. As a result of taking this medication, do you experience any side effects at all?
   - Yes
   - No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?
    Extremely bothersome
    Very bothersome
    Somewhat bothersome
    A little bothersome
    Not at all bothersome

6. To what extent do the side effects interfere with your **physical** health and ability to function (i.e. strength, energy levels etc)?
    A great deal
    Quite a bit
    Somewhat
    Minimally
    Not at all

7. To what extent do the side effects interfere with your **mental** function (i.e. ability to think clearly, stay awake etc)?
    A great deal
    Quite a bit
    Somewhat
    Minimally
    Not at all

8. To what degree have medication side effects affected your overall satisfaction with the medication?
    A great deal
    Quite a bit
    Somewhat
    Minimally
    Not at all

9. How easy or difficult is it to use the medication in its current form?
    Extremely difficult
    Very difficult
    Difficult
    Somewhat easy
    Easy
    Very easy
    Extremely easy

10. How easy or difficult is it to plan when you will use the medication each time?
    Extremely difficult
    Very difficult
    Difficult
    Somewhat easy
    Easy
    Very easy
    Extremely easy

11. How convenient or inconvenient it is to take the medication as instructed?
    Extremely inconvenient
    Very inconvenient
    Inconvenient

Somewhat convenient
Convenient
Very convenient
Extremely convenient

12. Overall, how confident are you taking this medication is a good thing for you?
    Not at all confident
    A little confident
    Somewhat confident
    Very confident
    Extremely confident

13. How certain are you that the good things about your medication outweigh the bad things?
    Not at all certain
    A little certain
    Somewhat certain
    Very certain
    Extremely certain

14. Taking all things in to account, how satisfied or dissatisfied are you with this medication?
    Extremely dissatisfied
    Very dissatisfied
    Dissatisfied
    Somewhat satisfied
    Satisfied
    Very satisfied
    Extremely satisfied

Appendix K Adverse Event (AE) Log

iBiSS AE log

No.	Description	Start date (DD/MM/YYYY)	Stop date (DD/MM/YYYY)	Severity	Causality	Action taken with IMP	Other action taken	Serious	Expected? (Yes/No)	Infusion reaction?

Severity
Mild
Moderate
Severe
Life threatening
Fatal

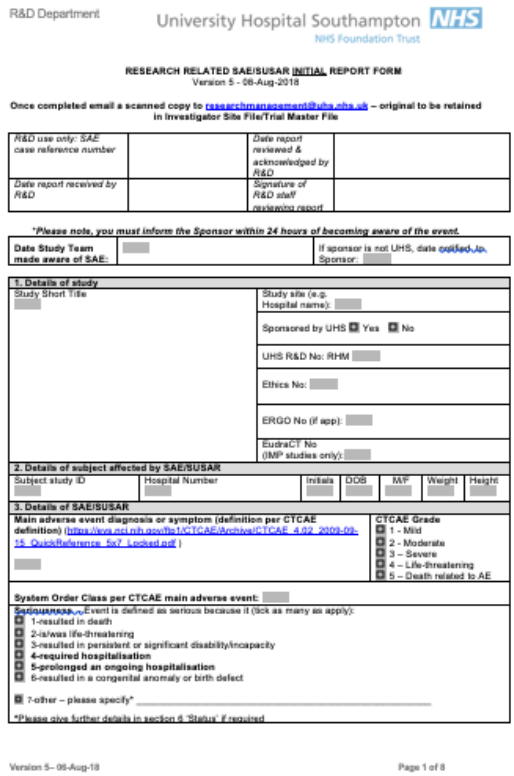
Causality
Not related
Unlikely
Possible
Probable
Definitely

Action taken with IMP
IP unchanged
IP interrupted
IP stopped

Other action taken
None
Medication given (please log in con meds)
Hospitalisation or prolongation of hospitalisation
Therapeutic or diagnostic procedure

Appendix L Serious Adverse Event (SAE) reports

SAE Report Form and Follow-up Report Form



R&D Department University Hospital Southampton NHS NHS Foundation Trust

RESEARCH RELATED SAE/SUSAR INITIAL REPORT FORM
Version 5 - 06-Aug-2018

Once completed email a scanned copy to researchmanagement@uhs.nhs.uk – original to be retained in Investigator Site File/Trial Master File

R&D use only: SAE case reference number		*Date report reviewed & acknowledged by R&D*	
Date report received by R&D		*Signature of R&D staff reviewing report*	

Please note, you must inform the Sponsor within 24 hours of becoming aware of the event.

Date Study Team made aware of SAE:	If sponsor is not UHS, date notified to Sponsor:

1. Details of study

Study Short Title	Study site (e.g. Hospital name):
	Sponsored by UHS ☐ Yes ☐ No
	UHS R&D No: RHM
	Ethics No:
	ERGO No (if app):
	EudraCT No (IMP studies only):

2. Details of subject affected by SAE/SUSAR

Subject study ID	Hospital Number	Initials	DOB	M/F	Weight	Height

3. Details of SAE/SUSAR

Main adverse event diagnosis or symptom (definition per CTCAE definition) (https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_5x7_Locked.pdf)

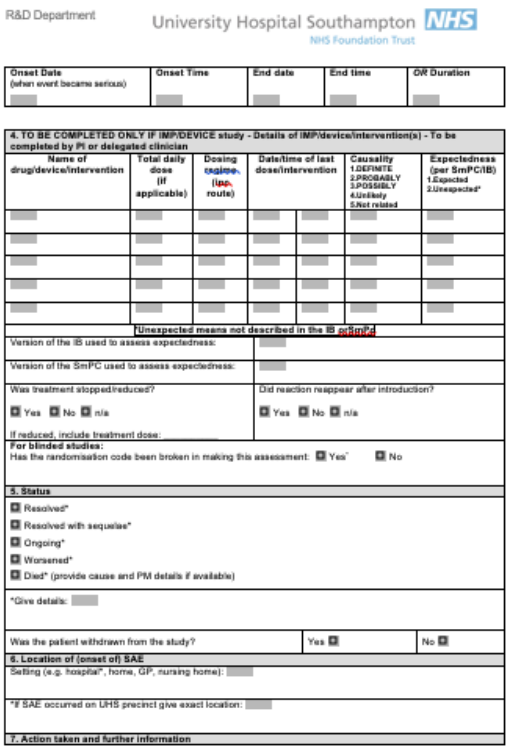
CTCAE Grade
☐ 1 - Mild
☐ 2 - Moderate
☐ 3 – Severe
☐ 4 – Life-threatening
☐ 5 – Death related to AE

System Order Class per CTCAE main adverse event:

Seriousness – Event is defined as serious because it (tick as many as apply):
☐ 1-resulted in death
☐ 2-is/was life-threatening
☐ 3-resulted in persistent or significant disability/incapacity
☐ **4-required hospitalisation**
☐ **5-prolonged an ongoing hospitalisation**
☐ 6-resulted in a congenital anomaly or birth defect

☐ 7-other – please specify* _____

*Please give further details in section 6 'Status' if required



R&D Department University Hospital Southampton NHS NHS Foundation Trust

Onset Date (when event became serious)	Onset Time	End date	End time	OR Duration

4. TO BE COMPLETED ONLY IF IMP/DEVICE study - Details of IMP/device/intervention(s) - To be completed by PI or delegated clinician

Name of drug/device/intervention	Total daily dose (if applicable)	Dosing regime (inc. route)	Date/time of last dose/intervention		Causality 1.DEFINITE 2.PROBABLY 3.POSSIBLY 4.Unlikely 5.Not related	Expectedness (per SmPC/IB) 1.Expected 2.Unexpected*

*Unexpected means not described in the IB or SmPC

Version of the IB used to assess expectedness:	
Version of the SmPC used to assess expectedness:	
Was treatment stopped/reduced? ☐ Yes ☐ No ☐ n/a	Did reaction reappear after introduction? ☐ Yes ☐ No ☐ n/a
If reduced, include treatment dose:	

For blinded studies:
Has the randomisation code been broken in making this assessment: ☐ Yes* ☐ No

5. Status

☐ Resolved*
☐ Resolved with sequelae*
☐ Ongoing*
☐ Worsened*
☐ Died* (provide cause and PM details if available)

*Give details:

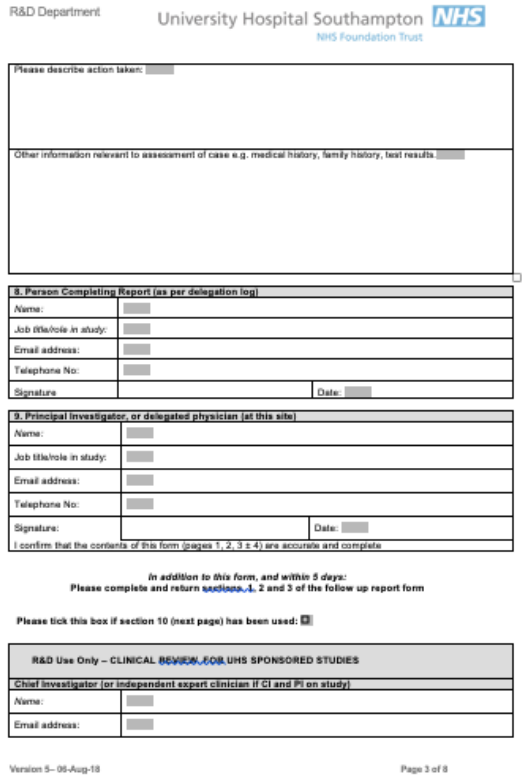
Was the patient withdrawn from the study?	Yes ☐	No ☐

6. Location of (onset of) SAE

Setting (e.g. hospital*, home, GP, nursing home):

*If SAE occurred on UHS precinct give exact location:

7. Action taken and further information



R&D Department University Hospital Southampton NHS NHS Foundation Trust

Please describe action taken:

Other information relevant to assessment of case e.g. medical history, family history, test results:

8. Person Completing Report (as per delegation log)

Name:	
Job title/role in study:	
Email address:	
Telephone No:	
Signature	Date:

9. Principal Investigator, or delegated physician (at this site)

Name:	
Job title/role in study:	
Email address:	
Telephone No:	
Signature:	Date:

I confirm that the contents of this form (pages 1, 2, 3 ± 4) are accurate and complete

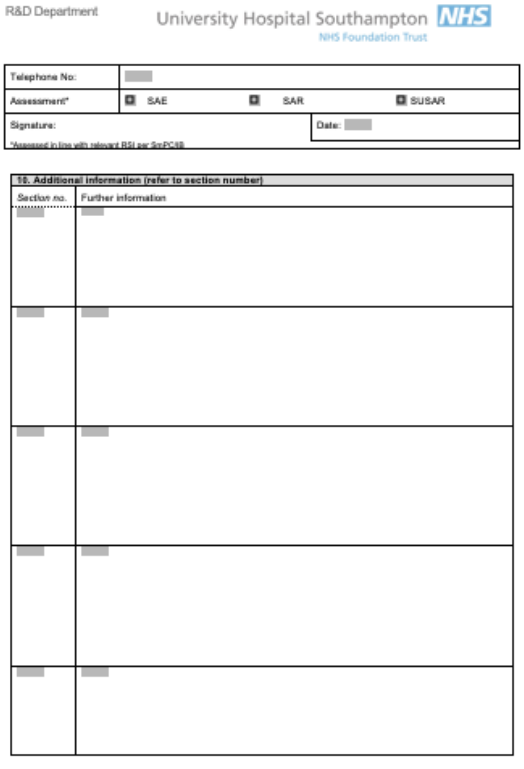
In addition to this form, and within 5 days:
Please complete and return sections 1, 2 and 3 of the follow up report form

Please tick this box if section 10 (next page) has been used: ☐

R&D Use Only – CLINICAL REVIEW FOR UHS SPONSORED STUDIES

Chief Investigator (or independent expert clinician if CI and PI on study)

Name:	
Email address:	



R&D Department University Hospital Southampton NHS NHS Foundation Trust

Telephone No:			
Assessment*	☐ SAE	☐ SAR	☐ SUSAR
Signature:		Date:	

*Assessed in line with relevant RSI per SmPC/IB

10. Additional information (refer to section number)

Section no.	Further information

RESEARCH RELATED SAE/SUSAR FOLLOW UP REPORT FORM
Version 4 11-Aug-2017

Once completed email a scanned copy to researchmanagement@uhs.nhs.uk – original to be retained in Investigator Site File/Trial Master File

R&D use only: SAE case reference number		*Date follow-up report reviewed by R&D*	
Date follow-up report received by R&D		*Signature of R&D person*	

To be completed by the person filling in the SAE form					
UHS R&D No.	RHM	Subject ID/Initials		Onset date of SAE	

1. Further details of SAE/SUSAR					
Further details of event/reaction, including body site, reported signs and symptoms and diagnosis where possible:					
CTCAE Grade	☐ 1 - Mild	☐ 2 - Moderate	☐ 3 – Severe	☐ 4 – Life-threatening	☐ 5 – Death related to AE

	End date	**End time**	**OR Duration**

2. Status

☐ Resolved*
☐ Resolved with sequelae*
☐ Ongoing*
☐ Worsened*
☐ Died* (provide cause and PM details if available)

*Give details:

Was the patient withdrawn from the study?	Yes ☐	No ☐

3. Additional action taken and further information since initial report

Please describe further action taken:
Further information or missing data relevant to assessment of case e.g. medical history, family history, test results:

8. Person Completing Report (as per delegation log)		
Name:		
Job title/role in study:		
Email address:		
Telephone No:		
Signature		Date:

9. Principal Investigator, or delegated physician (at this site)		
Name:		
Job title/role in study:		
Email address:		
Telephone No:		
Signature:		Date:
I confirm that the contents of this form (pages 1, 2, 3 & 4) are accurate and complete		

To be completed by the person filling in the SAE form (as per delegation log)					
UHS R&D number:		Subject ID/initials		Onset date of SAE	

Sheet number: _____ **of** _____

4. CONCOMITANT MEDICATION – details of administration of other medication concurrent with the IMP(s)/device/intervention.

Brand name:	Indication	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	Or duration of treatment

Continue on new sheet if necessary: please identify how many sheets have been used.

Name of person completing report: _____ **Role on Study:** _____

Signature of person making report: _____ **Date:** ___/___/____

To be completed by the person filling in the SAE form (as per delegation log)					
UHS R&D number:		Subject ID/initials		Onset date of SAE	

Sheet number: _____ **of** _____

5. STUDY IMP – details of administration. **NB complete for IMP studies only**

Brand name:	Indication	Batch no.	Route (e.g. oral)	Form (e.g. tablet)	Total dose/24h (specify units)	Regimen (e.g. BD)	Start date & time	Stop date & time	Or duration of treatment

For blinded studies, was the randomisation code broken?	☐	*Yes	☐	No
*If yes, give details:				

Continue on new sheet if necessary: please identify how many sheets have been used.

Name of person completing report: _____ **Role on Study:** _____

Signature of person making report: _____ **Date:** ___/___/____

Appendix M Drug levels, immunogenicity and cytokine profiles

Description of method used at the University of Lisbon by Professor Gonçalves and his team

Infliximab serum concentrations were measured using an in-house enzyme-linked immunosorbent assay (ELISA). The limit of detection was 0.014 mg/L, and the lower limit of quantification was 0.04mg/L. Serum concentrations of antibodies to infliximab (ATI) were analysed using a bridging ELISA with acidic treatment, which was also capable of detecting anti-drug antibodies (ADA) in the presence of the drug. Infliximab (0.5 mg/mL) was added to ELISA plates (Nunc, Denmark). Serum was added and incubated for 60 minutes at room temperature. After washing, the plates were incubated with biotin-labeled infliximab for one hour at room temperature followed by addition of streptavidin-HRP (Thermo Scientific, USA)(162). The reaction was developed with TMB (Thermo Scientific, USA) substrate and stopped with 2M H_2SO_4. Absorbances were read at 450/540nm and the results were expressed as µg/ml after normalisation using a standard curve of mouse anti-human antibody (Abcam, UK). The assay's cut-off level for detection of anti-Remicade antibodies was 1µg/mL.

Sera samples containing ADAs for infliximab were compared for the presence of IgG1, IgG2, IgG3 and IgG4. The levels of these antibodies for each subclass were assessed using an adapted ELISA(163). In this assay, pre-coated plates with the anti-IgG4 antibody (Thermo Scientific, USA) were incubated with 1/10 diluted ADA. After washing, plates were similarly incubated with biotin-labeled infliximab for one hour at room temperature followed by addition of streptavidin-HRP. The reaction was developed with TMB substrate and stopped with 2M H_2SO_4. Absorbances were registered at 450/540nm, and the results were

expressed as µg/ml after normalisation using a standard curve of mouse anti-human antibody.

For cytokine analysis samples were thawed upon receipt, centrifuged and the plasma samples were prepared in to aliquots of 70 to 125µl that were refrozen at −80°C until testing. Thus, all samples had the same freeze-thaw history at the time of testing in each laboratory. A Luminex/Bio-Plex instrument was used ∂that was validated using a Bio-Plex validation kit within two weeks of each assay and calibrated on assay days using a Bio-Plex or Luminex validation kit. Each assay was performed strictly according to the manufacturer's protocol for serum or plasma samples, utilising recommended sample dilutions and standard curve concentrations, with all samples and standards assayed in duplicate. For Luminex assays, thawed aliquots were gently vortexed and then centrifuged at 13,200rpm for ten minutes at 4°C immediately prior to testing. Luminex data were analysed using Bio-Plex Manager software version 4.1 (Bio-Rad).

Appendix N Standards for Reporting Qualitative Research (SRQR)

Title and abstract	Page/line no(s)
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	

Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	
Purpose or research question - Purpose of the study and specific objectives or questions	

Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	
Context - Setting/site and salient contextual factors; rationale**	
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	

Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	
Limitations - Trustworthiness and limitations of findings	

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Appendix O Topic guides

TOPIC GUIDE FOR INTERVIEW TO EXPLORE THE SWITCHING EXPERIENCE FROM CT-P13 TO SB2 IN PATIENTS WITH ULCERATIVE COLITIS (UC) OR CROHN'S DISEASE (CD)

Introduction:
Re-confirm consent to participate (written consent will have been obtained on recruitment)

Explain role of interviewer:
"My role here is as a research student. My background is that I am a specialist doctor in gastroenterology with experience in inflammatory bowel disease. I am frequently involved in the medical care of patients with IBD and prescribing medications such as infliximab.

However, my role today is to understand *your* experience of this situation - having your medication switched. It is important for you to understand that there are no right or wrong answers and I am purely interested in your thoughts and views. All your responses will remain anonymised and have no bearing on your ongoing clinical care."

Confirm consent to audio record and turn on audio recorder.
"I may take occasional notes to remind myself to ask you something instead of interrupting you."

Questions:
Can you tell me your thoughts on the information that was provided to you regarding this planned switch of your infusion and how this was discussed with you?
If not volunteered – specifically probe about;
- How information was communicated?
- Clarity of information?
- Timing?
- What worked well?
- Were there any major problems?
- How could we improve this process?
- Did it matter to you who gave you the information?

Were you given the opportunity to discuss this? Was this important to you?

Have you previously been involved in a switch from one type of infliximab to another? Can you tell me your experience of that?
If not volunteered – specifically probe about;
- How this switch related to the first experience of switching to a biosimilar?
- Would you have liked further information since you first switched?
- In what format and why?
- Was it easier to switch this time given you have had previous experience? Or conversely, was it harder because of your previous experience?
- What aspects of the previous switch made you willing to switch again this time?

What is your understanding of 'biosimilars'?

Do you have any concerns about this switch?
If not volunteered –

- Specifically probe about safety, efficacy.
- Any concerns about disease flares following the switch if currently in remission?

Do you see/have you experienced any major positive benefits to this switch?

If there is a cost saving from switching do you have any strong views on where this should be invested in the NHS?

Given your experience over the last 3-4 months, what would your views be on being asked to switch your medication again in the future?

Of all the information that you were given, which parts do you think would be most useful for other patients who are being asked to switch medicines in usual clinical practice in the future when they are NOT part of a research trial?

Ending
Is there anything else you would like to tell me today?
Turn off recorder.
Thank you.

TOPIC GUIDE FOR SUBJECTS WHO DISCONTINUED EARLY DURING THE TRIAL PERIOD DUE TO PATIENT CHOICE

Introduction:
Re-confirm consent to participate (written consent will have been obtained on recruitment)

Explain role of interviewer:
"My role here is as a research student. My background is that I am a specialist doctor in gastroenterology with experience in inflammatory bowel disease. I am frequently involved in the medical care of patients with IBD and prescribing medications such as infliximab.

However, my role today is to understand *your* experience of this situation - having your medication switched. I would particularly like to focus on the reasons why the medication was stopped and your views about this. It is important for you to understand that there are no right or wrong answers and I am purely interested in your thoughts and views. All your responses will remain anonymised and have no bearing on your ongoing clinical care."

Confirm consent to audio record and turn on audio recorder.
"I may take occasional notes to remind myself to ask you something instead of interrupting you."

Questions:
Can you tell me your thoughts on the information that was provided to you regarding this planned switch of your infusion and how this was discussed with you?
If not volunteered – specifically probe about;
- How information was communicated?
- Clarity of information?
- Timing?
- What worked well?
- Were there any major problems?
- How could we improve this process?

Were you given the opportunity to discuss this? Was this important to you?

What is your understanding of 'biosimilars'?

What were your reasons for wanting to stop this particular medication?
If not volunteered –
- Probe about side effects, relapse of disease?
- Ask about severity of these and effects on day to day life.
- Do you attribute these changes to the new infusion? Could there be any other causes?
- Do you see stopping this medication as the only option?

Have you had similar problems previously with biologic medication used for IBD? Can you tell me your experiences of this?

Have you previously been involved in a switch from one type of infliximab to another? Can you tell me your experience of that?
If not volunteered – specifically probe about;
- Was your experience good or bad?
- How did this switch relate to the first experience of switching to a biosimilar?
- Was it easier to switch this time given you have had previous experience? Or conversely, was it harder because of your previous experience?

- What aspects of the previous switch made you willing to switch again this time?

Did you have any concerns prior to the switch? Did you discuss these with anyone? Were they acknowledged?
If not volunteered –
- Specifically probe about safety, efficacy.
- Any concerns about disease flares following the switch if they were in remission at the time of the switch?

Did you predict that this may happen and that you may have to stop the medication?

Have there been any positive aspects to this switch for you?

Given your experience over the last 3-4 months, what would your views be on being asked to switch your medication again in the future?
If subjects states that they would be unwilling based on this experience – **Is there anything that would help you to reconsider this? If so, what? Can you explain a bit more for me?**
Consider things such;
- Further information/reassurance.
- By whom?
- At what time point in the process?
- In what format?

Of all the information that you were given, which parts do you think would be most useful for other patients who are being asked to switch medicines in usual clinical practice in the future when they are NOT part of a research trial?

Ending
Is there anything else you would like to tell me today?
Turn off recorder.
Thank you.

TOPIC GUIDE FOR SUBJECTS WHO DECLINED TO TAKE PART IN THE SWITCH FROM CTP-13 TO SB2 FROM THE OUTSET DUE TO THEIR OWN CHOICE

Introduction:
Re-confirm consent to participate.

Explain role of interviewer:
"My role here is as a research student. My background is that I am a specialist doctor in gastroenterology with experience in inflammatory bowel disease. I am frequently involved in the medical care of patients with IBD and prescribing medications such as infliximab.

However, my role today is to understand *your* experience of this situation. I would particularly like to focus on your reasons for not wanting to take part in the switch from one brand of Infliximab to the other. It is important for you to understand that there are no right or wrong answers and I am purely interested in your thoughts and views. All your responses will remain anonymised and have no bearing on your ongoing clinical care."

Confirm consent to audio record and turn on audio recorder.
"I may take occasional notes to remind myself to ask you something instead of interrupting you."

Questions:
Can you tell me your thoughts on the information that was provided to you regarding the planned switch from one brand of Infliximab to the other and how this was discussed with you?
If not volunteered – specifically probe about;
- How information was communicated?
- Clarity of information?
- Timing?
- What worked well?
- Were there any major problems?
- How could we improve this process?

Were you given the opportunity to discuss this? Was this important to you?

What is your understanding of 'biosimilars'?

What were your reasons for not wanting to take part in the switch?
If not volunteered –
- Probe about side effects, safety, efficacy, concerns about relapse?

Did your current clinical status influence your decision to remain on CTP-13?

Have you previously been involved in a switch from one type of infliximab to another? Can you tell me your experience of that?
If not volunteered – specifically probe about;
- Was your experience good or bad?
- Did your previous experience affect your decision to not swap this time?

In the future, it is likely that you will be asked to switch to SB2 as part of routine NHS care. Can you tell me your thoughts about that?

At the time the switch was first discussed with you was there anything that we could have said or done for you to reconsider this? If so, what? Can you explain a bit more for me?

Consider things such;

- Further information/reassurance.
- By whom?
- At what time point in the process?
- In what format?

Ending

Is there anything else you would like to tell me today?
Turn off recorder.
Thank you.

List of References

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54.e42; quiz e30.

2. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389(10080):1756-70.

3. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017;389(10080):1741-55.

4. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012;380(9853):1606-19.

5. Tremaine WJ. Review article: Indeterminate colitis--definition, diagnosis and management. Aliment Pharmacol Ther. 2007;25(1):13-7.

6. Burisch J, Jess T, Martinato M, Lakatos PL, -EpiCom E. The burden of inflammatory bowel disease in Europe. J Crohns Colitis. 2013;7(4):322-37.

7. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427-34.

8. Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature. 2011;474(7351):298-306.

9. Choy MC, Visvanathan K, De Cruz P. An Overview of the Innate and Adaptive Immune System in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(1):2-13.

10. Romagnani S. Lymphokine production by human T cells in disease states. Annu Rev Immunol. 1994;12:227-57.

11. Di Sabatino A, Biancheri P, Rovedatti L, MacDonald TT, Corazza GR. New pathogenic paradigms in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(2):368-71.

12. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A. 1975;72(9):3666-70.

13. Ruder B, Atreya R, Becker C. Tumour Necrosis Factor Alpha in Intestinal Homeostasis and Gut Related Diseases. Int J Mol Sci. 2019;20(8).

14. Friedrich M, Pohin M, Powrie F. Cytokine Networks in the Pathophysiology of Inflammatory Bowel Disease. Immunity. 2019;50(4):992-1006.

15. Geremia A, Biancheri P, Allan P, Corazza GR, Di Sabatino A. Innate and adaptive immunity in inflammatory bowel disease. Autoimmun Rev. 2014;13(1):3-10.

16. Spehlmann ME, Begun AZ, Burghardt J, Lepage P, Raedler A, Schreiber S. Epidemiology of inflammatory bowel disease in a German twin cohort: results of a nationwide study. Inflamm Bowel Dis. 2008;14(7):968-76.

17. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010;42(12):1118-25.

18. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 2011;43(3):246-52.

19. Kucharzik T, Maaser C, Lügering A, Kagnoff M, Mayer L, Targan S, et al. Recent understanding of IBD pathogenesis: implications for future therapies. Inflamm Bowel Dis. 2006;12(11):1068-83.

20. Bamias G, Nyce MR, De La Rue SA, Cominelli F, Physicians ACo, Society AP. New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med. 2005;143(12):895-904.

21. Yamamoto S, Ma X. Role of Nod2 in the development of Crohn's disease. Microbes Infect. 2009;11(12):912-8.

22. Shaw MH, Kamada N, Warner N, Kim YG, Nuñez G. The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. Trends Immunol. 2011;32(2):73-9.

23. Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013;62(10):1505-10.

24. Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. J Allergy Clin Immunol. 2020;145(1):16-27.

25. Jain S, Ahuja V, Limdi JK. Optimal management of acute severe ulcerative colitis. Postgrad Med J. 2019;95(1119):32-40.

26. TRUELOVE SC, WITTS LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041-8.

27. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53.

28. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.

29. van Hees PA, van Elteren PH, van Lier HJ, van Tongeren JH. An index of inflammatory activity in patients with Crohn's disease. Gut. 1980;21(4):279-86.

30. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980;1(8167):514.

31. Summers RW, Switz DM, Sessions JT, Becktel JM, Best WR, Kern F, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology. 1979;77(4 Pt 2):847-69.

32. Sostegni R, Daperno M, Scaglione N, Lavagna A, Rocca R, Pera A. Review article: Crohn's disease: monitoring disease activity. Aliment Pharmacol Ther. 2003;17 Suppl 2:11-7.

33. Lewis JD, Rutgeerts P, Feagan BG, D'haens G, Danese S, Colombel JF, et al. Correlation of Stool Frequency and Abdominal Pain Measures With Simple Endoscopic Score for Crohn's Disease. Inflamm Bowel Dis. 2020;26(2):304-13.

34. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625-9.

35. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008;14(12):1660-6.

36. Bojic D, Bodger K, Travis S. Patient Reported Outcome Measures (PROMs) in Inflammatory Bowel Disease: New Data. J Crohns Colitis. 2017;11(suppl_2):S576-S85.

37. Ket SN, Palmer R, Travis S. Endoscopic Disease Activity in Inflammatory Bowel Disease. Curr Gastroenterol Rep. 2015;17(12):50.

38. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956-63.

39. Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy. 2009;41(7):618-37.

40. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut. 2012;61(4):535-42.

41. Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. Gut. 2006;55 Suppl 1(Suppl 1):i1-15.

42. Feakins RM, Gastroenterology BSo. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. J Clin Pathol. 2013;66(12):1005-26.

43. Samuel S, Bruining DH, Loftus EV, Becker B, Fletcher JG, Mandrekar JN, et al. Endoscopic skipping of the distal terminal ileum in Crohn's disease can lead to negative results from ileocolonoscopy. Clin Gastroenterol Hepatol. 2012;10(11):1253-9.

44. Panés J, Bouzas R, Chaparro M, García-Sánchez V, Gisbert JP, Martínez de Guereñu B, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther. 2011;34(2):125-45.

45. Patel H, Barr A, Jeejeebhoy KN. Renal effects of long-term treatment with 5-aminosalicylic acid. Can J Gastroenterol. 2009;23(3):170-6.

46. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane Database Syst Rev. 2016;9(9):CD003715.

47. Curkovic I, Egbring M, Kullak-Ublick GA. Risks of inflammatory bowel disease treatment with glucocorticosteroids and aminosalicylates. Dig Dis. 2013;31(3-4):368-73.

48. D'Haens G. Systematic review: second-generation vs. conventional corticosteroids for induction of remission in ulcerative colitis. Aliment Pharmacol Ther. 2016;44(10):1018-29.

49. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-s106.

50. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45(12):2615-23.

51. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther. 2007;26(6):795-806.

52. MacLellan A, Moore-Connors J, Grant S, Cahill L, Langille MGI, Van Limbergen J. The Impact of Exclusive Enteral Nutrition (EEN) on the Gut Microbiome in Crohn's Disease: A Review. Nutrients. 2017;9(5).

53. Bodger K, Ormerod C, Shackcloth D, Harrison M, Collaborative IC. Development and validation of a rapid, generic measure of disease control from the patient's perspective: the IBD-control questionnaire. Gut. 2014;63(7):1092-102.

54. Jairath V, Levesque BG, Vande Casteele N, Khanna R, Mosli M, Hindryckx P, et al. Evolving Concepts in Phases I and II Drug Development for Crohn's Disease. J Crohns Colitis. 2017;11(2):246-55.

55. Administration UFaD. Remicade (Infliximab) Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf: US Food and Drug Administration; 2013. Contract No.: 3403013.

56. Agency EM. Remicade (Infliximab). https://www.ema.europa.eu/en/documents/overview/remicade-epar-summary-public_en.pdf: European Medicines Agency; 1999. Contract No.: EMA/76495/2012.

57. van Linschoten RCA, Visser E, Niehot CD, van der Woude CJ, Hazelzet JA, van Noord D, et al. Systematic review: societal cost of illness of inflammatory bowel disease is increasing due to biologics and varies between continents. Aliment Pharmacol Ther. 2021;54(3):234-48.

58. Avila-Ribeiro P, Fiorino G, Danese S. The Experience with Biosimilars of Infliximab in Inflammatory Bowel Disease. Curr Pharm Des. 2017;23(44):6759-69.

59. Peng K, Blais JE, Pratt NL, Guo JJ, Hillen JB, Stanford T, et al. Impact of Introducing Infliximab Biosimilars on Total Infliximab Consumption and Originator Infliximab Prices in Eight Regions: An Interrupted Time-Series Analysis. BioDrugs. 2023;37(3):409-20.

60. Moorkens E, Vulto AG, Huys I. An overview of patents on therapeutic monoclonal antibodies in Europe: are they a hurdle to biosimilar market entry? MAbs. 2020;12(1):1743517.

61. Moorkens E, Godman B, Huys I, Hoxha I, Malaj A, Keuerleber S, et al. The Expiry of Humira. Front Pharmacol. 2020;11:591134.

62. Administration UFaD. Biosimilar development, review and approval https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval2017 [

63. Commission EMAatE. Biosimilars in the EU Information guide for healthcare professionals. https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf: European Medicines Agency; 2019.

64. Hong J, Lee Y, Lee C, Eo S, Kim S, Lee N, et al. Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab). MAbs. 2017;9(2):364-82.

65. Lamb YN, Scott LJ, Deeks ED. SB2: An Infliximab Biosimilar. BioDrugs. 2017;31(5):461-4.

66. Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):58-64.

67. Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. Rheumatology (Oxford). 2017;56(10):1771-9.

68. Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Ann Rheum Dis. 2018;77(2):234-40.

69. Shin D, Kim Y, Kim YS, Körnicke T, Fuhr R. A Randomized, Phase I Pharmacokinetic Study Comparing SB2 and Infliximab Reference Product (Remicade(®)) in Healthy Subjects. BioDrugs. 2015;29(6):381-8.

70. Agency EM. CHMP Assessment Report Flixabi. https://www.ema.europa.eu/en/documents/assessment-report/flixabi-epar-public-assessment-report_en.pdf: European Medicines Agency; 2016. Contract No.: EMA/CHMP/272283/2016.

71. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72(10):1605-12.

72. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72(10):1613-20.

73. Danese S, Gomollon F, ECCO GBaOBo. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). J Crohns Colitis. 2013;7(7):586-9.

74. Tovey D. How to clarify a clinical question https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/how-to-clarify-a-clinical-question/: BMJ Best Practice; 2022 [

75. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

76. Macaluso FS, Fries W, Viola A, Centritto A, Cappello M, Giuffrida E, et al. The SPOSIB SB2 Sicilian Cohort: Safety and Effectiveness of Infliximab Biosimilar SB2 in Inflammatory Bowel Diseases, Including Multiple Switches. Inflamm Bowel Dis. 2021;27(2):182-9.

77. Pagnini C, Di Paolo MC, De Angelis G, Torcolacci F, Milano M, Trinca D, et al. Similar But Not Identical: Plaque Psoriasis Exacerbation in a Patient With Crohn's Disease After Switching From CT-P13 to SB2 Infliximab Biosimilar. Inflamm Bowel Dis. 2020;26(8):e83-e4.

78. Gisondi P, Virga C, Piaserico S, Meneguzzo A, Odorici G, Conti A, et al. Switching from one infliximab biosimilar (CT-P13) to another infliximab biosimilar (SB2) in patients with chronic plaque psoriasis. Br J Dermatol. 2020;183(2):397-8.

79. Lauret A, Moltó A, Abitbol V, Gutermann L, Conort O, Chast F, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Semin Arthritis Rheum. 2020;50(6):1449-56.

80. Lovero R, Losurdo G, La Fortezza RF, Terracciano F, Biscaglia G, Martino G, et al. Safety and efficacy of switching from infliximab biosimilar CT-P13 to infliximab biosimilar SB2 in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2021;32(2):201-7.

81. Trystram N, Abitbol V, Tannoury J, Lecomte M, Assaraf J, Malamut G, et al. Outcomes after double switching from originator Infliximab to biosimilar CT-P13 and biosimilar SB2 in patients with inflammatory bowel disease: a 12-month prospective cohort study. Aliment Pharmacol Ther. 2021.

82. Verhagen AP. Beliefs about Medicine Questionnaire. J Physiother. 2018;64(1):60.

83. Tinsley A, Macklin EA, Korzenik JR, Sands BE. Validation of the functional assessment of chronic illness therapy-fatigue (FACIT-F) in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2011;34(11-12):1328-36.

84. Peyrin-Biroulet L, Lönnfors S, Roblin X, Danese S, Avedano L. Patient Perspectives on Biosimilars: A Survey by the European Federation of Crohn's and Ulcerative Colitis Associations. J Crohns Colitis. 2017;11(1):128-33.

85. Mazza S, Piazza O Sed N, Conforti FS, Fascì A, Rimondi A, Marinoni B, et al. Safety and clinical efficacy of the double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases (SCESICS): A multicenter cohort study. Clin Transl Sci. 2022;15(1):172-81.

86. Luber RP, O'Neill R, Singh S, Sharma E, Cunningham G, Honap S, et al. An observational study of switching infliximab biosimilar: no adverse impact on inflammatory bowel disease control or drug levels with first or second switch. Aliment Pharmacol Ther. 2021;54(5):678-88.

87. Tursi A, Mocci G, Allegretta L, Aragona G, Bianco MA, Colucci R, et al. Comparison of performances of infliximab biosimilars CT-P13 versus SB2 in the treatment of inflammatory bowel diseases: a real-life multicenter, observational study in Italy. Expert Opin Biol Ther. 2022;22(2):313-20.

88. Hanzel J, Jansen JM, Ter Steege RWF, Gecse KB, D'Haens GR. Multiple Switches From the Originator Infliximab to Biosimilars Is Effective and Safe in Inflammatory Bowel Disease: A Prospective Multicenter Cohort Study. Inflamm Bowel Dis. 2022;28(4):495-501.

89. Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. J Crohns Colitis. 2014;8(11):1548-50.

90. Danese S, Fiorino G, Michetti P. Changes in Biosimilar Knowledge among European Crohn's Colitis Organization [ECCO] Members: An Updated Survey. J Crohns Colitis. 2016;10(11):1362-5.

91. Siegel CA. Making therapeutic decisions in inflammatory bowel disease: the role of patients. Curr Opin Gastroenterol. 2009;25(4):334-8.

92. Siegel CA, Lofland JH, Naim A, Gollins J, Walls DM, Rudder LE, et al. Gastroenterologists' Views of Shared Decision Making for Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2015;60(9):2636-45.

93. Siegel CA, Lofland JH, Naim A, Gollins J, Walls DM, Rudder LE, et al. Novel Statistical Approach to Determine Inflammatory Bowel Disease: Patients' Perspectives on Shared Decision Making. Patient. 2016;9(1):79-89.

94. Danese S, Fiorino G, Raine T, Ferrante M, Kemp K, Kierkus J, et al. ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease-An Update. J Crohns Colitis. 2017;11(1):26-34.

95. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. Qual Health Res. 2012;22(10):1435-43.

96. van Vlijmen B, van Gool L, Repping-Wuts H, Ketels T, Kerstens M, Burger D, et al. [Successful switch from originator to biosimilar growth hormone: patients' experiences]. Ned Tijdschr Geneeskd. 2017;161:D1415.

97. Chau J, Delate T, Ota T, Bhardwaja B. Patient Perspectives on Switching from Infliximab to Infliximab-dyyb in Patients with Rheumatologic Diseases in the United States. ACR Open Rheumatol. 2019;1(1):52-7.

98. Teeple A, Ginsburg S, Howard L, Huff L, Reynolds C, Walls D, et al. Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States. Curr Med Res Opin. 2019;35(4):603-9.

99. Petitdidier N, Tannoury J, de'Angelis N, Gagniere C, Hulin A, Rotkopf H, et al. Patients' perspectives after switching from infliximab to biosimilar CT-P13 in patients with

inflammatory bowel disease: A 12-month prospective cohort study. Dig Liver Dis. 2019;51(12):1652-60.

100. Gasteiger C, Lobo M, Dalbeth N, Petrie KJ. Patients' beliefs and behaviours are associated with perceptions of safety and concerns in a hypothetical biosimilar switch. Rheumatol Int. 2021;41(1):163-71.

101. Young D, Cummings F, Latter S. Patient perspectives of successful adalimumab biosimilar transitioning in Crohn's disease: an interview study. Eur J Hosp Pharm. 2022;31(2):143-9.

102. D'Amico F, Solitano V, Magro F, Olivera PA, Halfvarson J, Rubin D, et al. Practical Management of Biosimilar Use in Inflammatory Bowel Disease (IBD): A Global Survey and an International Delphi Consensus. J Clin Med. 2023;12(19).

103. Panaccione R. The Great Debate With IBD Biosimilars: Con: Biosimilars Should Not Be Routinely Used as a First Line Biologic and Not Switched From Reference Biologics. Crohns Colitis 360. 2021;3(3):otab038.

104. Pouillon L, Danese S, Hart A, Fiorino G, Argollo M, Selmi C, et al. Consensus report: clinical recommendations for the prevention and management of the nocebo effect in biosimilar-treated IBD patients. Aliment Pharmacol Ther. 2019;49(9):1181-7.

105. Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther. 2017;4(2):209-18.

106. Tweehuysen L, van den Bemt BJF, van Ingen IL, de Jong AJL, van der Laan WH, van den Hoogen FHJ, et al. Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab. Arthritis Rheumatol. 2018;70(1):60-8.

107. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011;73(7):598-603.

108. Colloca L, Finniss D. Nocebo effects, patient-clinician communication, and therapeutic outcomes. JAMA. 2012;307(6):567-8.

109. Busetto L, Wick W, Gumbinger C. How to use and assess qualitative research methods. Neurol Res Pract. 2020;2:14.

110. Shorten A, Smith J. Mixed methods research: expanding the evidence base. Evid Based Nurs. 2017;20(3):74-5.

111. Halcomb E, Hickman L. Mixed methods research. Nurs Stand. 2015;29(32):41-7.

112. Zhang W, Creswell J. The use of "mixing" procedure of mixed methods in health services research. Med Care. 2013;51(8):e51-7.

113. Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. Inflamm Bowel Dis. 2006;12(6):524-34.

114. Excellence NIfHaC. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. https://www.nice.org.uk/guidance/dg11/chapter/1-Recommendations2013 [

115. Miehsler W, Weichselberger M, Offerlbauer-Ernst A, Dejaco C, Reinisch W, Vogelsang H, et al. Which patients with IBD need psychological interventions? A controlled study. Inflamm Bowel Dis. 2008;14(9):1273-80.

116. Moser G. Should we incorporate psychological care into the management of IBD? Nat Clin Pract Gastroenterol Hepatol. 2006;3(8):416-7.

117. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. Psychol Health. 2015;30(11):1361-85.

118. Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(6):837-44.

119. Hill S. The Illness Perceptions Questionnaire-Revised (IPQ-R). J Physiother. 2010;56(4):280.

120. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12.

121. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.

122. Mays N, Pope C. Rigour and qualitative research. BMJ. 1995;311(6997):109-12.

123. Kitto SC, Chesters J, Grbich C. Quality in qualitative research. Med J Aust. 2008;188(4):243-6.

124. Ritchie J, Lewis J. Qualitative research practice: A guide for social science students and researchers: SAGE; 2003.

125. Austin Z, Sutton J. Qualitative research: getting started. Can J Hosp Pharm. 2014;67(6):436-40.

126. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med. 2014;89(9):1245-51.

127. Creswell J, Plano Clark V. Designing and conducting mixed method research. Third ed: Sage; 2011.

128. Siegel CA. Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. Gut. 2012;61(3):459-65.

129. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health. 2015;42(5):533-44.

130. Jackson CA, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. Am J Gastroenterol. 2010;105(3):525-39.

131. Coyne IT. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? J Adv Nurs. 1997;26(3):623-30.

132. van Rijnsoever FJ. (I Can't Get No) Saturation: A simulation and guidelines for sample sizes in qualitative research. PLoS One. 2017;12(7):e0181689.

133. Silverman D. Qualitative Research. Fifth Edition ed: SAGE Publications Limited; 2020. 520 p.

134. Webb C. Analysing qualitative data: computerized and other approaches. J Adv Nurs. 1999;29(2):323-30.

135. Barbour RS. Checklists for improving rigour in qualitative research: a case of the tail wagging the dog? BMJ. 2001;322(7294):1115-7.

136. Cypress BS. Rigor or Reliability and Validity in Qualitative Research: Perspectives, Strategies, Reconceptualization, and Recommendations. Dimens Crit Care Nurs. 2017;36(4):253-63.

137. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. BMJ. 2000;320(7227):114-6.

138. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2008;3(2):77-101.

139. Jonker D, Deacon E, van Rensburg E, Segal D. Illness perception of adolescents with well-controlled type 1 diabetes mellitus. Health Psychol Open. 2018;5(2):2055102918799968.

140. Miyazaki M, Nakashima A, Nakamura Y, Sakamoto Y, Matsuo K, Goto M, et al. Association between medication adherence and illness perceptions in atrial fibrillation patients treated with direct oral anticoagulants: An observational cross-sectional pilot study. PLoS One. 2018;13(9):e0204814.

141. Elera-Fitzcarrald C, Fuentes A, González LA, Burgos PI, Alarcón GS, Ugarte-Gil MF. Factors affecting quality of life in patients with systemic lupus erythematosus: important considerations and potential interventions. Expert Rev Clin Immunol. 2018;14(11):915-31.

142. Farrell D, McCarthy G, Savage E. Self-reported Symptom Burden in Individuals with Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(3):315-22.

143. Hindryckx P, Laukens D, D'Amico F, Danese S. Unmet Needs in IBD: the Case of Fatigue. Clin Rev Allergy Immunol. 2018;55(3):368-78.

144. Vegni E, Gilardi D, Bonovas S, Corrò BE, Menichetti J, Leone D, et al. Illness Perception in Inflammatory Bowel Disease Patients is Different Between Patients With Active Disease or in Remission: A Prospective Cohort Study. J Crohns Colitis. 2019;13(4):417-23.

145. D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis. 2012;18(12):2218-24.

146. Afzali A, Furtner D, Melsheimer R, Molloy PJ. The Automatic Substitution of Biosimilars: Definitions of Interchangeability are not Interchangeable. Adv Ther. 2021;38(5):2077-93.

147. England HE. Commissioning framework for biological medicines (including biosimilar medicines). In: England HE, editor. 2017.

148. Gomes T, McCormack D, Kitchen SA, Paterson JM, Mamdani MM, Proulx L, et al. Projected impact of biosimilar substitution policies on drug use and costs in Ontario, Canada: a cross-sectional time series analysis. CMAJ Open. 2021;9(4):E1055-E62.

149. Liu Y, Yang M, Garg V, Wu EQ, Wang J, Skup M. Economic Impact of Non-Medical Switching from Originator Biologics to Biosimilars: A Systematic Literature Review. Adv Ther. 2019;36(8):1851-77.

150. Hughes A, Marshall JK, Moretti ME, Ungar WJ. A Cost-Utility Analysis of Switching from Reference to Biosimilar Infliximab Compared to Maintaining Reference Infliximab in Adult Patients with Crohn's Disease. J Can Assoc Gastroenterol. 2021;4(1):48.

151. Jacobs I, Singh E, Sewell KL, Al-Sabbagh A, Shane LG. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. Patient Prefer Adherence. 2016;10:937-48.

152. Macaluso FS, Leone S, Previtali E, Ventimiglia M, Armuzzi A, Orlando A, et al. Biosimilars: The viewpoint of Italian patients with inflammatory bowel disease. Dig Liver Dis. 2020;52(11):1304-9.

153. Peyrin-Biroulet L, Lönnfors S, Avedano L, Danese S. Changes in inflammatory bowel disease patients' perspectives on biosimilars: A follow-up survey. United European Gastroenterol J. 2019;7(10):1345-52.

154. Sullivan E, Piercy J, Waller J, Black CM, Kachroo S. Assessing gastroenterologist and patient acceptance of biosimilars in ulcerative colitis and Crohn's disease across Germany. PLoS One. 2017;12(4):e0175826.

155. Boone NW, Liu L, Romberg-Camps MJ, Duijsens L, Houwen C, van der Kuy PHM, et al. The nocebo effect challenges the non-medical infliximab switch in practice. Eur J Clin Pharmacol. 2018;74(5):655-61.

156. Moots R, Azevedo V, Coindreau JL, Dörner T, Mahgoub E, Mysler E, et al. Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician. Curr Rheumatol Rep. 2017;19(6):37.

157. UK CsaC. Shared decision making in IBD https://www.crohnscolitisfoundation.org/science-and-professionals/patient-resources/shared-decision-making [

158. Julia R. Majority of patients not asked for consent before being switched to a bio similar, survey finds. The Pharmaceutical Journal. 2019;303:1928.

159. Mysler E, Azevedo VF, Danese S, Alvarez D, Iikuni N, Ingram B, et al. Biosimilar-to-Biosimilar Switching: What is the Rationale and Current Experience? Drugs. 2021;81(16):1859-79.

160. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut. 2009;58(4):492-500.

161. Bronswijk M, Moens A, Lenfant M, Tops S, Compernolle G, Van Assche G, et al. Evaluating Efficacy, Safety, and Pharmacokinetics After Switching From Infliximab Originator to Biosimilar CT-P13: Experience From a Large Tertiary Referral Center. Inflamm Bowel Dis. 2020;26(4):628-34.

162. Ternant D, Mulleman D, Degenne D, Willot S, Guillaumin JM, Watier H, et al. An enzyme-linked immunosorbent assay for therapeutic drug monitoring of infliximab. Ther Drug Monit. 2006;28(2):169-74.

163. Klaus B, Morten S. Detection and Quantification of Antibodies to Biopharmaceuticals : Practical and Applied Considerations2011.