UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Human Development and Health

Evaluation of the feasibility and acceptability of liraglutide 3.0mg as a management of overweight and obesity in people with severe mental illness

By

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Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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Evaluation of the feasibility and acceptability of liraglutide 3.0mg as a management of overweight and obesity in people with severe mental illness
(LOSE Weight trial)

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Abstract

Background

People with severe mental illness (SMI) are 2-3 times more likely to be overweight and obese than the general population and this is associated with significant morbidity and premature mortality. This study investigated the feasibility and acceptability of using daily injections of liraglutide 3.0 mg to address this problem.

Methods

Design: Double-blind, randomised, placebo-controlled pilot trial.

Setting: Mental health centres and primary care within Southern Health NHS Foundation Trust.

Participants: Adults with schizophrenia, schizoaffective, or first episode psychosis prescribed antipsychotic medication who were overweight or obese.

Intervention: Participants were allocated to either once daily subcutaneous liraglutide or placebo, titrated to 3.0 mg daily, for 6 months.

Primary outcome: recruitment, consent, retention, adherence and acceptability.

Secondary exploratory outcomes: weight, HbA_{1c} and Brief Psychiatric Rating Scale.

Results

799 individuals were screened for eligibility. The commonest reasons for exclusion were ineligibility (44%) and inability to make contact (28%). The acceptance rate, as a proportion of all eligible participants, was 12.2%. The main reason why eligible candidates declined to participate related to the study specific medication and protocol (n= 50). 47 participants were randomised with 79% completing the trial. Participants in the liraglutide arm had lost a mean 5.7±7.9 kg compared with no significant weight change in the placebo group (treatment difference −6.0 kg, p=0.015). BMI, waist circumference and HbA_{1c} reduced in the intervention group. The intervention was acceptable to the trial participants.

Conclusions

A pilot study has been undertaken in people with in people with SMI looking at the use of liraglutide (maximum dose 3.0 mg daily) which appeared to be acceptable, safe and effective without adversely affecting the mental health status of the participants This study supports the need for a larger randomised controlled trial to evaluate use of liraglutide (maximum dose 3.0 mg daily) in the management of obesity in people with SMI.

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Academic Thesis: Declaration of Authorship

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

Evaluation of the feasibility and acceptability of liraglutide as a management of overweight and obesity in people with severe mental illness

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

Antipsychotic Medication and Type 2 diabetes and Impaired Glucose Regulation. Clare Alexandra Whicher, Hermione Clare Price, Richard Ian Gregory Holt. European Journal of Endocrinology 2018 **178** (6): p. 245

Antipsychotics and schizophrenia, and their relationship to Diabetes. Clare Alexandra Whicher, Sarah Brewster, Richard Ian Gregory Holt. Practical Diabetes 2019 **36** (4): p 147

Liraglutide and the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first-episode psychosis: protocol for a pilot trial. Clare Alexandra Whicher, Hermione Clare Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Claire Reidy, Kerensa Thorne, Carolyn Asher, Robert Peveler, Joanne McCarthy, Richard Ian Gregory Holt. Trials, 2019. **20** (1): p. 633.

The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomised double-blind placebo-controlled trial. Clare Alexandra Whicher, Hermione C Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Kandala Ngianga, Kerensa Thorne, Carolyn Asher, Robert C Peveler, Joanne McCarthy, Richard IG Holt. Diabetes, Obesity and Metabolism, 2021 https://doi.org/10.1111/dom.14334

A qualitative results paper has been written by Professor Katharine Barnard-Kelly and the candidate (second author) which was submitted to Psychiatry Research on the 10th March 2021 and is currently undergoing peer review. The following members of the trial team have also contributed to the paper and are authors; Richard IG Holt, Hermione C Price, Peter Phiri, Shanaya Rathod, Carolyn Asher and Robert C Peveler.

Signed: .....

Date: 10/05/2021 .....

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The candidate is grateful to all the study participants and the research staff who collected data, undertook study activity and monitoring and would like to acknowledge the members of SHFT Public Involvement Network for Research Community who contributed to this project. In particular the candidate wishes to thank Joanne McCarthy, Kieran Davies, Maria Lane, Lizi Graves and Qi Zheng.

Finally, the candidate would like to thank the Trial Steering Committee: Christopher Dickens (chair), John Wilding, Irene Stratton, and Don Robertson for their helpful support and advice.

Definitions and Abbreviations

AE – Adverse event

ALT - Alanine aminotransferase

AR – Adverse reaction

ASD – Autism spectrum disorder

BAP - British Association for Psychopharmacology

BMI – Body mass index

BPRS – Brief Psychiatric Rating Scale

CATIE - Clinical Antipsychotic Trials of Intervention Effectiveness

CCGs - Clinical Commissioning Groups

CCO - Care coordinator

CI – Confidence intervals

CRIS - Clinical Records Interactive Search

CRF – Case report forms

DKA – Diabetic ketoacidosis

DPP-4 - Dipeptidyl peptidase-4

eGFR - estimated Glomerular Filtration Rate

EMA – European Medicines Agency

FBG – Fasting blood glucose

FGA – First generation antipsychotics

FPFV - First participant first visit

GCP – Good Clinical Practice

GDPR - General Data Protection Regulation

GLP-1 – Glucagon-like peptide 1

GP - General practitioner

HbA_{1c} -Glycated haemoglobin

HRA - Health Research Authority

IMP- Investigational medicinal product

LAR - Long-acting release

LPLV - Last participant last visit

MDT - Multidisciplinary team

NICE - National Institute for Health and Care Excellence

NHS DPP – NHS Diabetes prevention programme

OGTT - Oral glucose tolerance test

OSA – Obstructive sleep apnoea

PIC – Participant identification centres

PIS - Participant information sheet

PPI – Patient and public involvement

R&D -Research and development

RCT – Randomised controlled trial

SAE - Serious adverse events

SAR – Serious adverse reaction

SCALE - Satiety and Clinical Adiposity Liraglutide Evidence in Nondiabetic and Diabetic people

SD – Standard deviation

SGA – Second generation antipsychotics

SHFT - Southern Health NHS Foundation Trust

SMI – Severe mental illness

SmPC – Summary of Product characteristics

SUSAR – Suspected unexpected serious adverse reaction

TMG – Trial management group

TSC - Trial steering committee

Chapter 1 **Introduction**

This chapter is based on the two following published articles of which the candidate was the first author:

Antipsychotic Medication and Type 2 diabetes and Impaired Glucose Regulation. Clare Alexandra Whicher, Hermione Clare Price, Richard Ian Gregory Holt. European Journal of Endocrinology 2018 **178** (6): p. 245

Antipsychotics and schizophrenia, and their relationship to Diabetes. Clare Alexandra Whicher, Sarah Brewster, Richard Ian Gregory Holt. Practical Diabetes 2019 **36** (4): p 147

1.1 Search criteria

The candidate searched for articles and registered trials on MEDLINE/PUBMED databases and on the ClinicalTrials.gov website respectively in August 2017, February 2020 and February 2021. Searches were performed using the terms:

1. obesity/ or obesity, abdominal/ or obesity, metabolically benign/ or obesity, morbid/

2. obes*.ti,ab.

3. 1 or 2

4. exp Antipsychotic Agents/

5. antipsychotic*.ti,ab.

6. 4 or 5

7. 3 and 6

8. schizophrenia/ or schizophrenia, paranoid/

9. schizophreni*.ti,ab.

10. schizoaffective.mp.

11. first episode psychosis.mp.

12. 8 or 9 or 10 or 11

13. 7 and 12

14. limit 13 to English language

The candidate also reviewed the Cochrane database and the latest guidelines addressing overweight and obesity and mental illness, together and individually.

1.2 Overweight and obesity introduction

Overweight and obesity are terms that refer to an excess of body fat such that health may be impaired and usually relate to increased weight-for-height. While it is recognised that the consequences of weight gain is not equal for all, with effect of age, sex, menopausal status and site of weight gain important considerations, the most common and widely accepted method of measuring overweight and obesity is Body Mass Index (BMI) =person's weight (kg) / person's height (in metres) ^{2}. In adults, a BMI of 25kg/m^2 to 29.9kg/m^2 means that person is considered to be overweight, a BMI ≥ 30kg/m^2 is considered to be obese and a BMI ≥ 40kg/m^2 means that person is considered to be morbidly obese. These cut offs are based on well-established risks for cardiometabolic morbidity and premature mortality [1]. Some population groups however, such as people of Asian family origin, have BMIs that are abnormal at different levels. BMI cut-offs are lower for adults of Asian family origin as they have higher weight-related disease risks at lower BMI [2, 3]. This may be because of body fat; when compared to white Europeans of the same BMI, Asians have 3 to 5 percent higher total body fat [4].

While BMI is a practical estimate of adiposity it does not distinguish body fat and muscular physique as it is not a direct measure of fat and does not take into account the distribution of fat, with visceral adipose tissue being of most interest, as it is strongly associated with metabolic complications [5]. The National Institute for Health and Clinical Excellence (NICE) therefore recommends the use of BMI in conjunction with waist circumference as the method of measuring abdominal obesity and determining health risks [6]. Waist circumference is categorised by sex-specific thresholds as can be seen in Table 1.

Table 1 Classification of waist circumference for both sexes [5]

Classification of waist circumference	**Male**	**Female**
Low	< 94cm	<80cm
High	94-102cm	80-88cm
Very high	>102cm	>88cm

1.2.1 Prevalence

In 2017 64% of adults (≥ 16 years) in England, according to the Health Survey for England (HSE), were overweight or obese (67% of men and 62% of women)[7]. The UK reports an adult obesity level of 26% which is 14% lower than the USA which reports the highest adult obesity level. Japan and Korea report the lowest obesity levels of less than 10%. The prevalence of overweight and obesity has increased in the UK year on year since 1993. Morbid obesity has also increased, from less than 1% in 1993, to nearly 4% in 2017 [7].

Being overweight but not obese is more common among men; however, obesity (including morbid obesity) is more common in women. The proportion of adults who are overweight or obese increases with age and is highest among men aged between 45 and 74 (78%), and women aged between 65 and 74 (73%) [7]. There is also a relationship between deprivation and obesity. In both reception year (age 5) and year 6 (age 11), obesity prevalence was over twice as high in the most deprived areas than the least deprived areas. Between 2006/07 and 2017/18 the gap between obesity prevalence for the most and least deprived areas has also increased [7]. Children's' weight is also associated to that of their parents; based on data from 2016 and 2017 combined 28% of children of mothers with obesity were also obese (24% father with obesity), versus 17% whose mothers were overweight but not obese (14% father overweight but not obese), and 8% of children whose mothers were neither overweight nor obese (9% fathers had normal weight) [7].

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been an increase in the availability of cheap energy-dense foods that are high in sugar and fat. Advertising has made food more desirable and attractive and portion sizes have increased over a short period time [8]. There has also been a decrease in physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization [9]. Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing, and education [9]. In England and Scotland only 67% of men and 55% of women are meeting recommended physical activity levels - two and a half hours a week of moderate activity such as swimming, cycling or walking on the flat [10].

1.2.2 Body weight regulation

Body weight is regulated by interrelated processes that maintain energy stores at appropriate levels for given environmental conditions. Fat in adipose tissue, glycogen in the liver and blood glucose levels are all regulated by the hypothalamus which receives continuous information about energy stores and fluxes in critical organs. The brain in turn controls tissues that have important roles in energy homeostasis, like the liver and musculoskeletal system, as well as the secretion of key metabolically active hormones, primarily through the autonomic nervous system [11].

Multiple neuropeptide hormones play a role in this regulation. This includes gastrointestinal transmitters such as glucagon-like peptide 1 (GLP-1) and cholecystokinin which have an anorectic effect in response to food, insulin and glucagon (pancreatic peptide hormones), neurotransmitters and leptin, an adipokine [11]. Insulin and leptin are secreted in proportion to the amount of fat in the body and have key roles in the regulation of body weight and energy homeostasis as highlighted by the fact that people with obesity have demonstrated resistance to these hormones. Serotonin, noradrenaline and dopamine all act as appetite suppressants unlike glutamate which stimulates appetite. GABA, the main inhibitory neurotransmitter in the central nervous system, acts by secreting glucagon and so is thought to improve insulin resistance and glucose tolerance. [12].

1.2.3 Consequences of overweight and obesity

Overweight and obesity are major risk factors for cardiovascular disease (CVD) , mainly coronary heart disease (CHD) and cerebrovascular accidents (CVA) through thrombosis or atherosclerosis [13]. In 2016, around 152,000 people in the UK died from CVD; the most common cause of death after cancer with CHD accounting for around 66,000 of these deaths [14]. The Framingham Heart Study identified type 2 diabetes as a key, potentially modifiable, risk factor relating to CVD and the association of obesity and type 2 diabetes is well established with each additional 1 kg/m^2 in BMI increasing the risk of type 2 diabetes by 8.4% [15]. In people who are overweight and obese who do not have diabetes there is also a strong positive correlation between adiposity and fasting insulin levels [16]. Insulin resistance has been showed to be often accompanied by a constellation of cardiovascular risk factors including hypertension, low high density lipoprotein (HDL) and high triglycerides. This cluster has become known as the ‘metabolic syndrome’. Hypertension is defined by Hypertension in adults NICE guideline (NG136) as persistently raised clinic arterial systolic blood pressure (BP) above or equal to 140 mmHg, or diastolic BP above or equal to 90 mmHg, or both [17].

A myriad of other effects of chronic excess adipose tissue include:

- obstructive sleep apnoea (OSA) syndrome- repetitive apnoea and symptoms of sleep fragmentation with excessive daytime sleepiness which is associated with an increased risk of CVA, independent of other cerebrovascular risk factors, and an independent role in the pathogenesis of hypertension [18];
- Non-alcoholic fatty liver disease - the most common cause of chronic liver disease in Western countries [19]
- musculoskeletal disorders such as osteoarthritis,
- cancers including endometrial, breast, ovarian, prostate, gallbladder, kidney and colon
- mental health issues such as depression, anxiety [13];
- the stigma of overweight and obesity which can have negative social and economic implications [20].

1.2.3.1 Dysglycaemia and Type 2 diabetes

Overweight and obesity are responsible for 80 to 85% of an individual's risk of developing type 2 diabetes. Intensive lifestyle interventions which have produced long-term beneficial reductions in weight through changes in diet, physical activity, and clinical and biochemical measurements reduce or delay the onset of type 2 diabetes [21]. In one 2018 study the prevalence of total diabetes was greatest among those who were obese (14% of men and 11% of women) compared to those who were overweight but not obese (6% of both men and women), or those who were not obese or overweight (4% and 2% respectively) [7]. Data published in 2013 found that six in ten people had no symptoms at time of type 2 diabetes diagnosis and it is estimated that around one million people have type 2 diabetes but have not yet been diagnosed. This is of particular concern as complications can start five to six years before a diagnosis of type 2 diabetes [22, 23]. CVD remains the leading cause of death in people with type 2 diabetes, accounting for two-thirds of all deaths in those aged over 65 years [13].

12.3 million people in the UK are at increased risk of type 2 diabetes [24]. In June 2016 the process for roll out of the Healthier You: NHS Diabetes Prevention Programme (NHS DPP) began and is now available nationwide. The programme, however, has not been validated for its use in people with severe mental illness (SMI). The most effective and cost-effective methods for identifying, assessing and managing the risk of type 2 diabetes among high-risk, vulnerable adults therefore remains an important research question.

Glycated haemoglobin (HbA_{1c}) is used as both a screening and monitoring blood test in type 2 diabetes. As the average amount of plasma glucose increases, the fraction of glycated haemoglobin increases in a predictable way. From June 2011 HbA_{1c} values have been reported in the UK in mmol/mol, known as the International Federation of Clinical Chemistry (IFCC) units.

Previous to that the Diabetes Control and Complications Trial (DCCT) method reported HbA_{1c} as a percentage. Interferences which were causing falsely high results with the latter method resulted in the need for the change to IFCC units [25].

1.2.4 Treatment of overweight and obesity

Overweight and obesity should be recognised and treated as a chronic disease. Treating obesity with either lifestyle or pharmacological interventions is both clinically and cost effective in the general population and as such NICE recommend the approach in Table 2. According to this all people with SMI and overweight and obesity should be considered for medication or surgery in addition to lifestyle advice but current options are limited. If treatment of overweight and obesity can be achieved, however, the individual may be in a better place to self-manage their physical health and adopt the advised treatment plans aimed at reducing their cardiovascular risks. Equivalent physical health care in people with and without mental illness remains aspirational and this needs to be addressed in order to improve mental health outcomes and reduce the risk of CVD in people with SMI.

Table 2 NICE Obesity guidance intervention recommendations [5]

BMI classification	**Waist circumference**			**Comorbidities present**
	Low	High	Very high	
25-29.9 kg/m^2	1	2	2	3
30-34.9 kg/m^2	2	2	2	3
35- 39.9 kg/m^2	3	3	3	4
≥ 40 kg/m^2	4	4	4	4
1	General advice on healthy weight and lifestyle			
2	Diet and physical activity			
3	Diet and physical activity; consider drugs			
4	Diet and physical activity; consider drugs; consider surgery			

1.2.4.1 Bariatric surgery

According to the Obesity NICE guidelines (CG189) bariatric surgery is the option of choice (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50 kg/m^2 when other interventions have not been effective[6]. It is also a treatment option for people with obesity if they meet the following criteria:

- They have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease (for example, type 2 diabetes or hypertension) that could be improved if they lost weight.
- All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.
- Has been receiving or will receive intensive management in a tier 3 service.
- Generally fit for anaesthesia and surgery.
- Commits to the need for long-term follow up [6].

In 2017/18 there were 6,627 hospital admissions (79% female) with a primary diagnosis of obesity and a main or secondary procedure of bariatric surgery [24]. While this is an increase of 2% on 2016/17 it remains a low proportion of people who are eligible according to the NICE guideline. There are limited data about the use of bariatric surgery in people with SMI. Psychiatric or psychological assessment prior to bariatric surgery is widely recommended; and while the candidate is not aware of any consensus, the purpose of this assessment is often described as identifying “psychosocial contraindications” to obesity surgery. A survey, sent by bariatric surgeons to the mental health professionals to whom they refer surgery candidates for preoperative evaluations, found that 91.2% identified “psychiatric issues” as “clear contraindications” to weight loss surgery [26].

1.3 Severe mental illness

SMI refers to people with major psychological problems which impair their ability to engage in functional and occupational activities. For the purpose of this thesis SMI will encompass schizophrenia, schizoaffective disorder and first episode psychosis. See 2.3.6.1.3 for the rationale behind this.

Schizophrenia is a major psychiatric disorder that alters the individual’s perception, thoughts, affect and behaviour. It may involve a loss of insight and has a lifetime prevalence of approximately 1% [27]. It is defined by ICD -10 code F20 as a major psychotic disorder characterized by abnormalities in the perception or expression of reality. It affects cognitive and

psychomotor functions and common clinical features include delusions, hallucinations, disorganised thinking, and retreat from reality. In men, symptoms usually start in the late teenage years and early 20s, for women, in the mid-20s to early 30s [28]. It has been hypothesized that different timing in brain development and hormonal changes may account for this. Schizoaffective disorder is recognised as a separate condition to schizophrenia and is more likely to occur in women at a later age. This disorder affects an individual's thoughts and emotions [29]. Schizoaffective disorder is defined by ICD -10 code F25 as a mental disorder characterized by the presence of both affective symptoms (e.g., depression or bipolar disorder) and schizophrenia-like symptoms [28]. For the purpose of this piece of work first episode psychosis was defined as less than 3 years since first presentation to the mental health team or since first antipsychotic medication prescription. The rationale for this was that 85% of people presenting with a non-affective psychotic episode (i.e. not mania and not depressive psychosis) will still meet criteria for a schizophrenia spectrum disorder 2 years later [30]. Further reasons for including people with first episode psychosis is discussed in the inclusion criteria (2.3.6.1.3).

1.4 Overweight and obesity in SMI

The average life expectancy of an individual with schizophrenia is 62.8 years in UK men and 71.9 years in UK women [31]. This is 14.6 and 9.8 years earlier than expected for men and women without mental illness respectively. Approximately 75% of all deaths in people with SMI are now caused by physical illness with CVD being the commonest cause of death [32].

Recent studies indicate that obesity is 2-3 times more common among people with SMI [33]. Obesity occurs early in the natural history with a significant proportion of people with first episode psychosis being overweight prior to any treatment [34]. Whilst most weight gain occurs early in treatment longer term observational studies suggest that weight gain continues for at least 4 years after diagnosis albeit at a slower rate [35]. If weight gain is attributed to antipsychotic medication treatment this can also lead to non-adherence of medication and risk of relapse [36]. Many factors can potentially be implicated in the development of overweight and obesity including other co-morbid conditions, recovery towards health and concurrent medications but across the literature it appears that three themes emerge. These are environmental factors, disease specific effects and antipsychotic medication treatment and are now each considered in turn.

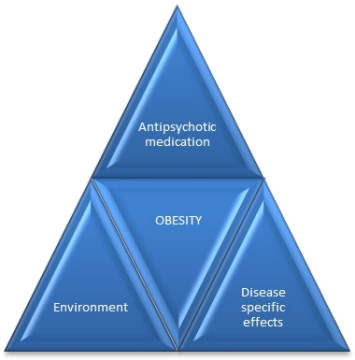


Figure 1: Key factors involved in overweight and obesity and SMI

1.4.1 Disease specific effects

Long before the introduction of antipsychotic medication medications, there was a recognised association between SMI, obesity and diabetes. Given this longstanding link, a metabolic phenotype intrinsic to SMI has been suggested. Under-activity is a negative symptoms of schizophrenia per se and other negative symptoms, such as marked apathy and passivity and lack of motivation also predispose individuals to inactivity [28]. There may also be genetic susceptibilities that have additive or synergistic actions to increase body weight further or disease specific effects of SMI on neuro-endocrine function, affecting the hypothalamic–pituitary–adrenal and growth hormone axes, and inflammation [33].

1.4.2 Environment

It seems likely that the environmental changes that have provoked the increased prevalence of overweight and obesity in the general population have also affected people with SMI; in fact the rates of overweight and obesity have increased even more rapidly in this cohort [37]. Individuals with schizophrenia are more likely to consume a diet that is rich in fat and refined carbohydrates while containing less fibre, fruit and vegetables than the general population [38]. It has been suggested that food intake, particularly carbohydrates and sugar, shares features of addiction, and that carbohydrates could stimulate the mesolimbic dopaminergic pathway, which is intimately linked to psychosis and addiction supporting a link between psychosis, food and addiction [39]. Although there are fewer studies, people with first episode psychosis have also been shown to have poor diets [40]. Physical inactivity and the social and urban deprivation experienced by those with SMI may contribute further to the increased obesity rates [41, 42].

1.4.3 Antipsychotic medication

People with SMI, especially those taking antipsychotic medications, appear to be at increased risk of overweight and obesity. These potential adverse effects, however, need to be balanced against the improved and lasting mental health benefits. Randomised controlled trials (RCT) have shown that antipsychotic medications prevent relapse and hospitalisation in SMI and decrease mortality from suicide [43]. It is important that people with SMI are not denied effective treatment without good reason and individual factors must be considered in each case. Nevertheless, greater attention to the possible impact of antipsychotics on the physical health of people is needed. Substantial weight gain (>7%) often occurs rapidly within 6-8 weeks after antipsychotic medication treatment initiation for SMI [44]. 7% is used as a measurement to reflect significant weight gain as it has been shown to predict long-term weight gain with antipsychotic medications. Magnetic resonance imaging has shown that drug naïve individuals receiving antipsychotic medications had a significant increase in both subcutaneous and the more problematic intra-abdominal fat. [45]. Second-generation antipsychotic medication medications (SGA) were developed with less occupancy of dopamine D2 receptors to avoid the stigmatising extrapyramidal symptoms of first generation antipsychotics (FGA). Since the introduction of SGA, with less D2 receptor antagonism, concerns have arisen that these newer agents lead to side effects of a different nature, namely, weight gain and type 2 diabetes. Weight gain is now reported as the commonest side effect of SGA affecting up to 80% of individuals taking them [46, 47]. In a 3-year study of treatment with quetiapine, ziprasidone, and aripiprazole the proportion of patients gaining ≥7% baseline weight was 23% for ziprasidone, 32% for quetiapine, and 45% for aripiprazole [48]. Weight gain has also been found to be 3- to 4-fold greater in studies with limited previous exposure to antipsychotic agents in both short-term studies (7.1-9.2 kg for olanzapine, 4.0-5.6 kg for risperidone) and long-term trials (10.2-15.4 kg and 6.6-8.9 kg respectively) [47]. Antipsychotic medications have variable mechanisms of action (see1.4.3.1) and individuals respond differently to these medications, both in regards to efficacy and side effects, meaning the choice of treatment remains challenging. Studies have therefore attempted to identify risk factors for weight gain but predictors are generally unclear and poorly understood. A 2020 systematic review of 25,952 patients did not find strong evidence of an association between change in weight or BMI with any baseline variables and comparative effects of 18 antipsychotic medications [49]. This considerable unexplained variance may imply that genetic factors are substantial contributors.

The situation regarding metabolic side effects and antipsychotic medications is complex not only because of the multiple confounders in people with mental illness but also because of frequent changes in antipsychotic medication in comparison to the long natural history of obesity. In order

Commented [CW1]: Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *Vandenberghe F, Gholam-Rezaee M, Saigí-Morgui N, Delacrétaz A, Choong E, Solida-Tozzi A, Kolly S, Thonney J, Gallo SF, Hedjal A, Ambresin AE, von Gunten A, Conus P, Eap CB*
J Clin Psychiatry. 2015 Nov; 76(11):e1417-23.

to unpick this relationship, adequately powered prospective RCT with weight as a primary outcome are ideally needed. By design, the likelihood of significant bias and confounding would be reduced but no such RCTs have been reported. This is perhaps unsurprising given the length of trial that would be needed and researchers' potential concerns around recruitment, adherence to trial protocol and retention rates in a large study design.

The candidate reviewed the Cochrane database in August 2017, June 2020 and February 2021 but no review has specifically examined antipsychotic medication and weight gain. There has, however, been one review looking at switching antipsychotics for people who have neuroleptic induced weight or metabolic problems and the findings of this are discussed later (1.5.3) Weight measurements have, however, been included in 17 Cochrane reviews which have been carried out comparing various antipsychotic medications when used in schizophrenia. Overall they recognise their conclusions are based on limited data and include studies sponsored by manufacturers. Nevertheless, these reviews are a useful resource for clinicians considering newer antipsychotic medications which have not been included in older meta-analyses.

Antipsychotic medications are amongst the most obesogenic medications and this indirect route is coherent with our understanding of the pathophysiology of the development of type 2 diabetes. This often occurs within eight weeks of drug initiation, especially in younger or antipsychotic medication naive individuals but can continue, albeit at a slower rate, for up to four years [44]. Furthermore, antipsychotic medications are associated with a predisposition to depositing adipose tissue centrally and adiposity levels during antipsychotic medication treatment have been separately confirmed to be strongly related to insulin resistance [50-52].

There is a generally accepted hierarchy of effect on weight with olanzapine and clozapine being most strongly associated with weight gain, risperidone and quetiapine having an intermediate effect on body weight while aripiprazole and ziprasidone have the least effect [53, 54]. A post hoc analysis of 4626 patients with schizophrenia, who had completed 3 years of antipsychotic monotherapy with clozapine, olanzapine, quetiapine, risperidone, amisulpride, or oral and depot first generation antipsychotics (20), indicated that the mean weight gain was highest with olanzapine (4.2 kg) and lowest with amisulpride (1.8 kg). Roughly the same hierarchy for risk of weight gain with these agents has been identified. In children and adolescents [55]. At all ages, however, there is also considerable variation between individuals; for example, the 5^{th} to 95^{th} centile for weight change is 1.4 to 9.5 lb/month with olanzapine [56], and so no antipsychotic medication should be considered truly weight neutral. Current guidance is that the choice of antipsychotic medication should be made by the service user and healthcare professional

together and possible metabolic side effects (including weight gain and diabetes) should be discussed [6].

1.4.3.1 Mechanism of action

A number of hormones, neurotransmitter receptors and neuropeptides have been implicated in the mechanism of antipsychotic medications induced weight gain but those that regulate appetite stimulation and consequently increased food consumption are thought to be more specifically involved. These have been considered in the following basic science studies.

Hormones

Leptin is disproportionally high in relation to adiposity and there is no consequent suppression of appetite in those taking antipsychotic medications which raises the possibility that the leptin signalling mechanism may be disrupted by these medications [57]. This would be consistent with the increased appetite reported by people taking antipsychotic medications with significant weight gain [43]. Serum prolactin is known to stimulate β-cell proliferation, insulin production, and insulin secretion during the second half pregnancy and epidemiological studies have shown that serum prolactin is inversely associated with the risk of diabetes [58]. Hyperprolactinaemia is a well-recognised side effect of FGAs risperidone and amisulpride while the incidence of hyperprolactinaemia is much lower with the other SGA [59]. It has been postulated that this may partly explain the difference in the risk of weight gain and type 2 diabetes between FGA and SGA. By contrast, aripiprazole, which is a partial D2 receptor agonist and has the lowest rate of hyperprolactinaemia of all antipsychotic medications also has a low propensity for weight gain [60]. There has also been interest that clozapine related weight gain and type 2 diabetes is mediated through reduced GLP-1 raising the possibility that GLP-1 receptor agonists could be co-administered with antipsychotic medication.

Neurotransmitters

A key receptor postulated to mediate homeostatic and hedonic aspects of feeding is the histamine H1 receptor, which reduces food intake [61]. This is blocked by many SGA but clozapine and olanzapine have the highest affinity. The anorexigenic serotonin 5-HT_{2c} receptor has also been implicated [61]. While both clozapine and olanzapine are potent 5-HT_{2c} receptor antagonists and deletions of the gene for this receptor in mice results in obesity, other SGA associated with less weight gain, such as ziprasidone, also have a high affinity for this receptor. Antipsychotic medications also bind to the adrenergic α 1 receptors and, whilst the affinity for these receptors is

weak, there is correlation between antagonism of this receptor and weight gain for several antipsychotic medications possibly through physical inactivity [60].

Table 3 Summary of key effect of common antipsychotic medications on neurotransmitter receptors

Neurotransmitter receptors		**Effect of blocking receptor**	**SGAs which have key interaction with these receptors**
Serotonin	$5\text{-}HT_{2C}$	Increased food intake	Clozapine, olanzapine and ziprasidone all antagonists
	$5\text{-}HT_{1a}$	Reduce dopamine	Aripiprazole and ziprasidone partial agonists
Noradrenaline (α 1)		Physical inactivity	Ziprasidone reuptake inhibitor
Dopamine (D2)		Increased food intake	All antipsychotics D2 antagonists (SGAs less than FGAs) Aripiprazole partial D2/D3 agonists
Histamine (H1)		Sedation causing reduced physical inactivity	Clozapine and Olanzapine are antagonists

Neuropeptides

Neuropeptides, such as Melanocortin 4 receptor and Brain Derived Neuropeptide Factor, play a role in weight regulation. Antipsychotic medications increase expression of the latter in the hippocampus and prefrontal cortex and may play a role in antipsychotic medication induced weight gain [57].

1.4.3.2 Children and adolescents

Antipsychotic medication trials and reviews have overwhelmingly concentrated on the adult population, whose adverse events may not be applicable to children and adolescents. Accelerated weight gain in young individuals is a particularly serious side-effect posing substantial health risks later in life [55]. Pre-pubertal children run the greatest risk of alarmingly rapid weight gain although there are conflicting views as to whether disproportionately greater weight gain is seen in children and adolescents. Some authors argue that greater weight gain is not seen in this population but appears more apparent because older studies include adults who were already on

antipsychotic medications and therefore were not starting from the same baseline [55]. Cochrane undertook a review in 2013 looking at 'Atypical antipsychotics for psychosis in adolescents'. This review concluded, from 7 studies which they reported as having usable data on weight, that treatment with olanzapine, clozapine and risperidone was often associated with weight gain whereas treatment with aripiprazole was not [62].

It is concerning that the relative risk of type 2 diabetes associated with antipsychotic medications appears to be greatest in those younger than 24 years (OR 8.9 CI 7.0-11.3) [63]. SGA were associated with an elevated fasting plasma glucose levels or type 2 diabetes in 21.5% compared with 7.5% of the drug naïve group [64]. While type 2 diabetes in antipsychotic medication-exposed youths is rare, systematic reviews and meta-analyses recognise that the relative risks are significantly higher than the general population and those not on antipsychotic medications [65]. Some report this risk to be three fold higher [66]. The majority of systematic reviews in children and adolescents with SMI conclude that antipsychotic medication exposure time and, specifically olanzapine, are the main modifiable risk factors for type 2 diabetes [65, 67]. The association between deleterious insulin resistance has also been shown especially with regard to olanzapine. UK guidance therefore recommends that olanzapine is not used first line in children and adolescents because of its potential metabolic effects [68].

In the paediatric population, antipsychotics are not only licensed in SMI but also in autism spectrum disorder (ASD) and Tourette syndrome. In clinical practice, antipsychotics are used even more broadly, including off-label, in other behavioural disorders. There is a paucity of data in this area but a 2007 Cochrane review in children with ASD reported additional weight gain of 1.7 kg with risperidone and 1.13 kg with aripiprazole compared to placebo [69].

1.4.3.3 Antipsychotic medication use in adults outside of SMI

Antipsychotic medications are also prescribed for people who do not have SMI. SGAs may be used in psychotic depression, drug resistant depression or obsessive-compulsive disorder (OCD) in addition to antidepressant medication. In a double-blind RCT of olanzapine plus sertraline versus olanzapine and placebo for psychotic depression, participants from all age groups experienced significant increases in weight (45.1 – 65.0%) while fasting blood glucose (FBG) levels increased significantly among younger adults. These metabolic changes are consistent with those reported during olanzapine treatment among younger adults with schizophrenia but the weight gain may also be due to recovery of weight lost during the depressive episode [70]. A recent review of antipsychotic augmentation in the treatment of OCD reported weight gain as the most common adverse effect and reason for discontinuation in both olanzapine studies [71].

Despite a lack of evidence of their effectiveness and safety concerns around increased mortality and cerebrovascular accidents, antipsychotics are also used to treat psychosis and persistent agitated behaviour in dementia and, less commonly, delirium. The metabolic adverse effects of antipsychotics, including weight gain, in this older population are less studied but appear to be less marked. A recent systematic review in this population included 16 drug-placebo RCTs and only four reported significant weight gain [72]. Hypotheses for this include the fact that weight loss is commonly seen in advanced dementia, particularly in nursing home populations. As this was the setting for many of the larger scale studies (median duration of stay 5.3 months in one study [73]), this reduced metabolic risk may not necessarily be similar for people living with dementia in the community. An extension of the original Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) examined efficacy and safety of SGA in 421 outpatients with Alzheimer's dementia. Reassuringly this found no adverse effect on glucose despite clinically significant weight gain in women taking SGA for more than 24 weeks. Compared to those not taking antipsychotics, the odds ratio for weight gain was 3.38 (95% CI 1.24 to 9.23)) [74]. Whether this weight gain could ultimately affect glucose metabolism is unknown. While disentangling a drug effect is again challenging, it appears that awareness by healthcare professionals is relevant in all people whatever their reason for antipsychotic medication use.

1.4.3.4 Dysglycaemia and type 2 diabetes

As in the general population type 2 diabetes is not inevitable in everyone who gains weight and the candidate is not aware of any prospective study that shows a clear relationship between antipsychotic medication related weight gain and incident type 2 diabetes. Glucose and diabetes have also been described as secondary outcomes in a number of RCTs and systematic reviews. Although we can use these data, the trials are generally underpowered to examine the link between antipsychotic medication use and diabetes, not least because the reporting of glucose has frequently been poor. There are several other sources of evidence that can also be considered. Case reports initially raised the question of a link between antipsychotic mediations and type 2 diabetes but are limited as the findings cannot be extrapolated to the wider population. Similarly drug safety reporting is limited by a lack of a control and can be influenced by selective reporting and recall bias. Nevertheless, they may provide an indication of the size of the association. The literature is fairly consistent in showing rates of type 2 diabetes in people with SMI that are two to threefold higher than the general population [75]. The majority of studies also suggest that antipsychotic medication treatment is associated with a higher prevalence of diabetes than those on no treatment [34, 76]. One meta-analysis found the prevalence of type 2 diabetes was 2.1% in untreated people with early schizophrenia compared to 12.8% in those taking antipsychotic medication [77].

The association with type 2 diabetes appears to differ between antipsychotic medications with SGA more strongly implicated. A number of systematic reviews and meta-analyses of RCT have been published on this topic with one meta-analysis reporting a 32% higher relative risk of type 2 diabetes in adults prescribed a SGA than in those on a FGA [78]. A meta-analysis of head-to-head comparisons of the SGA found olanzapine and clozapine, considered the most potent for symptom control, produced a statistically significantly greater increase in glucose levels from baseline to endpoint than amisulpride, aripiprazole, quetiapine, risperidone and ziprasidone [54]. In one small RCT involving 15 normal weight healthy volunteers, olanzapine showed a 42% increase in the glucose area under the curve compared to placebo during an oral glucose tolerance test (OGTT) [79]. A recent systematic review of population based studies also concluded that clozapine and olanzapine are the SGA most strongly associated with type 2 diabetes [80]. A meta-analysis has also reported that the association of type 2 diabetes for olanzapine and clozapine also appears to be independent of whether they are used in antipsychotic medication naïve or chronic disease (RR 1.45, 95% CI 1.28-1.64 for clozapine and RR 1.29, 95% CI 1.20-1.37 for olanzapine) [76].

A large number of observational pharmaco-epidemiological studies and meta-analyses have linked antipsychotic medications with the development of type 2 diabetes. While these types of studies include large numbers of people exposed to antipsychotic medications, many fail to adjust for known important confounding risk factors for type 2 diabetes. Further limitations include the quality of clinical data and confounding by indication, namely as reports emerged about the association between type 2 diabetes and antipsychotic medications it is likely that clinicians took into account perceived metabolic side effects when choosing an antipsychotic medication. It is, therefore, possible that drugs with a lower propensity to cause weight gain or metabolic side effects may be preferentially used in people with the highest risk of type 2 diabetes, thereby attenuating any observed difference in diabetes or glucose changes with drugs with a higher propensity to cause metabolic side effects. Despite these limitations, however, they add to the body of evidence and along with secondary outcomes from RCTs need to be considered to build a full picture.

It is important for healthcare professionals and people with SMI to consider that most people taking antipsychotic medications will not develop diabetes. The two largest RCTs to assess the effectiveness of antipsychotic medications for psychiatric symptoms (primary outcome) included glucose measurements [44, 81]. Small differences in glucose measurements were seen but there were no reported differences in rates of type 2 diabetes. While CATIE [81] showed an increase in HbA_{1c}, especially in those treated with olanzapine (+0.41 % (4 mmol/mol) from baseline), 25.7% of participants had evidence of impaired glucose metabolism at the start of the trial as assessed by a

fasting glucose concentration of >5.6 mmol/L. Arguably therefore, those with and without initial glucose abnormalities should have been analysed separately. In the Effectiveness of antipsychotic medication drugs in first-episode schizophrenia trial (EUFEST), the mean change in glucose concentration over 12 months ranged from 0.2 to 0.5 mmol/L; no statistically significant differences between antipsychotic medications were seen [44]. Dysglycaemia below the diagnosis cut off for diabetes is, however, also a risk marker for future CVD and mortality and, therefore, it is worth bearing in mind that these small changes in glucose might translate into clinical consequences in the long term.

Weight independent insulin resistance mechanism

An alternative explanation is that antipsychotic medications directly cause type 2 diabetes through increased insulin resistance independent of changes in BMI, impaired β-cell function or both. This is an important area to consider as a number of people develop type 2 diabetes while taking antipsychotic medications without weight gain and these medications have also been associated with potentially fatal diabetic emergencies.

A unifying property of all antipsychotic medications is their blockade of dopamine D2 and D3 receptors. Dopamine plays a role in central glucose regulation and D2 and D3 receptors are also found in beta cells. Through negative feedback, dopamine inhibits further insulin release, and chronic insulin secretion may promote insulin resistance similar to hyperinsulinemia in type 2 diabetes [82]. In type 2 diabetes, insulin resistance may contribute to the exhaustion of β-cells.

The hypothesis that antipsychotic medications provoke glucose and insulin disturbances independent of weight-gain is also supported by the clinical trial of olanzapine in healthy volunteers that was discussed earlier. A further clinical trial showed increased fasting insulin resistance levels in hospitalised patients taking olanzapine over 5 months compared to risperidone, despite no significant weight change. There were no differences between C-peptide levels or measures of insulin secretion [83]. Marked acute hepatic insulin resistance has also been demonstrated with intravenous olanzapine in healthy rats [84].

Insulin secretion

A recent systematic review reported 72 cases of antipsychotic medication associated diabetic ketoacidosis (DKA), a state of marked insulin depletion [85]. The review found associated weight gain in only half of the reported cases and DKA was the first clinical presentation of diabetes in the majority. More than half were associated with polypharmacy which, for individuals not on clozapine, is only appropriate in a few circumstances but remained at an average of 11% in the 2014 National Audit of Schizophrenia [86]. Autoantibodies were only measured in 13 cases but

were negative in 85%, supporting the argument that these are generally not new cases of autoimmune type 1 diabetes and a direct toxic effect of the antipsychotic medication should be considered.

Antipsychotic medications act on multiple receptors that are found both in the brain and the islet β-cells and could affect insulin secretion. Antagonism of the muscarinic M3 receptor is one such example [61]. One RCT concluded that amisulpiride but not olanzapine appears to acutely increase pancreatic insulin secretion in healthy individuals and that stimulation of β-cells could be a protective factor against the development of type 2 diabetes. Antipsychotic medications have partial $5HT_{2c}$ properties; full agonists have been shown to reduce insulin secretion in isolated islets in animal studies [84]. Finally *in vitro* effects have suggested clozapine has a direct effect to inhibit glucose-dependent insulin release by β-cell membrane hyperpolarization [87].

In summary, there appears to be a link between the use of antipsychotic medications and the development of overweight and obesity. The overall absolute risk of antipsychotic medications and type 2 diabetes, however, is small and it is likely that the drugs may accelerate the presentation of diabetes rather than precipitate the disease *de novo* in most cases.

1.5 Current management of overweight, obesity and type 2 diabetes in people with SMI

The burden of overweight and obesity in people with SMI is a concerning issue. Given the increased risk of CVD in people with SMI, special attention needs to be paid to preventing obesity and type 2 diabetes in this population where possible. Intentional weight loss in the general population is associated with decreased mortality and improved health [88]. It is likely that similarly effective interventions for people with SMI will also lead to improvements in health and would be a major step towards reducing the health inequalities experienced by people with mental illness.

1.5.1 Screening and monitoring

Monitoring and prevention of weight gain as well as screening for its potentially reversible consequences are important components of the physical health care of those taking antipsychotic medications. This has been acknowledged in numerous national and international guidelines [89].

While the fundamental principles of many of the guidelines are in agreement, there are some areas where recommendations differ. Conflicting views on both clinical matters and ambiguity over roles (i.e. who should do the monitoring) can result in inertia. A review of UK psychiatry

healthcare professionals found that 17% thought it was not part of their role to provide advice about weight [90] despite national guidance stating that 'the secondary care team maintains responsibility for screening and monitoring metabolic risk factors for the first twelve months or until the condition has stabilised – whichever is longer' [68]. Reasons from mental health professionals for this discrepancy included 57% being worried about treating obesity and type 2 diabetes and a lack of incentive. This highlights the need for education of healthcare professionals as some may be unfamiliar with the notion of metabolic risk and the importance of assessing and treating this. Appropriate agreement about clinical responsibility is also needed to ensure joint working across mental and physical as well as primary and secondary care teams. Recently integrated pathways have proven beneficial in ensuring adequate monitoring and advice but long term outcomes are yet to be evaluated [91].

Thorough evaluation is essential to identify those at greatest risk of metabolic side effects and to plan appropriate monitoring and therapy. Initial evaluation should ideally include pre-treatment screening as well as education. Medical history should include personal and family history of obesity and diabetes and other non-modifiable risk factors for diabetes such as age, sex and ethnicity. Clinicians should also enquire about lifestyle, diet and exercise history. The candidate will now consider screening and monitoring of overweight or obesity and its consequences but interventions for other key cardiovascular risk factors such as smoking cessation should not be forgotten.

1.5.1.1 Weight

All people with SMI and their carers should be made aware of the risk of weight gain as part of their psychiatric diagnosis. This is especially important for people who are overweight or obese at the start of therapy or have a family history of obesity or diabetes. All people taking antipsychotic medications should also be encouraged to monitor their own weight and report any weight change to their treating clinician. Giving quantitative estimates of expected weight gain with different antipsychotic medications can help individuals make an informed decision about treatment [92]. Guidelines, which focus on children and adolescents, advocate that primary prevention of overweight and obesity should be the highest priority in this age group [93].

The British Association for Psychopharmacology (BAP) guidelines recommend that BMI is calculated weekly for the first 4-6 weeks for up to 12 weeks, then six monthly and at least annually thereafter [94]. The European consensus statement [95] suggests that the frequency of testing will depend on the person's history and prevalence of risk factors. Pragmatic recommendations such as 'monitoring may be carried out less frequently once weight has

stabilised, but closer monitoring of weight may be required in those gaining weight or changing antipsychotic medication' seems reasonable.

Weight gain and a diagnosis of type 2 diabetes can also reinforce an individual's negative view of themselves and individuals may wish to stop the implicated medication [90]. If the weight gain associated with antipsychotic medications results in some people discontinuing their medication, the candidate hypothesises that effective weight management strategies may also lead to improved adherence to antipsychotic medication and reduced relapse and hospitalisation.

Whilst measurement of waist circumference provides a better indication of adiposity linked to CVD, it is generally felt to be intrusive and may be less practical in psychiatric settings. NICE advocate its use, in addition to BMI, in people with a BMI less than 35 kg/m^2 [6].

1.5.1.2 Dysglycaemia and type 2 diabetes

From a dysglycaemia point of view, the BAP guidelines advise using fasting or random blood glucose measurements initially and at 12 weeks but HbA_{1c} in the longer term [96]. This is to avoid false negative HbA_{1c} results shortly after initiation if glucose levels rise sharply. While many other guidelines recommend the use of FBG in the longer term, this is likely because they were published at a time when this measurement was seen as the "gold standard" prior to the World Health Organisation inclusion of HbA_{1c} as a diagnostic test for diabetes. HbA_{1c} has the advantage of not requiring fasting, which can be challenging, and is therefore generally considered appropriate. The fact that HbA_{1c} may not detect all glucose abnormalities, as it is a reflection of glycaemia over a 3 month period and therefore not useful for detecting acute changes and can be affected by other factors such as haemolytic anaemia, should be remembered [97]. As this blood test is a reflection of glycaemia if symptomatic, fasting or random blood glucose measurements should be taken. Finally while the use of simple finger prick tests is sometimes advocated for simplicity, any results outside the normal range must be confirmed by laboratory testing. In order for people to seek advice and testing to confirm a diagnosis of diabetes, the importance of education concerning the acute symptoms of diabetes cannot be underestimated. Once established on medication, quarterly, biannually or annually measurements of HbA_{1c} are advised depending on the guideline. A repeat metabolic risk assessment is universally recommended if individuals are switched from one medication to another.

While the numerical cut off at which one has 'pre-diabetes' remains controversial, it is well accepted that there is a group of the population at high risk of developing type 2 diabetes. Closer monitoring of weight and glucose measurements, combined with intensive advice and support on diet and exercise is generally recommended. Some guidelines recommend using a specific

diabetes risk score assessment tool, such as the QDiabetes risk calculator or the Leicester practice risk score [98]. Others, however, worry that these tools were designed for adults over the age of 50 years and given the concerns about risk of type 2 diabetes in children and adolescents as well as young adults, believe a more specific SMI validated risk score is needed for this population [95].

It is recognised that this screening and monitoring is often not being done in routine clinical practice. A recent audit in the UK found that only 56% of people with schizophrenia had a record of blood glucose control [90]. This figure was identical in a meta-analysis of studies examining routine metabolic screening practices in those taking antipsychotic medication in five countries (56.1% (95% CI 32.4-63.7)) [99]. In a number of cases, local or national guidelines were then implemented and direct head-to-head pre- and post-guideline implementation showed a modest but significant (15.4%) increase in glucose testing. Although guidelines can increase monitoring, unfortunately most people still do not receive adequate testing. Access to healthcare settings can be perplexing for people with SMI and equality of access and communication across boundaries is therefore required to ensure that this is not a barrier. The importance of opportunistic screening of established and modifiable risks for the development of type 2 diabetes in psychiatric inpatient settings, if not already performed in the community, was therefore discussed in the UK's first joint diabetes and psychiatry guidelines [92].

1.5.1.3 Dyslipidaemia and hypertension

Given the morbidity and mortality associated with SMI other cardiovascular risk factors caused by overweight and obesity, namely dyslipidaemia and hypertension must also be addressed. The Lester UK 'Don't just screen; intervene' guidelines were designed to help front line staff make assessments of cardiac and metabolic health. In these they advocate aiming for a BP<140/90mmHg and considering statin treatment for primary prevention if an individual's Qrisk-2 score is ≥10% or aiming to reduce non-HDL cholesterol by 40% if an individual has already had a cardiovascular event [100].

1.5.2 Lifestyle interventions

Most SMI guidelines recommend advice on physical activity, diet, psychoeducation of the individual and their family, and referral for advice and treatment. These should aim to help someone who is overweight or obese to achieve and maintain a 5–10% weight loss and progress to a healthy weight. Advice should be simple and focused on the importance of diet and exercise in preventing initial weight gain. The importance of behaviour change should be frequently emphasised to enable this to be put into practice. Providing information on local facilities for exercise and physical activity or relevant support groups and weight management groups should

be made available to individuals who are already overweight. The NICE guidance recommends that this guidance should be provided as a combined programme by mental health care providers [37]. Only 58.2% of people asked, however, felt they had been given advice about diet and nutrition as part of their mental health care [90].

While lifestyle interventions remain the cornerstone intervention in the management of SMI guidelines many mental health trusts struggle to implement this. This may be because it is unclear how these should be delivered in this specific population. As discussed earlier, evidence based programmes such as the NHS DPP, did not included individuals with SMI. Although no lifestyle diabetes prevention trials have been undertaken in people with SMI, a number of studies have assessed the effect on body weight. A meta-analysis of non-pharmacological interventions in people with SMI reported a mean reduction in weight of 3.12 kg over a period of 8-24 weeks [101]. However, the results of longer-term studies are more mixed. A recent meta-analysis found significant weight loss in only two of six studies with interventions lasting longer than a year [102]. Most studies have included a mixed population of people with SMI and two large studies which included only people with schizophrenia found no effect of a lifestyle intervention on body weight [103, 104]

Two long-term trials from the US have shown that intensive lifestyle management over a year can achieve significant weight loss. The ACHIEVE study studied the effect of combined group weight-management sessions (weekly in the first 6 months then monthly), monthly individual visits and thrice weekly group activity classes in 291 people attending community psychiatric outpatients [105]. The intervention resulted in a mean weight loss of -3·2 kg over 18 months. The more recent STRIDE study found a 4.4 kg weight reduction in intervention participants compared to usual care after 6 months but this difference fell to 2.6 kg by 12 months when the intensity of the intervention was reduced [106].

In both of these studies, significant numbers of the participants had mental illness other than schizophrenia spectrum disorders, for whom behaviour change may be easier to achieve. The importance of these diagnostic differences may explain why the UK STEPWISE and Danish CHANGE study had different outcomes [103, 104]. STEPWISE was a two-arm, analyst-blind, parallel-group, RCT of a lifestyle intervention versus standard care in 414 participants. After 12 months, weight change did not differ between the groups (mean difference 0.0 kg, 95% confidence interval -1.59 to 1.67 kg; p = 0.964) [103]. CHANGE randomised 428 people with schizophrenia spectrum disorders and abdominal obesity to 12 months of intensive lifestyle coaching plus care coordination, or care coordination, or usual care alone and found no reduction in body weight or waist circumference with either intervention [104].

The PRIMROSE trial also showed no improvement in cholesterol levels in the intervention group despite appointments with a trained primary care professional involving manualized interventions for CVD (mean total cholesterol 5.4mmol/l [SD 1.1] *vs.* 5.5 mmol/l [1.1]) [107]. Whilst these three large trials have highlighted how prevention is key two other studies, the SCIMITAR+ (smoking cessation) and Keeping the Body in Mind (a lifestyle and life skill intervention for positive cardio metabolic health in youth with first episode psychosis), demonstrated more positive results. The SCIMITAR+ study showed a reduction in smoking rates and in Keeping the Body in Mind participants maintained their baseline weight although this was a non-randomised service evaluation [108, 109].

1.5.3 Antipsychotic medication switching

In clinical practice, switching antipsychotic medication is common; however, evidence for an effect on weight and glucose metabolism is limited. Although switching to an antipsychotic medication with a lower propensity to increase weight may help, given the heterogeneity of weight gain amongst individuals this is by no means a guaranteed solution. Situations where this approach may be appropriate, include people who experience a >5% increase in body weight from baseline or worsening glycaemia. Four studies were included in a Cochrane review looking at 'Antipsychotic switching for people with schizophrenia who have neuroleptic induced weight or metabolic problems'. There was a mean weight loss of 1.94kg (2 RCT, n=287, CI -3.9 to 0.08) when switched to aripiprazole or quetiapine from olanzapine [110]. Antipsychotic medications should be cross-titrated gradually and abrupt withdrawal should be avoided. Particular caution should be taken when considering withdrawal of clozapine because of the potential for serious psychological sequelae.

Another strategy considered by the BAP guidelines was the addition of an antipsychotic medication with a perceived lower obesogenic potential as the addition of aripiprazole to clozapine and olanzapine led to a 2 kg weight loss [111]. The degree of polypharmacy in this scenario must also be considered.

1.5.4 Current pharmacological options

The psychosis and schizophrenia NICE guidance recommends offering interventions in line with their obesity guidance if a person has rapid or excessive weight gain [37]. A variety of treatments have been subject to clinical studies but Rimonabant, a central cannabinoid acting receptor antagonist was withdrawn by the European Medicines Agency in 2009 because of concerns of psychiatric adverse events and sibutramine was similarly withdrawn in 2010 due to concerns

around increased rates of CVD [112, 113]. Currently no drug treatments are licensed for the treatment of antipsychotic medication associated weight gain or obesity in people with SMI with the exception of orlistat which has been available for use in the UK since 2010 [114]. Orlistat acts by reducing the absorption of dietary fat. The long-term use of the latter, however, is extremely limited by high discontinuation rates, making it of little value in routine clinical practice [115]. The use of topiramate is also severely limited by adverse effects (including anxiety, ataxia and confusion) however, three out of four RCTs of topiramate as an adjunct to antipsychotic medication reported statistically significant weight loss, ranging from 1.5 kg to 5 kg including one RCT supporting an effect to attenuate weight gain in people with a first episode psychosis [94].

Short term studies suggest metformin, a biguanide, may attenuate antipsychotic medication associated weight gain while it has also been shown to reduce the incidence of type 2 diabetes in the general population [116]. Despite metformin having little effect on body weight in the general population, this drug has been extensively studied in people taking antipsychotic drugs. Systematic reviews of short term RCTs of metformin found metformin reduced antipsychotic medication associated weight gain by a mean of -3.17 Kg (95%CI - -1.90 to -4.4) over a period of three to six months [116]. Greater weight loss, however, is likely to be needed to prevent health implications. A double blind clinical trial of metformin versus placebo in combination with antipsychotic medications with a primary outcome of glucose measurements (HbA_{1c} and OGTT) is currently recruiting [117]. While metformin is generally safe it requires multiple daily doses, is not licensed for weight loss and is not appropriate for individuals with alcohol dependence syndrome, 20.6% lifetime risk in people with SMI, because of the risk of lactic acidosis.

While the optimal weight management of people with SMI remains uncertain, the candidate hypothesises it is likely to include a multimodal approach which includes individually tailored lifestyle advice, optimisation of antipsychotic medication and adjuvant therapies.

1.5.5 Type 2 diabetes management

Type 2 diabetes is initially often asymptomatic and it is estimated that up to 70% of cases in people with SMI are undiagnosed. However, appropriate monitoring should establish this diagnosis and guidelines generally then advise a referral to the general practitioner or local diabetes team. The management of type 2 diabetes in people taking antipsychotic medication should follow the same principles and guidance of the general population with type 2 diabetes [118]. In addition, it is worth considering a multidisciplinary team (MDT) approach as it is recognised that people with SMI often benefit from this. Medications that may contribute to weight gain should be avoided where possible while newer agents, such as GLP-1 receptor

agonists and sodium glucose cotransporter 2 inhibitors, may be appropriate. Cardiovascular risk should be aggressively managed along with an annual assessment to review and screen for early signs of retinopathy, neuropathy and diabetic nephropathy.

While there is agreement that people with type 2 diabetes taking antipsychotic medications should have access to the same high quality care as the general population making this a reality is more challenging. Less than half of those with SMI and type 2 diabetes met the glycaemic control target of HbA_{1c} <58mmol/mol (7.5%) and their risk of diabetic complications is increased [98]. Care pathways for people with mental health problems and type 2 diabetes are often fragmented which builds barriers for people with SMI [90]. Stigma around mental health remains an issue and it is recognised that individuals with psychiatric disorders often struggle to access routine physical healthcare or establish timely contact for acute issues as a result of both mental health and organisational reasons. The ability for healthcare providers to share core relevant information is also often lacking.

1.6 Glucagon - like peptide 1

GLP-1 is a physiological regulator of appetite and food intake [119]. GLP-1 is an incretin hormone which is produced and secreted by intestinal endocrine L-cells which are most prevalent in the ileum and colon [119]. Incretins are released after eating and have a broad range of actions. They augment the secretion of insulin released from pancreatic beta cells of the islets of Langerhans [120] and also inhibit glucagon release from the alpha cells of the islets of Langerhans which together with its actions on beta cells lowers blood glucose levels [119]. The effects are more pronounced at higher levels of blood glucose and cease as values reach 4-5mmol/L [120]. In addition, the hormone slows the rate of absorption of nutrients into the blood stream by reducing gastric emptying and secretions. GLP-1 is extremely rapidly metabolised and inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) even before the hormone has left the gut meaning it has a half-life of 1-2 minutes [119]. Given the short half-life and the fact that the glucagon-like peptide 1 receptors (GLP-1r) are found not only on beta cells of the pancreas but also on neurons of the brain the neural mechanisms of GLP-1 action is of interest. Centrally acting GLP-1 also reduce food intake through at least two mechanisms. GLP-1r in the hypothalamus appear to reduce intake by acting on caloric homeostatic circuits , whereas GLP-1r in the amygdala reduce food intake by eliciting symptoms of stress or malaise [11].

1.6.1 GLP-1 receptor agonists

Owing to dual benefits on glycemic control and body weight, GLP-1 receptor agonists have a unique therapeutic action for both type 2 diabetes and obesity and as such were originally licensed for the treatment of type 2 diabetes in 2005. By mimicking the GLP-1 hormone they stimulate insulin secretion and lower glucagon secretion in a glucose-dependent manner which results in a lowering of fasting and post-prandial glucose levels. The glucose-lowering effect is more pronounced in patients with pre-diabetes and diabetes compared to patients with normoglycaemia. Clinical trials suggest that GLP-1 receptor agonists also improve and sustain beta-cell function, according to homeostatic model assessment of beta cell function, and the proinsulin-to-insulin ratio [121].

As a class of drugs they mediate weight loss in humans mainly by reducing appetite and caloric intake, rather than increasing energy expenditure and have therefore become of interest for the management of obesity [122]. In animal studies, peripheral administration of GLP-1 receptor agonists led to uptake in specific brain regions involved in regulation of appetite, where, via specific activation of the GLP- 1r, increased key satiety and decreased key hunger signals, thereby leading to lower body weight. Beneficially they lower body weight in humans mainly through loss of fat mass with relative reductions in visceral fat being greater than for subcutaneous fat loss.

1.6.2 Liraglutide (maximum dose 1.8mg)

Liraglutide is an acylated human GLP-1 analogue with 97% amino acid sequence homology to endogenous human GLP-1 and binds to and activates the GLP-1r but has a significantly longer half-life (12-14 hours) [122]. It was was originally licensed for the treatment of type 2 diabetes, up to a maximum dose of 1.8mg, under the trade name Victoza®[123]. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids [122]. In the Liraglutide (maximum dose 1.8mg) Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial fewer participants, who had insufficiently controlled type 2 diabetes and of whom the vast majority also had established CVD, died from cardiovascular causes in the liraglutide group (219 participants [4.7%]) than in the placebo group (278 [6.0%]); (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). [124]

1.6.3 Liraglutide (maximum dose 3.0 mg) - Saxenda®

Liraglutide administered once daily, at the higher dose of 3.0 mg (trade name Saxenda®) was first approved for the management of obesity or in those with a BMI >27.5 Kg/m^2 if the individual has

an overweight related consequence in 2015 [123]. Going forward the candidate will refer to liraglutide (maximum dose 3.0 mg daily) by its trade name Saxenda® to avoid confusion. Weight loss is dose dependent. The efficacy and safety of Saxenda® has been evaluated in four double-blind, placebo-controlled phase 3 RCTs known as the Satiety and Clinical Adiposity Liraglutide Evidence in Nondiabetic and Diabetic people (SCALE) trials. A total of 5,358 participants were enrolled in these four studies. Superior weight loss was achieved with Saxenda® compared to placebo in people who are overweight or obese in all groups studied and Saxenda® is, therefore, one of the most potent licensed weight loss medications available.

The first trial, SCALE Obesity & pre-diabetes, involved 3,731 participants without diabetes who were stratified according to their pre-diabetes state at screening. People with severe psychiatric disorders were not eligible to take part. The candidate hypothesizes that this was due to a key exclusion criteria being was the use of medications that cause clinically significant weight gain or loss (i.e. antipsychotic medication) and the fact that rimonabant, another weight loss medication, was withdrawn worldwide in 2008 due to severe psychiatric side effects. Those without pre-diabetes were randomised to 56 weeks of treatment where as those with pre-diabetes were randomised to 160 weeks of treatment. 2,590 participants completed the study. At 56 weeks the Saxenda® group had lost a mean of 8.4±7.3kg of body weight in comparison to 2.8±6.5kg in the placebo group; a difference of -5.6kg ($p<0.001$). This equates to 63.2% of the intervention arm compared with 27.1% in the placebo arm group losing at least 5% of their body weight, and 33.1% and 10.6%, respectively, losing more than 10% of their body weight [125]. In the 160 week part of the trial, the primary efficacy endpoint was the proportion of participants with onset of type 2 diabetes evaluated as time to onset. 3% treated with Saxenda® and 11% treated with placebo were diagnosed with type 2 diabetes. The estimated time to onset of type 2 diabetes for people treated with Saxenda® was 2.7 times longer (with a 95% confidence interval of [1.9, 3.9]), and the hazard ratio for risk of developing type 2 diabetes was 0.2 for Saxenda® versus placebo [125].

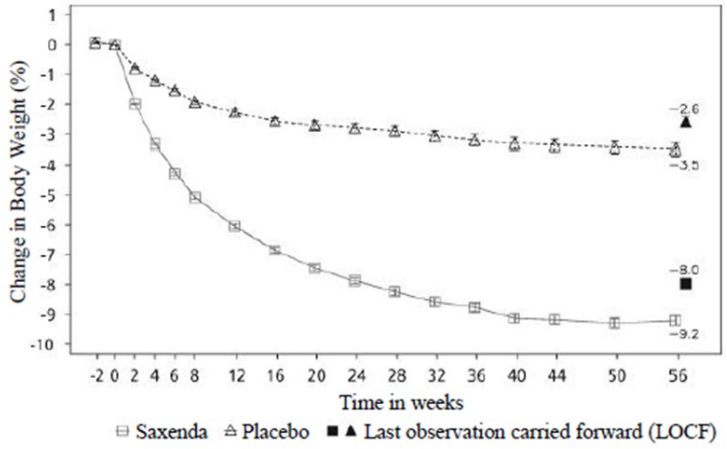


Figure 2 Change from baseline in body weight (%) by time in trial 1 (0-56 weeks) [122]

The second and third trial looked at people with insufficiently controlled type 2 diabetes (HbA_{1c} range 53-86mmol/mol) and moderate or severe obstructive sleep apnoea respectively [126, 127]. From a mean baseline weight of approximately 106 kg and a BMI of 37 kg/m^2, the weight loss for people treated with liraglutide 3 mg and liraglutide 1.8 mg after 56 weeks were 6% and 5%, respectively compared to a 2% weight loss for people treated with placebo. The proportion of people achieving a weight loss of at least 5% or 10% was 50% and 22% for liraglutide 3 mg, 35% and 13% for liraglutide 1.8 mg, and 13% and 4% for placebo treatment[126]. Treatment with liraglutide also significantly reduced the severity of OSA as assessed by change from baseline in the Apnoea-Hyponea index compared with placebo in a 32 week trial in 276 completers [127].

In the final SCALE trial body weight maintenance and weight loss in 422 randomised (305 completers) participants who were obese and overweight with hypertension or dyslipidaemia after a preceding weight loss of ≥5% induced by a low-calorie diet was assessed. More individuals maintained the weight loss achieved prior to treatment initiation with Saxenda® than with placebo (81.4% and 48.9%, respectively) [125].

In summary superior weight loss was achieved with Saxenda® compared to placebo in participants who were obese or overweight in all groups studied. Across the trial populations, greater proportions of participants achieved ≥5% and >10% weight loss with Saxenda® than with placebo. Early responders, defined as participants who achieved ≥5% weight loss after 12 weeks of Saxenda® treatment, predicted those who would have the greatest response at 1 year - 51% are predicted to achieve a weight loss of ≥10% after 1 year of treatment versus 93.4% who will not

reach ≥10% after 1 year if not in the early responders group [128]. Treatment with Saxenda® also significantly improved glycaemic parameters across sub-populations with normoglycaemia, pre-diabetes and type 2 diabetes. In the 56 week part of trial 1, fewer participants treated with Saxenda® had developed type 2 diabetes compared to participants treated with placebo (0.2% vs. 1.1%). More participants with pre-diabetes at baseline had reversed their pre-diabetes compared to participants treated with placebo (69.2% vs. 32.7%). Finally Saxenda® also significantly improved systolic blood pressure and waist circumference compared with placebo, both known cardiometabolic risk factors.

From a safety point of Saxenda® has been evaluated for safety in five double blind, placebo RCT that have enrolled 5813 participants in total. Gastrointestinal symptoms, namely nausea and diarrhoea, were the most common recorded adverse reactions (≥1/10) [122]. Most episodes were mild to moderate, transient and did not result in discontinuation of the medication (9.9% withdrew due to adverse events in the SCALE Obesity trial). These reactions usually occurred in the first weeks of treatment and subsided with continued treatment over days or weeks. Saxenda® has also be shown to cause a number of serious adverse events namely cholelithiasis, acute cholecystitis and acute pancreatitis.

The outcome of NICE's review into the use of Saxenda® in the NHS for the management of obesity was published in December 2020. Before publication The Royal College of Physicians felt there was urgency to reach a decision on its appropriate use as it had been licensed for 3 years and available for over 18 months at the time of the scope consultation [129]. Saxenda® is now licensed alongside a reduced-calorie diet and increased physical activity in adults, only if:

- they have a body mass index (BMI) of at least 35 kg/m^2 (or at least 32.5 kg/m^2 for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the white population) and
- they have non-diabetic hyperglycaemia (defined as a HbA_{1c} level of 42 mmol/mol to 47 mmol/mol [6.0% to 6.4%] or a fasting plasma glucose level of 5.5 mmol/litre to 6.9 mmol/litre) and
- they have a high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia and
- it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service [130].

1.6.4 Previous trials using GLP-1 receptor agonists in SMI

To date, there have been three completed trials of GLP-1 receptor agonists in people with SMI and a systematic review and meta-analysis of their data [131-134]. Two of the studies were published in 2017 during the grant application process for the candidate's study and one in 2018 during the ethical approval process. This feasibility study, however, is the first to look at the use of a GLP-1 receptor agonist at the obesity dose rather than using a diabetes dose, in some cases off label, in people with SMI. The obesity dose of liraglutide (3.0mg) is almost 2-fold the antidiabetes dose of liraglutide (max. dose 1.8mg). The previous trial in people with SMI using liraglutide (max. dose 1.8mg) also focused on changes in glucose levels rather than body weight [133].

In the first published study, 45 people with schizophrenia were randomised to receive once-weekly subcutaneous exenatide long-acting release (LAR) (n=23) or placebo (n=22) injections for 12 weeks. Both groups lost weight during the trial (2.2 ± 3.3 Kg (exenatide LAR) and 2.2 ± 4.4 Kg (placebo) after 12 weeks of treatment with no difference between groups [131]. By contrast, in another small study (n= 28) comparing exenatide LAR with usual care for 24 weeks in participants taking clozapine, those receiving exenatide LAR had greater mean weight loss (−5.29 vs. −1.12 kg; P = 0.015), and HbA_{1c} levels (−0.21% vs. 0.03%; P = 0.004) [132]. While exenatide LAR may have advantages over daily liraglutide as it is a once-weekly injection, liraglutide both at the 1.8mg and 3.0mg has been demonstrated to be more efficacious [135, 136]. These findings also support the decision to use Saxenda® for 6 rather than 3 months.

In the final study, 103 people with schizophrenia and prediabetes, were randomised to liraglutide (maximum dose 1.8mg, the maximum diabetes dose) or placebo for 16 weeks [133]. Prediabetes was defined as an elevated fasting plasma glucose level of 110 to 125 mg/dL, elevated glycated haemoglobin level of 6.1% to 6.4%, and/or impaired glucose tolerance with a 2-hour plasma glucose level of at least 140 mg/dL during a 75-g oral glucose tolerance test. In this study, participants had to be on stable doses of clozapine or olanzapine for more than 6 months to be eligible. Glucose tolerance improved in the liraglutide group and body weight decreased with liraglutide compared with placebo (−5.3 kg; 95%CI, −7.0 to −3.7 kg). Other cardiovascular risks factors improved in tandem with the weight reductions; systolic blood pressure (-4.9 mmHg; 95% CI, -9.5 to -0.3 mmHg) and low density lipoprotein levels (-0.4 mmol/L; 95% CI -0.6 to -0.2mmol/L).

These studies showed promise that GLP-1 agonists may be both effective and tolerable treatments to facilitate weight loss in people with SMI. There was a large range between the screening to randomisation rate amongst the three trials (Ishøy et al 69%, Larsen et al 48% and Siskind et al 22%). None of the trials were done in the UK and the two with the highest rates were

both done in Denmark. As there was such variability establishing what the screening to randomisation rate would be in the UK required a pilot trial. Consistent with the studies by Larsen et al and Ishøy et al, the candidate believed it was important to have a placebo rather than usual care arm. Siskind et al justified their trial design (control arm had usual care rather than placebo medication) due to ethical concerns within the context of a pilot study in mental health patients, as well as budget constraints and concerns about reduction in recruitment or retention rates. A placebo controlled arm would be needed for a definite RCT and the candidate felt that it was important to assess whether the inclusion of a placebo prevented the team from recruiting and retaining participants in the trial. Importantly, psychological harm was also not reported in either of the two studies that used a placebo arm.

Research to date also does not determine whether liraglutide can be used as a preventive adjunctive treatment during the emergence of weight gain and metabolic abnormalities. As discussed earlier antipsychotic related weight gain and metabolic disturbances can be most profound at the beginning of treatment. Inclusion criteria for the Larsen et al study (using the diabetes dose of liraglutide) required participants to be on a stable antipsychotic medication dose for at least 6 months which would have, therefore, excluded this group of people. The candidate postulated, therefore, that an obesity dose of liraglutide in participants on a stable does of antipsychotic medication for a minimum of one month may offer even greater weight loss in people with SMI than looked at in the previous studies. The provision of an effective intervention to reduce the burden of overweight and obesity in people with SMI could improve physical health and reduce the risk of developing obesity related illnesses as well as improving psychological well-being.

1.7 Conclusion

People with SMI, especially those taking antipsychotic medications are at increased risk of overweight and obesity which contributes to their excess mortality. Overweight and obesity and mental illness can both be challenging lifelong conditions but opportunities exist to improve the current situation for this potentially vulnerable and high-risk group. Although antipsychotic medications appear to increase the risk of overweight and obesity, these potential adverse effects need to be balanced against the improved and lasting mental health benefits. As discussed there is currently limited evidence regarding improving the physical health of people with SMI. Greater attention in this area is needed and in order to do that that people with mental illness need to be included in appropriate trials. This in turn may help reduce the risk of widening health inequality.

GLP-1 receptor agonists have been shown to cause statistically significant weight loss in the general population and show promise in people with SMI. Saxenda® is the most potent weight loss drug currently available and to date this had not been used in people with schizophrenia, schizoaffective disorder and first episode psychosis. The candidate hypothesises that people with SMI will be willing to be recruited, retained and adhere to a double blind randomised controlled trial using Saxenda® and matching placebo.

Chapter 2 **Methods**

This chapter is based on the following publication which the candidate was first author of: [137]

Liraglutide and the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first-episode psychosis: protocol for a pilot trial. Clare Alexandra Whicher, Hermione Clare Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Claire Reidy, Kerensa Thorne, Carolyn Asher, Robert Peveler, Joanne McCarthy, Richard Ian Gregory Holt. Trials, 2019. **20** (1): p. 633.

2.1 Aims and objectives

The aim of this pilot study was to undertake a double blind randomised controlled trial to assess the feasibility and acceptability of delivering a full scale trial evaluating treatment with liraglutide 3.0 mg daily (Saxenda®) in comparison to placebo in 60 people with obesity or overweight with schizophrenia, schizoaffective disorder or first episode psychosis.

2.2 Ethical arrangements and trial registrations

2.2.1 Research Governance

Southern Health NHS Foundation Trust (SHFT) was the sponsor for the study. The University of Southampton approved the Electronic Research Governance Online (ERGO) submission on 27th February 2018 (reference: 31952).

UK Research Ethics Committee (REC), South Central - Hampshire approved the study on the 17th April 2018 (reference: 18/SC/0085). The study was approved following a non-substantial amendment (NSA) which was made to the original REC application following a panel meeting on 28th February 2018. The following changes were made:

1. The definition of serious adverse reactions was clarified. See 2.6.2.
2. The protocol was updated to clarify that heart rate and glycaemia assessments were taken at baseline and during trial participation (at 3 and 6 months).
3. A definition of the end of the trial was added as: *the date of the last follow up (including qualitative interview) of the last participant in the trial.*
4. A table of follow up activities describing the trial activities was added to the protocol.

Health Research Authority (HRA) approval was granted on 23rd April 2018. A second NSA was submitted on 11th June 2018, during the final preparation phase, to clarify the following points:

1. The protocol was amended to include the neuropsychiatric safety data for both 1.8mg and 3.0 mg of liraglutide. See 2.4.1.
2. The participant information sheet (PIS) was updated to reflect these neuropsychiatric safety data as above.
3. The PIS was updated to reflect the latest General Data Protection Regulation (GDPR) legislation as per HRA guidance.
4. The protocol was amended to include a description of the education participants will receive regarding using the injection pens.
5. The protocol was amended to confirm that participants will be told the results of any tests undertaken as part of the study.
6. The protocol was updated to include a description of the optional text message reminder service.
7. The protocol was updated to explain the optional qualitative interviews in more detail.
8. The Informed Consent Form was updated to make clearer that points 7 and 8 (text message reminder service and qualitative interview respectively) were optional parts of the study.

SHFT Research and Development (R&D) approval was granted on 2nd July 2018. Protocol version 1.6 (dated 22nd May 2018) was used during the running of the trial until 6th August 2019 when version 1.8 was approved by the HRA.

SHFT Research and Development (R&D) approval was granted on 2nd July 2018. Protocol version 1.6 (dated 22nd May 2018) was used during the running of the trial until 6th August 2019 when version 1.8 was approved by the HRA. For completeness version 1.7 was submitted to HRA regarding the addition of participant identification centres (PIC) sites and version 1.8 resubmitted with the addition that the direct care team will send a text message reminder if there has been no response within 2 weeks.

The main ethical issue discussed in the Integrated Research Application (reference: 235189) was the potential increased burden for participants in taking the medication, any potential side effects related to the medication as well as completing trial visit assessments. To mitigate this, as much as possible, the trial team informed participants about exactly what was involved, allowed for as many breaks as were needed during visits, and handled the assessments sensitively. Overall the candidate felt these risks were low and acceptable in view of the potential benefits.

2.2.1.1 Amendments during recruitment period

Two NSA and one substantial amendment (SA) were successfully submitted to REC during the trial's recruitment period.

NSA 3, for an additional version of the PIS, poster and leaflet (with email addresses and telephone numbers removed), for use in the inpatient setting, was approved on 2nd August 2018. NSA 4, for extension of recruitment from 31st July 2019 until 31st October 2019, was approved on 17th July 2019. SA 1, for the addition of participant identification centres (PIC) within West Hampshire and Southampton Clinical Commissioning Groups (CCG's), was approved by REC on 4th July 2019 and by HRA on 6th August 2019. REC reference: 18/SC/0085/AM04/1.

2.2.2 Amendment during Covid-19 global pandemic

A NSA was submitted during the Covid-19 global pandemic (20th March 2020) to allow remaining trial visits to be carried out a telephone appointments in lieu of face to face trial visits. The amendment also allowed participants to weight themselves, if possible, at home for the final trial visit. Staff carrying out the telephone visit read out the Standard Operating Procedure regarding measuring weight to ensure these readings were as accurate and in line with the normal trial procedures as was possible. No additional plans were made for the additional missing data that was encountered as a result of this situation as the numbers were small.

Medicine and Healthcare Products Regulatory Agency (MHRA)

The MHRA approved the request for the clinical trial authorisation (CTA) on 31st March 2018 (reference: 40031/0001/001-0001. EudraCT Number: 2017-004064-35). As the trial used a licensed product which has a Summary of Product Characteristics (SmPC) [122] the candidate did not need to provide an investigational brochure.

2.2.4 Trial registrations

The candidate registered the trial to obtain a Universal Trial Number (UTN): U1111-1203-0068 and International Standard Randomised Controlled Trial Number (ISRCTN): ISRCTN61129760.

2.3 Design

2.3.1 Design oversight

A trial management group (TMG), chaired by the candidate, was set up to design and develop the protocol and implement the trial. The group consisted of psychiatrists, diabetologists, a psychologist, an R&D manager and patient and public involvement representative.

2.3.2 Overview

The trial was a double blind randomised interventional pilot study of the use of a once daily injection of liraglutide 3.0 mg (Saxenda®) in comparison to placebo. As an effective treatment does not already exist the trial did not deprive the placebo group from an already existing effective therapy. It was important to include a double-blind placebo for two main reasons. First, there is evidence that people are less likely to consent to a trial that includes a placebo arm because of the risk of not receiving an active treatment [138]. As an assessment of our ability to recruit was one of our key aims, and the team wanted this study to be a pragmatic pilot run, it was important to assess whether the inclusion of a placebo prevented us from recruiting to the trial. In addition previous experience from weight management trials, that include pharmaceuticals, have also been troubled by high dropout rates in the placebo arm as the participants are able to assess the effectiveness of the treatment [125]. Drop-out from obesity trials is generally non-linear as those on active treatment drop out earlier because of side effects while those on placebo drop out later because of lack of efficacy [125]. To adequately power a full RCT of Saxenda®; the candidate would need to know this likely dropout rate.

After confirmation of meeting eligibility criteria at screening visit participants were then randomised to Saxenda® or placebo. Each participant then attended visits every 4 weeks to return and collect trial medication and for concomitant medications and adverse events to be reviewed. In addition, at the baseline, 3 and 6 month visits, participants had clinical data collected (secondary exploratory outcomes) including drawing fasting blood samples. The blood samples were analysed for fasting plasma glucose, lipid profile and HbA_{1c}. Participants were also invited at baseline and study completion to take part in one-to-one telephone or face-to-face interviews to explore expectations and experience of their participation in the trial.

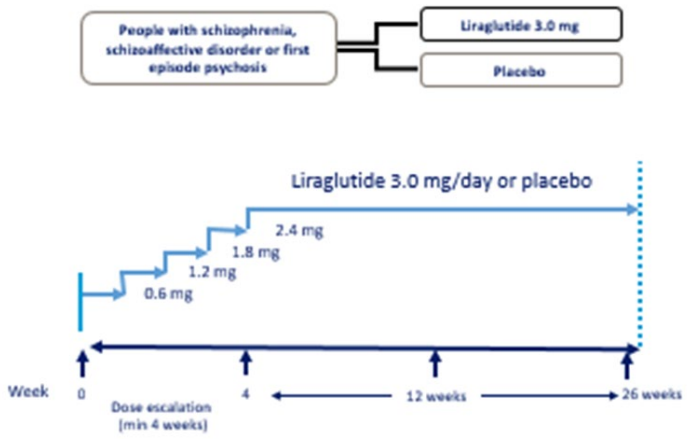


Figure 3 Overview of trial design

2.3.3 Sample size

The cohort size of a maximum of 60 was chosen, rather than calculated, as this pilot trial explored feasibility, practical issues of conducting a future definitive trial and estimating important parameters to help its design. In this regard, sample size was based on the need to estimate study parameters within a reasonable degree of precision rather than on hypothesis testing as there were limited data to base this on. Our recruitment target was an estimate, as in any pilot research study, of the number of people required to give a good approximation of these parameters. The trial team based the estimate on simulation work by Sim et al (2012) who recommended a minimum of 50 participants (25 per group) in order to achieve pilot/feasibility objectives, inflated to 60 to allow for drop-out [139]. A further paper by Whitehead et al recommended pilot trial sample sizes per treatment arm of 75, 25, 15 and 10 for standardised effect sizes that are extra small (≤0.1), small (0.2), medium (0.5) or large (0.8), respectively [140]. There are many other papers written on the appropriate sample size for feasibility studies which highlights the many differing views. Where there is no prior information, a sample size of 12 per group has been justified while other authors argue the number of participants to be included in the pilot study will depend on the parameter(s) to be estimated [141, 142].

Based on the participant acceptance rate from the SHFT site of the STEPWISE trial [103] the TMG assumed that 30% of service users would be willing to take part. In a pilot trial examining the use

of once daily exenatide LAR in people with schizophrenia, out of 123 potentially eligible participants, only 28 were randomised with 95 excluded (63 declining to participate and 32 not meeting the inclusion criteria) [132]. In a similar study by Larsen et al which used liraglutide (maximum dose 1.8 mg) 214 potential participants were assessed for eligibility and 103 were randomised. Of the 111 excluded 86 did not meet final inclusion/exclusion criteria, 23 declined to participate and two had too severe degree of mental illness to participate [133]. The candidate used these data to estimate the screen-to-randomisation rate. In the Larsen et al study, 10% of the liraglutide (maximum dose 1.8 mg) arm and 2% in the placebo arm dropped out of the trial by 16 weeks [133]. In the SCALE Obesity trial a total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the placebo group, completed the trial [125]. Based on this the candidate assumed a conservative dropout rate at 6 months of between 15% to 20%. Confirming these screening, enrolment and dropout rates was an important aim of the study.

2.3.4 Setting

The study was carried out in a variety of different community and inpatient mental health locations in SHFT, UK. For any trial the population sample needs to be representative in order that any conclusions are transferable. SHFT is one of the largest mental health foundation trusts on the south coast. The Trust covers a population of 1.4 million and covers a diverse mix of urban inner city and rural locations. Trial visits took place in the Tom Rudd unit in Moorgreen hospital, a community outpatient mental health site, because this was a convenient and familiar location for a number of participants.

To assess the feasibility of the study being carried out in SHFT, the number of people with a recorded diagnosis of schizophrenia or one of its subtypes attending community and inpatient settings was audited and found to be 842 individuals. 341 of this cohort had a recorded BMI and of these 193 (58%) were identified as obese and a further 96 (28%) had a BMI between 27 and 29.9 Kg/m^2. The TMG therefore estimated that ~70% of these individuals fulfilled the inclusion criteria equating to approximately 500 eligible individuals across the trust. SHFT had also recently recruited 55 participants, with similar entry criteria, for the STEPWISE trial over a 7 month time period. The candidate therefore estimated that the trial team could recruit 60 people for the study within a 12 month period.

2.3.5 Patient and public involvement

Patient and public involvement (PPI) was actively included throughout the development and running of the trial. A service user researcher, who was a member of the TMG, leads a team which

comprises of people with mental health diagnoses. Another PPI representative was on the Trial Steering Committee (TSC) which allowed them to support each other with their roles on the committees.

During the study design process the PPI lead recommended that people should be able to self-refer to the study via a poster and that participants should be given a leaflet summarising the injection technique that they would be taught at the randomisation visit. The poster, which was displayed in various mental health settings as part of the recruitment strategy, and other patient facing literature were designed with the support of this group. The PPI lead also recommended asking people if they wished to take part in the optional qualitative interviews at the visit beforehand to allow time to consider it. Finally it was suggested offering visits as an alternative to phone calls during the titration phase because some people with SMI do not like talking on the telephone.

One potential concern was whether participants could pretend to have taken the medication when they had not. The PPI team reassured the candidate that they felt this was unlikely and if an individual did not want to take the medication they would verbalise this and/or stop attending trial visits. They therefore thought that bringing empty injection pens would allow the trial team to assess adherence to the medications. A daily text message, asking if a participant had taken their daily dose, was agreed to be a useful reminder.

2.3.6 Selection and consent

Potential participants were identified in the following ways:

1. The study was promoted within outpatient and inpatient clinical teams and other clinical areas where community mental health services are delivered in SHFT. Potential participants were then approached by members of their clinical care team.
2. Leaflets and posters were displayed in various mental health service provision locations so that service users could self-refer.
3. A GP practice within SHFT, the Willow group, sent out invitation letters to 50 of their registered patients who were potentially eligible.
4. Using the trusts sharing information about research procedure. This records patients' preferences in relation to being directly contacted by researchers about research studies, for which they are eligible. The research team approached those who had 'opted in' to this.
5. PIC sites within West Hampshire or Southampton Clinical Commissioning Groups (CCGs).

Only those who agreed to provide written informed consent were included in the study. The study was conducted in keeping with Good Clinical Practice (GCP) and the International Conference of Harmonization standards. Each potential participant was provided with a PIS and given a minimum of 24 hours to consider their decision (usually much longer). The written information included the most common adverse events and the procedures involved in the study.

In order to include the most appropriate population to assess the feasibility of this study, clearly defined inclusion and exclusion criteria were drawn up and are listed below along with the rationale for each criterion. Eligibility was always assessed by an investigator.

2.3.6.1 Inclusion criteria

1. Age 18-75 years old.
2. Clinical diagnosis of schizophrenia or schizoaffective disorder or first episode psychosis using case note review. There was no limit on the duration of illness for those with schizophrenia or schizoaffective disorder.
3. Treatment with an antipsychotic medication, with a minimum duration of 1 month prior to entry in to the trial.
4. BMI, as defined by weight in kilograms (kg) divided by height in metres squared (m^2), of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related consequence such as dysglycaemia, hypertension, dyslipidaemia or OSA.
5. Ability to give written informed consent.
6. Ability and willingness to take Saxenda® or placebo.
7. Ability to speak and read English.

2.3.6.1.1 Age range

The therapeutic license of Saxenda® allows its use in patients aged 18 – 75 years [122]. Therapeutic experience of liraglutide in people older than 75 years of age is limited and use in this group is therefore not recommended.

2.3.6.1.2 Mental health clinical diagnosis

SMI diagnoses were confirmed with participants, and by consulting their electronic notes and GP summaries. Rationale for the inclusion of first episode psychosis and exclusion of bipolar disorder can be found below.

2.3.6.1.3 SMI definitions

For the purposes of this trial the following definitions were used:

- Schizophrenia was defined by ICD -10 code F20 [28]
- Schizoaffective disorder was defined by ICD -10 code F25 [28]
- First episode psychosis was defined as less than 3 years since first presentation to the mental health team or first antipsychotic medication prescription.

Although individuals with first episode psychosis do not fulfil the diagnostic criteria for schizophrenia or schizoaffective disorder the study team decided to include this group of people for the following reasons:

- 85% of people presenting with a non-affective psychotic episode (i.e. not mania and not depressive psychosis) will still meet criteria for a schizophrenia spectrum disorder 2 years later.
- People with first episode psychosis are more likely to be overweight prior to psychotropic drug initiation than the general population. This is mainly due to the negative symptoms that often make up the 'prodromal period'.
- Between 37 and 86% of individuals treated with antipsychotic medications during a first episode of psychosis gain more 7% of their body weight within 12 months, often within the first 12 weeks of treatment and therefore appear to be most susceptible to the risk of significant weight gain [143].
- There is a paucity of data in this group of people. While they were included in the STEPWISE trial this lifestyle intervention did not demonstrate a clinical benefit [103].

The study team therefore felt that people with first episode psychosis are a group at high risk of developing weight induced metabolic abnormalities and consequently the benefits of weight loss may be greater.

Bipolar disorder is often included under the SMI umbrella but people with this diagnosis were not included. The reason for this is that while some studies have suggested that short-term lifestyle interventions could support weight reduction in people with SMI [14] two large studies, which did not included people with bipolar disorder, found no effect of a lifestyle intervention on body weight [16, 17]. These latter studies suggest the weight management in people with bipolar disorder may be more receptive to lifestyle interventions.

2.3.6.1.4 Antipsychotic medication

No restriction was placed on the class or generation of antipsychotic medication. A minimum of one month on antipsychotic medication was stipulated as weight change is common within the first weeks after starting these medications.

2.3.6.1.5 Body mass index

BMI of ≥ 30 kg/m² (obese), or ≥ 27 kg/m² to < 30 kg/m² (overweight) with a weight related consequence. These were in line with the therapeutic license of Saxenda® as was the lifestyle treatment provided as randomisation which was unexacting [122].

2.3.6.1.6 Definitions for weight related consequences

For the purpose of the trial the following definitions for the weight related consequences were used:

2.3.6.1.6.1 *Dysglycaemia*:

Glycated haemoglobin (HbA_{1c}) greater than or equal to 42 mmol/mol.

2.3.6.1.6.2 *Hypertension*:

A documented diagnosis of hypertension or systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg.

2.3.6.1.6.3 *Dyslipidaemia*:

Known diagnosis of dyslipidaemia and/or taking lipid lowering drugs.

2.3.6.1.6.4 *Obstructive Sleep Apnoea*:

Known diagnosis from a respiratory physician.

2.3.6.1.7 Written informed consent

Only those who agreed to provide written informed consent were included in the study. The research team were aware that people with SMI may be more likely to decline to take part in randomised trials because of mistrust and lack of motivation; furthermore, ensuring fully written informed consent may be more time consuming with potentially vulnerable people compared with other groups of patients.

2.3.6.1.8 Ability and willingness to take Saxenda® or placebo

Participants in the trial had to self-inject Saxenda® or placebo daily for 6 months and therefore had to be personally motivated to do this. The candidate taught each participant how to use the injection device face-to-face and provided an instruction leaflet.

2.3.6.1.9 Ability to speak and read English

Eligibility for participation in the trial was restricted to those who were able to speak and read English. Given the qualitative element of the study and importance of understanding instructions regarding how to self-administer Saxenda®, the inclusion of non-English speakers was felt to be outside the scope of this project. If a fully powered RCT was to follow on from this study then efforts would be made to include non-English speakers.

2.3.6.2 Exclusion criteria

In order to safely recruit a homogenous cohort of people the following exclusion criteria were required:

1. Physical illnesses that could seriously reduce their life expectancy or ability to participate in the trial.
2. A co-existing physical health problem that would, in the opinion of the principal investigator, independently impact on metabolic measures or weight, e.g. Cushing's syndrome, poorly controlled type 2 diabetes defined by HbA_{1c} >8% (64 mmol/mol).
3. Inflammatory bowel disease and diabetic gastroparesis.
4. Contraindications to Saxenda®:
    a. Hypersensitivity to liraglutide or to any of the excipients:
    b. Any condition which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
    c. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma. Family was defined as a first degree relative.
    d. History or presence of pancreatitis (acute or chronic).
    e. History of diabetic ketoacidosis.
    f. Any of the following: myocardial infarction, stroke, hospitalization for unstable angina or transient ischaemic attack within the past 180 days prior to the day of screening.
    g. Participants presently classified as being in New York Heart Association Class IV.
    h. Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
    i. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 ml/min/1.73 m^2 at screening.
    j. Impaired liver function, defined as alanine aminotransferase (ALT) ≥2.5 times upper normal limit at screening.
    k. Proliferative retinopathy or maculopathy requiring acute treatment.

l. Presence or history of malignant neoplasms within the past 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma in-situ were allowed.

5. Use of other pharmacological products for weight management.
6. Mental illnesses that could seriously reduce their ability to participant in the trial, including significant suicidality.
7. Current pregnancy or a desire to become pregnant. Mothers who were less than 6 months post-partum or breastfeeding were also excluded.
8. Significant alcohol or substance misuse which, in the opinion of the principal investigator, would limit the patient's ability to participate in the trial.
9. A diagnosis or tentative diagnosis of psychotic depression or mania.
10. A primary diagnosis of learning disability or cognitive impairment which would impair participant's ability to self-administer trial medication.
11. Lack of capacity. Those who lost capacity any time during the study were ineligible to continue and were withdrawn from the study immediately with no further study procedures carried out.
12. History of type 1 diabetes.
13. Current or previous use of incretin based therapies (GLP-1 receptor agonist or DPP-4 inhibitors) or insulin.

2.3.6.2.1 Physical illness affecting life expectancy or ability to take part in trial

Conditions that might affect the ability to participate might include rheumatoid arthritis if the participant does not have the manual dexterity to administer the injection or Alzheimer's disease if they do not understand how to inject. Other conditions such as terminal cancer and Chronic Obstructive Pulmonary Disease (COPD) may cause weight loss and so mask the effect of Saxenda®. The trial team were not explicit as there are many conditions that could have fulfilled this and it was therefore left to the investigator's discretion.

2.3.6.2.2 Physical illness that would independently impact on metabolic measures or weight

Saxenda® is not recommended where obesity is secondary to an endocrinological illness, for example Cushing's syndrome, or from treatment with medicinal products that have caused weight gain.

Poorly controlled type 2 diabetes, defined by an HbA_{1c} >8% (64 mmol/mol), was also an exclusion criterion as this can cause weight loss in its own right. Intensification of diabetes medication

would also likely be indicated and could include medications listed in 2.8.13. While liraglutide would be one of the potential treatment options there would only be a 50% chance in the trial that an individual would actually receive Saxenda® and unlike Victoza® (liraglutide maximum dose 1.8mg) Saxenda® does not have a license as a treatment for diabetes.

2.3.6.2.3 Inflammatory bowel disease and diabetic gastroparesis

There is limited experience in people with inflammatory bowel disease and diabetic gastroparesis. Use of liraglutide is not recommended in these individuals since it is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

2.3.6.2.4 Contraindications to Saxenda®

Saxenda® is not recommended to be used in any of the scenarios listed in 2.3.6.2.4 for safety or unknown efficacy reasons. As such people with any of these were excluded from the trial.

2.3.6.2.5 Medication which may affect weight

The efficacy of Saxenda® for weight management has not been established in people treated with other products for weight management. Additionally, whilst this was mainly a feasibility trial, if participants were on additional weight loss medication this could affect a number of the secondary exploratory outcomes.

2.3.6.2.6 Mental illness that could affect ability to take part in the trial

High levels of psychiatric symptoms, including suicidal ideation, could seriously affect individuals' ability to take part in a clinical trial and reliably administer a daily injectable medication. As such these people were excluded. Every patient in contact with SHFT has a risk assessment which is recorded on the electronic patient record called RIO. If the risk assessment states that they were at "High" risk of harm to themselves, they were excluded from the study. Any concerns during the trial were referred to the clinical care team (care coordinator, key worker or consultant).

2.3.6.2.7 Pregnancy, breastfeeding and women of childbearing age

There are limited data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown and liraglutide should therefore not be used during pregnancy. If a participant wishes to become pregnant they would also be excluded for the above reasons. Due to a lack of experience, Saxenda® should also not be used during breast-feeding as it is not known whether liraglutide is excreted in human milk. Animal studies have shown that the transfer of liraglutide and metabolites of close structural

relationship into milk is low. Non-clinical studies have shown a treatment related reduction of neonatal growth in suckling rat pups [122].

Pregnancy, breast feeding and the postpartum period are also associated with changes in weight which would affect secondary exploratory outcomes of the trial [144].

Any women who were not planning pregnancy but were of child bearing potential and unwilling to use a highly effective method of birth control (e.g. such as implants, injectable, combined oral contraceptives, some Inter Uterine Devices, sexual abstinence or vasectomised partner) were not eligible for the trial. The contraceptive effect of oral contraceptive products is anticipated to be unaffected when co-administered with Saxenda® despite delayed gastric emptying [122].

All women of child bearing potential underwent a urinary pregnancy test at the screening visit and were excluded if this was positive.

If any woman had become pregnant during the trial they would have stopped the study medication and been withdrawn. They would have been followed up to see if there was any effect on the baby at one month postpartum.

2.3.6.2.8 Alcohol or substance abuse

If an investigator believed that an individual's alcohol or substance misuse would affect their ability to take part in the trial then they would be excluded. This was assessed by an investigator taking a history from potential participants and reviewing their clinical notes. If there were any concerns the candidate discussed the scenario with the participants care co-ordinator with their permission.

Alcohol excess and substance misuse can impact an individual's weight and ability to take medication reliably. Typically this causes weight loss as excess alcohol can be associated with malnutrition [145].

2.3.6.2.9 Psychotic depression or mania

Epidemiological studies and studies of large samples of psychiatric populations indicate that 15-20% of individuals with major depression have psychotic features [146]. Individuals with a primary diagnosis of psychotic depression or mania have been found to be able to make lifestyle changes more effectively than those included in this study and have therefore been excluded [147].

2.3.6.2.10 Learning disability or cognitive impairment

A primary diagnosis of learning disability or cognitive impairment would exclude an individual if it prevented them from being able to independently administer the medication subcutaneously.

2.3.6.2.11 Lack of capacity

As with all research studies a potential participant would not be able to take part if they lacked capacity to give informed consent to be included in the trial. The study could include people who were detained under the Mental Health Act (most commonly Community Treatment Orders) if they had capacity to give informed consent to inclusion in the trial.

It should be highlighted that capacity to consent is an infrequent issue with people with schizophrenia; incapacity is most likely to occur when patients are just admitted to a psychiatric ward at the acute stage of illness. If there were any concerns from the clinical team about a participant's capacity in this situation then they would have been withdrawn from the trial.

2.3.6.2.12 Type 1 diabetes

Use of liraglutide, even at a lower dose (1.8mg) than used in this trial, in people with type 2 diabetes is associated with increased rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis [148]. All people with type 1 diabetes were therefore excluded for safety reasons.

2.3.6.2.13 Incretin based therapies or insulin

People who were already taking a GLP-1 receptor agonists were not able to take part in the study as there would be an unacceptable increased risk of side effects and adverse reactions. Any therapeutic effects of Saxenda® would also be diminished. People taking DPP-4 inhibitors were also excluded as this type of medication works by delaying the breakdown of GLP-1 and could therefore interfere with the efficacy of the trial medication.

The addition of Saxenda® in people treated with insulin has not been evaluated and is therefore not licensed. Insulin therapy can also be associated with weight gain due to episodes of hypoglycaemia and could therefore affect interpretation of secondary exploratory outcomes.

2.3.7 Randomisation and blinding

After baseline assessments, participants were randomised to either daily subcutaneous Saxenda® or matched placebo control. Treatment allocation was a 1:1 ratio. Equal numbers of participants were randomised to each arm of the trial using simple randomisation with permuted blinded block size. Novo Nordisk Ltd prepared and provided the subject randomisation list using a

computer based programme. All participants, carers, and study personnel except the pharmacy team were blinded to treatment assignment.

Once a participant was randomised a letter was sent to their general practitioner (GP) to inform them that they were taking part in the trial. Being aware that their GP would be informed was part of the consent process.

Emergency un-blinding was available 24 hours a day. This was available if a participant developed an adverse event that required knowledge of the treatment, an overdose of trial medication or there was a clinical need to start a participant on medication which had a risk of interaction with the trial drug.

2.3.8 Withdrawal

Participants were advised verbally and in writing that they were able to end their participation in the study at any point without affecting their clinical care. The investigators also had the right to withdraw participants from the medication. Any participants who withdrew from the medication for whatever reason were encouraged to remain in the trial. If withdrawing from the trial completely participants were encouraged to share their reasons for withdrawing and to undergo the same final clinical evaluations.

2.4 Investigational medicinal product and matching placebo

Saxenda® is one of the most potent weight loss medications with a licence in the UK. It is indicated as a once daily injection as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults [122]. All participants, therefore, received standardised written and verbal information about healthy eating, physical activity, alcohol and smoking. Novo Nordisk Ltd provided a matching placebo. The pen device for the active medication was entirely identical to the placebo as was the clear, colourless liquid which was visible in both devices.

2.4.1 Concerns regarding worsening mental health

In recent years there has been increasing attention on the influence of seemingly innocuous changes in body chemistry on mental health, especially centrally acting appetite suppressants. For this reason a neuropsychiatric safety review of results from randomised controlled phase 2 and 3a trials has been carried out for Saxenda®. Five double-blind, placebo controlled trials that included 3384 people with overweight or obesity treated for up to 160 weeks (range 32-160 weeks) were included [112]. This showed the overall proportions of participants reporting treatment-emergent psychiatric disorder events were comparable between groups (Saxenda® [12.2%] and placebo

[10.6%]) and that neuropsychiatric events leading to withdrawal appeared lower with Saxenda® (0.3%) than with placebo (0.7%) but were not statistically significant. Prospective questionnaires also demonstrated no increased suicidal ideation or behaviour. There were marginally higher rates of insomnia and anxiety reported, 2.4% and 2.0% of Saxenda®-treated participants compared to 1.7% and 1.6% of placebo-treated participants, respectively. Overall, however, this exploratory pooled analysis concluded there was no cause for concern [112].

In order to review whether there was any deterioration of participants' mental health during their participation in this pilot trial, all participants completed a Brief Psychiatric Rating Scale (BPRS) at baseline, 3 and 6 months. This is discussed in more detail in section 2.5.2.8.

2.4.2 Handling and disposal

The shelf life for Saxenda® is 30 months and 1 month after first use as long as the pre-filled pen is stored below 30 °C [122]. The trial team asked participants to return all pens and boxes at each trial visit. After documenting what was returned the pens were destroyed as per pharmacy protocol.

2.4.3 Method of administration

Participants' were taught that Saxenda® or matching placebo were given by subcutaneous use only and the pre-filled pens required a new disposable needle with each use. This was to ensure accurate dosing and prevent contamination, leakage and infection. The medication can be injected into the abdomen, thigh or upper arm. The smallest and thinnest Novo Nordisk Ltd needles were provided with the pens – 5 mm 32G. Sharps boxes were also provided for participants. Participants were taught face-to-face about using the injection pen and were witnessed giving their first injection. Participants were also given an instruction leaflet to take away with them.

Saxenda is administered once daily at any time, independent of meals but it is preferable that it is injected around the same time of the day if possible. As the majority of the participants signed up to the text message reminder service the investigator could ask what time they were planning to give the medication and time the daily text message reminder appropriately.

If a dose was missed within 12 hours from when it was usually taken participants could take the dose as soon as possible. If there was less than 12 hours to the next dose they missed a dose and resumed the once-daily regimen with the next scheduled dose.

2.4.4 Adherence

In order to support adherence to the trial medication there was an optional text message reminder service which sent a daily text reminder to take the medication at a time of day chosen by the individual. This would also request the receiver to reply with a YES/NO response. A paper diary was available for those who declined the electronic service. Participants were requested to bring back all pens, including empty ones, to each research visit.

2.4.5 Interaction with other medicinal products

There is no specific safety information concerning interactions between Saxenda® and antipsychotic medications. Liraglutide, albeit at the lower dose of 1.8mg, however, has been studied in people with schizophrenia spectrum disorders on antipsychotic medication medications. In a RCT it was found that '*altogether the liraglutide group experienced significantly fewer serious adverse events and no differences in quality of life, daily functioning, or psychiatric disease severity were found.'* Regarding admission to hospital for worsening schizophrenia there were 3 admissions in the liraglutide group (n=50) versus 9 in the placebo group (n= 51) [133]. *In vitro,* liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding. The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption. No dose adjustments are therefore required apart from on initiation of liraglutide treatment in participants on warfarin, or other coumarin derivatives, where more frequent monitoring of international normalised ratio is recommended.

2.4.6 Titration

Saxenda® (and matching placebo) were used according to the current European Union licence; the starting dose was 0.6 mg per day. The dose was increased each week by 0.6 mg to a maximum of 3.0 mg per day as tolerated. Each pen was able to deliver doses of 0.6 mg, 1.2 mg, 2.4mg and 3.0 mg. At least one week's interval was allowed to improve gastro-intestinal tolerability. Participants who did not tolerate up-titration remained on the highest tolerable dose.

Table 4 Dose escalation for Saxenda® [98]

	Dose	Weeks
Dose escalations	0.6 mg	1
	1.2 mg	1
	1.8 mg	1
	2.4 mg	1
Maintenance dose	3.0 mg	

2.4.7 Contraindications

All contraindications to Saxenda®, including hypersensitivity to liraglutide or any of the following excipients: disodium phosphate, dehydrate, propylene glycol, phenol, hydrochloric acid, sodium hydroxide or water for injections, have been included in the exclusion criteria.

2.4.8 Side effects

All side effects were reported as adverse events and are discussed in section 2.6.1.

2.4.9 Discontinuation

The SmPC states that treatment with Saxenda® should be discontinued after 12 weeks on the 3.0 mg daily dose if patients have not lost at least 5% of their initial body weight [122]. This was based on the fact that the outcome for early responders (defined as individuals who achieved ≥5% weight loss after 12 weeks) was found to be better in the SCALE trials [125]. As there were no significant safety concerns from participants who had been in Saxenda® trials for up to 56 weeks the candidate felt that following the 12 weeks withdrawal approach would not be appropriate for this trial for the following reasons:

- As discussed in the introduction, the population in this study typically find it more difficult to lose weight than the general population so the 12 week cut off may not be appropriate.
- During the trial the candidate would not know whether someone had not lost weight at 12 weeks because the liraglutide was ineffective for them or because they were taking the placebo, as it was a double-blind trial.

As discussed in 2.3.8 participants had the right to stop trial treatment at any time and for any reason. If a participant developed any of the exclusion criteria, including contraindications to Saxenda®, they would also be withdrawn from the medication by an investigator.

2.4.10 Placebo effect

The placebo effect is a recognised phenomenon [149]. The candidate hypothesised, however, that the therapeutic group would have additional weight and metabolic improvements. It is also recognised that participants in a blinded placebo arm report increased side effects [149]. The candidate did, therefore, consider having a third arm group to account for the fact that the placebo group could theoretically feel nauseous and consequently eat less and lose weight as result of this. This likelihood overall of this, however, was thought to be low and from a practical point of view of recruiting enough participants was not included in the final design.

2.5 Outcomes

2.5.1 Primary outcome

The primary objective of the pilot trial was to investigate the feasibility and acceptability of delivering a full scale trial evaluating whether Saxenda®, once daily injectable therapy, may be an effective treatment of overweight and obesity in people with schizophrenia, schizoaffective disorder and first-episode psychosis. In order to achieve our primary objective, the study gathered data on recruitment, consent, retention and adherence. Qualitative interviews with a purposive sub-sample of participants and healthcare workers provided data on intervention feasibility and acceptability.

Feasibility outcomes included:

1. Feasibility of recruitment to a larger, definitive study, defined as time to recruitment target.
2. Number and key characteristics of eligible participants approached for the study, including reasons for not joining the trial, recorded in line with the CONSORT criteria for clinical trials.
3. Reasons why eligible candidates agreed or declined to take part.
4. Participant attrition rate, defined as the number of participants not available for follow up.
5. Reasons why participants withdrew from the research protocol.
6. Qualitative information from participants and the research team working on the study about recruitment, acceptability and satisfaction with the research protocol, and satisfaction with the intervention.
7. The number of missing values, and the number of incomplete cases.
8. Adherence to the investigational medicinal product (IMP).

2.5.2 Secondary exploratory outcomes

The trial team were also interested in a number of exploratory outcomes, principally, weight change between the two groups at 6 months. Changes in waist circumference, BMI, fasting plasma glucose, HbA_{1c}, blood pressure, lipid profile, brief psychiatric rating scale (BPRS), smoking status and adverse events at 3 and 6 months were also assessed. Windows for 3 and 6 month follow-ups were defined as minus and plus two weeks to allow for missed appointments. A schedule of follow up activities is shown in the table below.

Table 5 Follow up activities

Trial period	Screening	Randomisation (R)	Treatment								
Type		Visit 1 (V1)	Telephone 1 (T1)	T2	T3	Final titration/V2	V3	V4	V5	V6	Final visit/V7
Timing	1 -3 weeks pre R	0	1	2	3	4	8	12	16	20	24
Participant related											
Informed consent	x										
On-going consent		x	x	x	x	x	x	x	x	x	x
In/exclusion criteria	x	x									
Randomisation		x									
Withdrawal criteria		x	x	x	x	x	x	x	x	x	x
Demographics	x										
Concomitant illness	x	x	x	x	x	x	x	x	x	x	x
Medical history	x										
Psychiatric history	x										

Trial period	Screening	Randomisation (R)	Treatment								
Type		Visit 1 (V1)	Telephone 1 (T1)	T2	T3	Final titration/V2	V3	V4	V5	V6	Final visit/V7
Timing	1 -3 weeks pre R	0	1	2	3	4	8	12	16	20	24
Diagnosis of diabetes	x										
Concomitant medication check	x										
Concomitant medication check (on study)		x	x	x	x	x	x	x	x	x	x
Smoking status		x						x			x
Urine Pregnancy test (not if > 50 and no period for 1 year or hysterectomy or bilateral tubal ligation)	x										
Safety											
Side effects			x	x	x	x	x	x	x	x	x
Adverse effects			x	x	x	x	x	x	x	x	x
ECG	x										
Renal function	x										
Liver function	x										

Trial period	Screening	Randomisation (R)	Treatment								
Type		Visit 1 (V1)	Telephone 1 (T1)	T2	T3	Final titration/V2	V3	V4	V5	V6	Final visit/V7
Timing	1 -3 weeks pre R	0	1	2	3	4	8	12	16	20	24
Physical examination		x									
Hypoglycaemic episodes			x	x	x	x	x	x	x	x	x
Clinical data											
Review diary			x	x	x	x	x	x	x	x	x
Height		x						x			x
Weight (kg)		x						x			x
BMI		x						x			x
Waist circumference		x						x			x
BPRS		x						x			x
HbA_{1c}		x						x			x
Fasting plasma glucose		x						x			x
Lipids		x						x			x

Trial period	Screening	Randomisation (R)	Treatment								
Type		Visit 1 (V1)	Telephone 1 (T1)	T2	T3	Final titration/V2	V3	V4	V5	V6	Final visit/V7
Timing	1 -3 weeks pre R	0	1	2	3	4	8	12	16	20	24
Systolic blood pressure		x						x			x
Diastolic blood pressure		x						x			x
Qualitative sub study (optional)		x					x		x		x
Trial material											
Dispensing visit		x				x	x	x	x	x	
Drug accountability		x				x	x	x	x	x	x
Reminders											
Fasting visit	x						x			x	
Pen training		x									
Direction for use handout		x									
Check pen training			x	x	x	x	x	x	x	x	
Hand out ID card	x										

Trial period	Screening	Randomisation (R)	Treatment								
Type		Visit 1 (V1)	Telephone 1 (T1)	T2	T3	Final titration/V2	V3	V4	V5	V6	Final visit/V7
Timing	1 -3 weeks pre R	0	1	2	3	4	8	12	16	20	24
Hand out and instruct diary	x	x				x	x	x	x	x	
End of treatment											x

2.5.2.1 Weight

Weight was measured in kilograms (kg) to one decimal place. The same weighing scales, which were placed on level floor, were zeroed before use. Any outdoor clothing, including shoes, which may restrict accurate measurement were removed. Any heavy objects from pockets were also removed. Our aim was to estimate effect size and standard deviation (SD) of the change in weight at 6 months in order to inform a power calculation for a fully powered RCT based on this feasibility pilot study.

2.5.2.2 Proportion who maintained or reduced weight

Proportion who maintained or reduced weight was to test the null hypothesis that there was no difference in weight loss between treatment groups.

2.5.2.3 Proportion of participants with 5% weight loss

The proportion of participants with at least 5% weight loss was chosen as the license for Saxenda® supports its continuation if individuals have lost this amount of their initial body weight.

2.5.2.4 Waist circumference

Waist circumference was defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. It was measured using a non-stretchable tape measure in centimetres (cm) to the nearest ½ cm. Participants were asked to stand with arms down by their sides, feet together, an empty bladder and wearing light clothing.

2.5.2.5 BMI

BMI was calculated using the equation = body weight (kg)/ ((height in metre) x (height in metre).

2.5.2.6 Fasting plasma glucose, lipid profile and HbA_{1c}

Participants were asked not to eat from midnight the night before the trial visit until the blood test. To assess glycaemic control HbA_{1c} and fasting plasma glucose (FPG) were measured in mmol/mol and mmol/l respectively. Fasting lipids were measured in mmol/l.

2.5.2.7 Blood pressure

Systolic and diastolic blood pressures were measured, after the participant had been resting for 5 minutes, with an automated blood pressure machine in mmHg.

2.5.2.8 BPRS

While the trial team did not expect a change in psychiatric symptoms a measure of these was needed to assess potential changes in psychopathology. The choice of the BPRS was largely pragmatic and matched the scale used in the STEPWISE study. BPRS is an instrument that has been used for assessing the positive, negative and affective symptoms of psychotic disorders, especially schizophrenia, since 1962 [150]. The scale consists of 18 symptom constructs and takes 20-30 minutes for the interview and scoring. Five of the items (tension, emotional withdrawal, mannerisms and posturing, motor retardation and uncooperativeness) are based on observations of the participant. The remaining 13 items are based on the participants' verbal report. Each symptom is rated from 1 (not present) to 7 (extremely severe). 0 is entered if the item is not assessed. The score is based on behaviour over the previous 2-3 days and this can also be reported by their family. The 18 items are added up to record the total score. The BPRS was chosen as the tool to assess any changes in mental health during the trial as it has undergone several revisions to improve its reliability and validity and is also easier for non-specialist researchers to administer. Inter-rater reliability for overall scores ranges from 0.52 to 0.90 [150]. Trial team members undertaking the BPRS questionnaire were signed off as attending training by Professor David Kingdon (18th June 2018).

2.5.2.9 Smoking status

It was recorded whether participants were

- Non smoker
- Previous smoker (year stopped)
- Current smoker.

2.5.2.10 Adverse events

Adverse events were also included as secondary exploratory outcomes and are discussed in detail in section 2.6.1.

2.6 Safety monitoring and adverse events

From a safety monitoring point of view the trial participants were followed up as per standard clinical practice. Heart rate and glycaemia assessments were taken at baseline and during trial participation (at 3 and 6 months). The study complied with SHFT minimum safety reporting standards and the applicable regulatory authorities. Serious Adverse Events (SAE) were reported in periodic safety reports to the REC and TSC.

At each trial visit or telephone consultation the study team enquired and recorded about any untoward or unintended events since previous contact. Severity was assessed by the team member recording the event and was graded as mild, moderate or severe. Causality was assessed by an investigator according to predefined definitions as given below:

- Probable - Good reason and sufficient documentation to assume a causal relationship.
- Possible - A causal relationship is conceivable and cannot be dismissed.
- Unlikely - The event is most likely related to aetiology other than the trial product.

There was a risk that participation in the study may increase anxiety about weight and its complications and if the treatment was unsuccessful this may lead to feelings of poor self-esteem. The candidate felt these risks were outweighed by the risk of widening health inequality and worsening health among people with SMI if the use of Saxenda® was not assessed.

2.6.1 Adverse Events

An adverse event (AE) was defined as any unfavourable or unintended events which occurred during trial participation. This included, but was not limited to, all medication side effects listed in the SmPC [122]. In line with previous studies the expected side effects of Saxenda® were nausea, diarrhoea, constipation, vomiting, decreased appetite, dizziness and injection site reactions. Medication error and laboratory outlier were also considered as AEs.

Table 6 Frequency of side effects as reported in SmPC

Organ system class	**Very common**	**Common**	**Uncommon**	**Rare**
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders		Hypoglycaemia	Dehydration	
Psychiatric disorders		Insomnia		
Nervous system disorders		Dizziness Dysgeusia		

Cardiac disorders			Tachycardia	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Constipation	Dry mouth Dyspepsia Gastritis Gastro-oesophageal reflux disease Abdominal pain upper Flatulence Eructation Abdominal distension	Pancreatitis	
Hepatobiliary disorders		Cholelithiasis	Cholecystitis	
Skin and subcutaneous tissue disorders			Urticaria	
Renal and urinary disorders				Acute renal failure Renal impairment
General disorders and administration site conditions		Injection site reactions Asthenia	Malaise	

		Fatigue		
Investigations		Increased lipase Increased amylase		

2.6.2 Adverse Reaction

An Adverse Reaction (AR) was defined as an unfavourable or unintended response in a participant to the IMP where a causal relationship between the event and the IMP is at least a reasonable possibility. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Healthcare professionals are asked to report any suspected adverse reactions via the MHRA Yellow card scheme regardless of whether the person taking the medication is in a trial or not. This allows continued monitoring of the benefit/risk balance of the medicinal product.

2.6.3 Serious Adverse Event and Serious Adverse Reaction

In accordance with GCP SAEs were defined as events that (a) result in death; (b) are life-threatening; (c) require hospitalisation or prolongation of existing hospitalisation; (d) result in persistent or significant disability or incapacity; (e) a congenital anomaly or birth defect; (f) are otherwise considered medically significant by the investigator. Suspicion of transmission of infectious agents would have been considered an SAE.

'Life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

The following SAEs were expected for the patient population: (a) psychiatric hospitalisation; (b) worsening of psychiatric symptoms; (c) self-harm; (d) suicide attempt; (e) death from suicide. If the investigator deemed that any of these expected events were at least possibly related to the study drug then these were reported as Serious Adverse Reactions (SAR) i.e. a serious (as defined above) event where a causal relationship between the event and the IMP is at least a reasonable possibility. Given the risk of suicide attempt in this trial population the candidate looked at clinical

trials and post-marketing use of Saxenda® overdoses. These have been reported up to 72 mg which is 24 times the recommended dose for Saxenda® [122]. Events reported included severe nausea and severe vomiting which given the side effect profile would be expected. None of the reports included severe hypoglycaemia and all recovered without complications. In the event of overdose, appropriate supportive treatment would have been initiated according to the patient's clinical signs and symptoms, specifically, clinical signs of dehydration and/or low blood glucose levels.

No serious adverse outcomes were anticipated with use (or not) of the trial medication and as such no interim statistical analysis was planned regarding safety. The TSC did, however, review all SAE/SARs regularly.

2.6.4 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) was defined as a SAR where the nature and severity is not consistent with either of the following:
(a) the information about the medicinal product as set out in the SmPC
(b) expected SAEs for the patient population as listed above in2.6.3.

2.7 Recruitment and retention

The recruitment strategy had a five pronged approach as outlined below. The recruitment rate was reviewed at 12 weeks post study start compared to the planned trigger points. Key trigger points were defined as hitting 10%, 40%, 75% and 100% of the recruitment targets.

Table 7 Proposed recruitment trigger points

Trigger point	**Screened**	**Screened (cumulative)**	**Randomised (per month)**	**Randomised (cumulative)**	**Date due (end)**
1	6	6	2	2	July 2018
2	**13**	**19**	**4**	**6 (10%)**	**August 2018**
3	12	31	4	10	September 2018
4	18	49	5	15	October 2018
5	16	65	5	20	November 2018

6	**14**	**79**	**4**	**24 (40%)**	**December 2018**
7	10	89	5	27	January 2019
8	19	108	6	33	February 2019
9	21	129	6	39	March 2019
10	**20**	**149**	**6**	**45 (75%)**	**April 2019**
11	19	168	6	51	May 2019
12	17	185	5	56	June 2019
13	**15**	**200**	**4**	**60 (100%)**	**July 2019**

2.7.1 Outpatient recruitment strategy

Potential participants were approached by the direct care team during routine clinic visits, first episode psychosis clinics, depot medication clinic visits or other contact with patients. Research team members additionally discussed the study in their allocated sites with all staff at MDT meetings. During these meetings staff:

- Provided a summary of the study
- Handed out leaflets and PISs
- Took the names of staff members who had people on their caseload who may be eligible.

2.7.2 Inpatient recruitment strategy

The research team visited each of the inpatient sites and took posters, information leaflets and PIS to discuss with clinical teams about the best way to proceed in their setting e.g. attend business meeting, MDT etc.

2.7.3 Willow group GP practice

A primary care practice called The Willow group is also part of SHFT and has a patient population of approximately 37,500. A screen was undertaken and invitation letters then sent by the GP practice to potential participants.

2.7.4 Self-referrals

Posters were displayed in various SHFT venues which could be seen by patients. A telephone number and email address to contact the research team directly were provided.

2.7.5 Clinical Records Interactive Search (CRIS)

CRIS allows researchers to see patient's preferences in relation to being directly contacted about any research studies for which they are eligible. A database search, using the inclusion and exclusion criteria, was undertaken as part of the recruitment strategy. If individuals electronic health records (Open RiO) reflected the 'opt in' status then the research team could contact them directly by telephone call or participant invitation letter (v1.0) with a freepost labelled return envelope. If their preference was not to be directly contacted then the team approached their care coordinator (CCO) first to see if their service user may be appropriate or interested.

2.7.6 PIC sites

GP practices within West Hampshire and Southampton CCG were able to screen their patient lists from the 6th August 2019 for potentially eligible participants. The GP practice sent identified individuals an invitation letter with the trial teams contact details. If the study team had not heard from potential participants two weeks after the letters were sent a text message reminder was sent from the GP practice asking if they would like to hear more and requesting a YES/NO reply.

2.7.7 Retention

In order to maximise retention in the study the following strategies were used. The team designed the trial so that participants attended for trial visits monthly and, with their consent, also sent participants a daily text message reminder regarding the study medication and appointment reminders. The candidate hoped this level of contact would keep people engaged but would not be overwhelming. If a participant withdrew from the study medication, but agreed to stay in the trial, they were then offered the option to do their non-clinical visits (visit 2, 3, 5 and 6) over the telephone.

2.8 Qualitative study

Qualitative interviews with a purposive sub-sample of participants and healthcare workers provided data on intervention feasibility and acceptability. This is described in detail in Chapter 5.

2.9 Data collection methods

Source data were collected on case report forms (CRFs) which were created for each trial visit. They were designed so that data were attributable, contemporaneous and complete. Each participant recruited into the study was assigned a unique trial identification number at the time of randomisation. This participant identification number (PIN) was written on all clinical assessment forms/datasheets and databases used to record data on study participants. Each participant's file, containing all CRFs, AE forms and logs and BPRS questionnaires, were placed securely in a locked filling cabinet. All source data were verified by the monitoring team to ensure data quality, this included legibility and accuracy. Data were kept secure and confidential at all times and maintained in accordance with the requirements of the GDPR, and archived according to clinical trial GCP regulations.

2.10 Monitoring

Monitoring was carried out independently of investigators but by SHFT staff. The first monitoring visit occurred within one week of the first screening visit and then a minimum of once every 4 weeks during the recruitment period and once every 6 weeks during the maintenance phase. The monitors also oversaw the close out visit. Monitors had access to all necessary facilities, data, and documents. Reports, produced after each visit, were sent to the investigators and, where relevant, key study personnel for their review, along with a summary of the findings. Investigators responded to the findings raised within 4 weeks if non urgent, or within 24 hours for urgent issues. A signed copy of the report and responses were kept in the investigator site file for reference.

A Trial Steering Committee (TSC) was set up in May 2018 and included an independent chair and three other independent members, including a service user. All TSC members completed declaration of interest forms. The main trial investigators, including the candidate, also attended TSC meetings. As our risk assessment deemed participation in the study comparable to the risk of standard medical care (type A risk) [151] the TSC also took on the role of the data monitoring committee. As this was a pilot trial using a licensed medication a separate data monitoring and ethics committee was not convened.

2.11 Statistical analysis

Data were analysed on an intention-to-treat basis, as the most conservative approach, in accordance with the trial's detailed statistical analysis plan; all randomised participants,

regardless of their eligibility, according to the treatment they were randomised to receive were included. A per protocol analysis was not undertaken but this may have amplified the treatment effect and therefore increase the risk of type I error. Imputation of data was not done as this was a feasibility trial and these analyses were exploratory. Sub-group analysis was not undertaken because of the small numbers in the study. Continuous variables were analysed by mean or median, with groups compared statistically using either paired t-test or Wilcoxon signed rank test as appropriate. Data are presented as mean ± SD. Categorical variables were presented as n (%) with groups compared using chi-squared or Fisher's exact tests. The difference in weight change between groups was analysed using generalised linear models, both unadjusted and adjusted for covariates that were identified as potential confounders in univariate testing. Estimated mean change was reported with 95% confidence intervals. All statistical tests were 2-sided with statistical significance assumed at 0.05. The analysis was carried out using Statistical Analysis Software (SAS) version 9.4 in August and September 2020.

2.11.1 Bias

Whilst designing the trial the candidate considered where potential areas could be subject to bias, the systematic tendency to underestimate or overestimate a parameter of interest, so that it could be minimised or where this was not possible assess its impact and take that into account.

2.11.1.1 Selection bias

To reduce selection bias, so that the trial participants were representative of people with SMI who were overweight or obese, the team kept the inclusion criteria broad where possible. One such example was to include all antipsychotic medications. A number of inclusion criteria were, however, necessary to enable the study to answer the hypothesis and exclusion criteria, equally, were needed to protect people from unacceptable risk.

To reduce unconscious bias between the two arms of the study the participants were randomised to their different groups and this was double blind.

2.11.1.2 Recall bias

Rather than asking participants to recall how many doses of medication they may have missed the team collected used IMP at each visit so drug usage could be estimated.

2.11.1.3 Observer bias

Observer bias was most likely to play a role when the study team were carrying out the BPRS. To reduce this the study team attended the same training and then discussed how they had

individually scored a video to understand where any differences may be and what mild to severe scores for the observed questions would look like for this trial. The number of study personnel who carried out the BPRS was also minimised.

The other area of potential unconscious observer bias was when the candidate was carrying out qualitative interviews as she had prior knowledge of the interviewees. This was not the case for Professor Katharine Barnard-Kelly.

2.11.1.4 Information and measurement bias

Standardised methods of measurements were defined to ensure information was not collected differently between groups. Standard operation procedures described these definitions and the precise way they were to be carried out. These were discussed at the site initiation visit. All equipment was calibrated yearly and a single laboratory processed all of the pathology samples so that only a singular type of assay was used for each measurement.

2.11.2 Data management

The trial team used an electronic data management system called REDCap, a secure web application, to store all of our electronic data. This was built within the R&D department during the trial set up phase and overseen by the candidate. REDCap has a demonstration area where the team could input mock participants to see how the system worked before it went live. The candidate also could go back into the system builder and amend sections, such as adding an additional telephone visit.

The candidate designed the data management system so it was not possible to leave blanks, which helped to minimise the loss of any vital data. The data management system was also able to set appropriate range and format checks on measurements so that incoherent values were not accepted. The layout was clean and well-spaced which made it easy to navigate and, crucially, to input the data. All of this ensured that the quality of the data collected was accurate. Data would be available to external researchers if requested and approved by the chief investigator.

A dedicated member of the study team entered the data from the CRFs onto REDCap. All data were checked for errors by the monitoring team before being transferred to the appropriate statistical package.

2.11.3 Screening data and participant flow

Key characteristics and reasons for not joining the trial were recorded for all potential participants who were contacted. A CONSORT diagram was used to estimate the number of eligible participants in the recruitment area (from a CRIS search of the SHFT database) and number of participants who were:

- Pre-screened for eligibility via medical notes
- Invited for screening visit; accepted and not accepted*
- Assessed for eligibility at screening visit; eligible and not eligible*
- Eligible and randomised
- Eligible but not randomised*
- Received the randomised allocation
- Did not receive the randomised allocation*
- Lost to follow-up*
- Discontinued the intervention*
- Randomised and included in the analyses

*reasons provided.

2.11.4 Baseline participant characteristics

Participants are described with respect to age, sex, ethnicity, smoking status, diagnosis of type 2 diabetes (yes/no), time since diagnosis of type 2 diabetes if applicable, diabetes treatment if applicable, type of psychiatric diagnosis and time since this diagnosis, type of antipsychotic medication, weight, BMI, waist circumference, BPRS, HbA_{1c}, FPG, lipids, systolic and diastolic blood pressure at baseline, both overall and separately for the two randomised groups.

Categorical baseline data are summarised by numbers and percentages. Continuous baseline data are summarised by mean and SD when the data were normal or median and IQR if data were skewed. Tests of statistical significance were not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

2.11.5 Analysis outcome definitions

a. Time to reach recruitment target was defined as the time from first participant screened to randomisation of the 60^{th} participant.
b. Number of participants required to be screened in order to reach recruitment target was defined as the number of participants attending a screening visit.

c. Participant attrition rate was defined as the number of participants not available for follow-up at the final study visit.

d. Adherence to the IMP was defined as the number of empty cartridges returned at each visit by trial participants divided by the total number of cartridges prescribed. Adherence was analysed both as a continuous variable and by the number of participants using at least 70% of prescribed trial medication at 3 and 6 months. The candidate asked Novo Nordisk Ltd for their experience in this area who reported that they used the *at least one dose per week'* definition, i.e. if a patient takes at least one dose of Saxenda during the week in question, she (or he) probably take most doses and use the intended dose level. The candidate was concerned that using a cut-off this low would undermine the impact of any later statements that people "adhered to treatment" during this pilot and on discussion with the TSC concluded that if participants were not missing more than 2 doses per week then this would be a useful assessment of adherence.

2.11.6 Analysis of primary objectives

a. Time to reach recruitment target was reported as a number (in weeks). The mean number of participants recruited per week was also presented with 95% confidence interval.

b. Number of participants required to be screened: the rate of successful screens was evaluated as the number of participants randomised divided by the number of participants screened; presented as proportion with 95% CI.

The following was analysed at 3 and 6 months, both overall and within treatment groups:

c. Participant attrition rate was evaluated as the number of participants not available for follow-up, divided by the number of participants randomised; presented as proportion with 95% CI.

- Adherence to the IMP – (defined as the proportion of medication used by each person ranging 0-100%)
    - Either mean (SD) or median (IQR) adherence are presented as appropriate
    - Number of participants using at least 70% of prescribed trial medication with 95% CI.

2.11.7 Analysis of secondary exploratory outcomes

Changes in weight (defined as weight in kg) at 3 or 6 months minus weight in kg at randomisation), BMI, waist circumference, brief psychiatric rating scale (BPRS), HbA_{1c}, fasting

plasma glucose (FPG), lipids, systolic and diastolic blood pressure, and adherence to randomised treatment (including the effect of the using the optional text messaging reminder service or not), type of diabetes medication, change in type or dose of diabetes medication, type of antipsychotic medication, change in type or dose of antipsychotic medication between the two treatment groups are reported using mean (SD) or median (IQR) according to the distributions, and compared statistically using either paired t-test or Mann-Witney U test. The number of participants experiencing a weight loss of at least 5% from baseline to 3 and 6 months was also reported and tested for significance.

The trial team then used a generalised linear model (GLM) adjusted for baseline in order to compare the change in body weight between the two groups at 6 months. This was done:

1. Unadjusted for covariates
2. Adjusted for any covariates that are significantly different between the two treatment groups in the univariate analysis described above.

2.11.8 Missing data

Analysis was completed using list wise deletion of missing data.

Participants with and without missing data were compared for differences in demographic and physiological data where possible, by looking at appropriate summary statistics with statistical tests, as follows:

- Mean (SD) with t-test or Median (IQR) with Mann-Whitney test for continuous data
- N (%) with either chi-squared test or Fisher's Exact test for categorical data

Differences between the participants were taken into account in deducing the feasibility of a full study.

2.11.9 Harms

The number (and percentage) of participants experiencing each AE/SAE is presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE is displayed. The number (and percentage) of occurrences of each AE/SAE is also presented for each treatment arm. No formal statistical testing was undertaken.

2.12 Post-trial care

Potential participants were made aware that ongoing funding of Saxenda® would not be available once their six month period in the trial came to an end.

2.13 Funding

The study team were awarded an Investigator led grant by Novo Nordisk Ltd. The funding from Novo Nordisk Ltd created a potential bias which the trial team tried to mitigate against this in a number of ways. Firstly, the trial was sponsored by Southern Health NHS Foundation Trust, which had the responsibility for the initiation, management, conduct, analysis, reporting and publication of the trial. Although Novo Nordisk Ltd provided support financially and the product for the trial, Novo Nordisk Ltd were not involved in the conduct, management and delivery of the trial. Additionally, the initial idea and rationale for the trial came from Professor Holt, the Chief Investigator.

Chapter 3 **Primary outcome: feasibility**

This chapter reports the primary feasibility outcomes of the LOSE Weight study. The chapter is based on the following publication of which the candidate was first author and was published in January 2021:

The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomised double-blind placebo-controlled trial. Clare Alexandra Whicher, Hermione C Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Kandala Ngianga, Kerensa Thorne, Carolyn Asher, Robert C Peveler, Joanne McCarthy, Richard IG Holt. Diabetes, Obesity and Metabolism, 2021 https://doi.org/10.1111/dom.14334

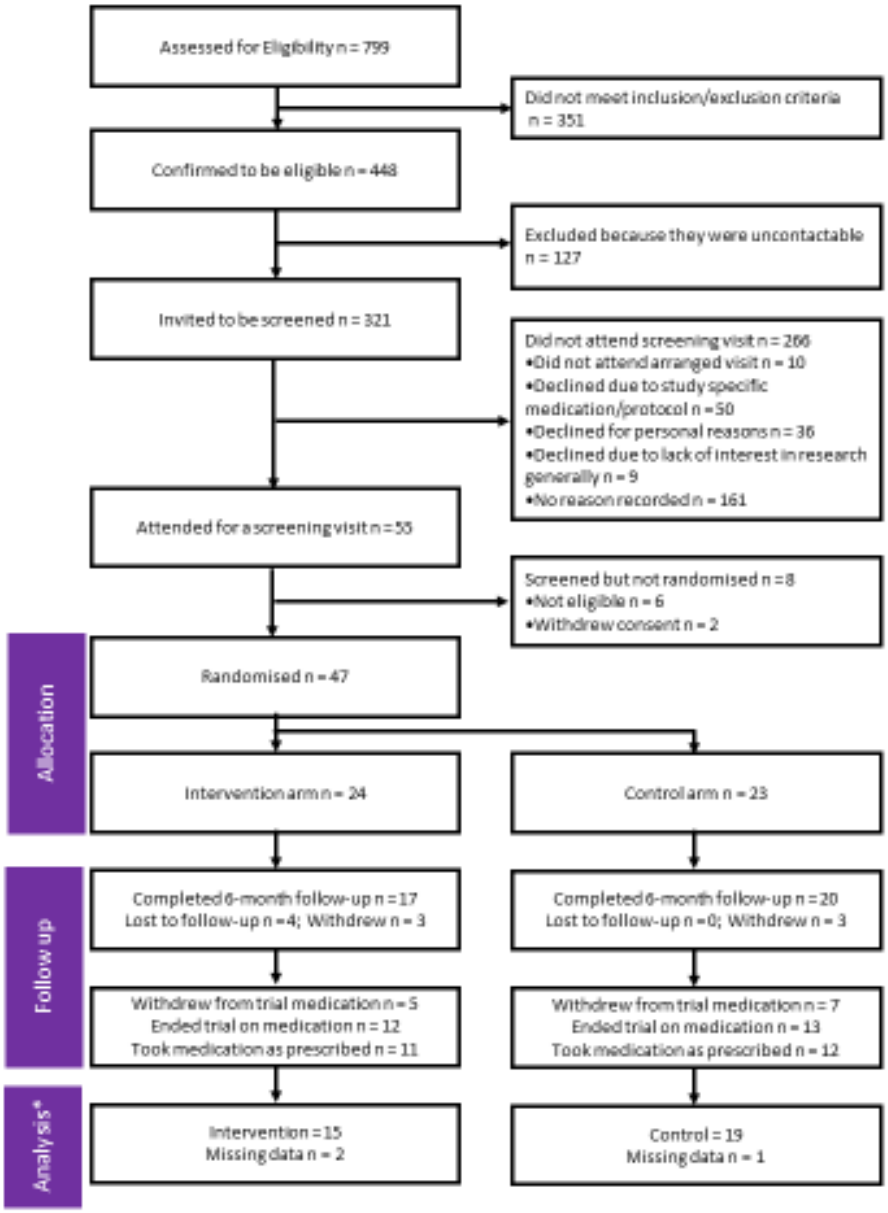
The candidate completed all of the screening and randomisation visits. Follow up visits were predominately done by the research nursing team but all were overseen by the candidate throughout. The analysis of the data was done by the candidate and Associate Professor Kandala Ngianga.

3.1 Introduction

The primary objective of this pilot study was to investigate the feasibility and acceptability of undertaking a full scale double blind RCT evaluating treatment with liraglutide 3.0 mg daily (Saxenda®) in comparison to placebo in a maximum of 60 people with obesity or overweight with schizophrenia, schizoaffective disorder or first episode psychosis. In order to achieve the primary objective, the study gathered data on recruitment, eligibility, consent, attrition and adherence to the study medication.

3.2 CONSORT diagram

The findings of the trial are summarised in the following CONSORT diagram.


Assessed for Eligibility n = 799
Did not meet inclusion/exclusion criteria n = 351
Confirmed to be eligible n = 448
Excluded because they were uncontactable n = 127
Invited to be screened n = 321
Did not attend screening visit n = 266
•Did not attend arranged visit n = 10
•Declined due to study specific medication/protocol n = 50
•Declined for personal reasons n = 36
•Declined due to lack of interest in research generally n = 9
•No reason recorded n = 161
Attended for a screening visit n = 55
Screened but not randomised n = 8
•Not eligible n = 6
•Withdrew consent n = 2
Allocation
Randomised n = 47
Intervention arm n = 24
Control arm n = 23
Follow up
Completed 6-month follow-up n = 17
Lost to follow-up n = 4; Withdrew n = 3
Completed 6-month follow-up n = 20
Lost to follow-up n = 0; Withdrew n = 3
Withdrew from trial medication n = 5
Ended trial on medication n = 12
Took medication as prescribed n = 11
Withdrew from trial medication n = 7
Ended trial on medication n = 13
Took medication as prescribed n = 12
Analysis*
Intervention = 15
Missing data n = 2
Control = 19
Missing data n = 1

3.3 Identification of eligible participants within SHFT using CRIS

In January 2019 a CRIS search (see 2.7.5) was undertaken on the SHFT database to estimate the number of eligible participants in the recruitment area. 345 individuals were found to meet the search criteria which was broken down into those identified through

- their diagnosis code (F20, F25, or F29), or referral to Early Intervention Psychosis or a diagnosis within progress note text (("schizo" OR "first episode psychosis")
- AND ("BMI", "obese", OR "overweight")).

The search also took into account age (18-75 years), those without a diagnosis code of F30 or F32 (bipolar disorder and major depressive disorder), or which mention the specific exclusion criteria, namely inflammatory bowel disease, diabetic gastroparesis, mania/manic, depression with psychosis or psychotic depression, type 1 diabetes or insulin in their progress note text. Of interest when undertaking the CRIS search it became apparent that a significant proportion (38%) of people within this search did not have weight/height or weight and height recorded on their electronic health record (Open RiO). Even if these individuals were overweight or obese they would not have been identified by this search.

3.4 Time to recruitment

In order to access the feasibility of recruitment to a larger, definitive study, the first outcome was defined as the time to recruitment target. It was hypothesised that 60 participants could be recruited over a 12 month time period.

The planned first participant first visit (FPFV) was the 1st July 2018. Recruitment in fact opened on the 17th July 2018 due to contract delays and the FPFV was on the 24th July 2018. Recruitment closed on the 31st October 2019 and the last participant last visit (LPLV) was on the 5th May 2020. 47 participants were randomised in total (78% of the proposed figure). Time to reach 47 participants randomised was 67 weeks and 2 days. Mean recruitment was 0.70: 95% CI (0.6 - 0.8) recruited/week.

Of note three participants were successfully screened and randomised to an arm of the trial but did not attend their baseline visit. Of these three, one was lost to follow up, another withdrew consent between screening and their randomisation visit and the final individual had a significant medical event requiring hospitalisation between these visits.

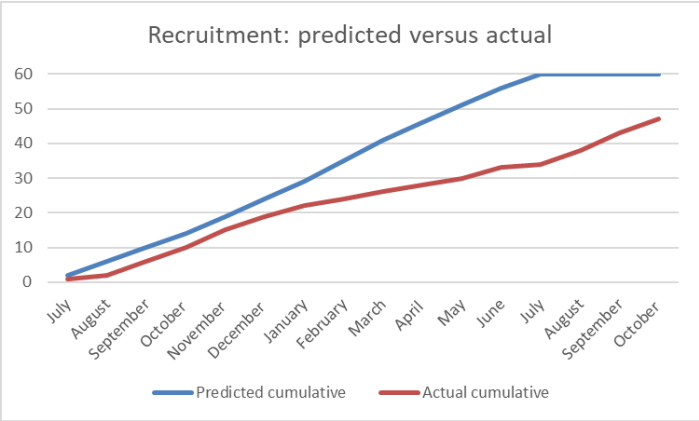


Figure 4 Actual recruitment rates versus predicted rates from July 2018 to October 2019

3.4.1 First recruitment trigger point

The first recruitment trigger point was for 6 participants (10%) to be randomised by 31/8/2018. Recruitment started a month late and recruitment initially remained a month behind schedule meaning that the sixth participant was recruited in September 2018.

3.4.1.1 12 week recruitment review

In October 2018 recruitment was evaluated 12 weeks after the trial opened as specified by the protocol. A total of 200 sets of notes had been reviewed by this time point and 10 participants had been randomised. Of those approached there was a 23% uptake rate which was lower than the 30% predicted. Given that the preliminary audit had found 842 people in SHFT who met the trial criteria it was highlighted at this early point in the study that the trial may not hit the maximum target of 60. Given this situation the recruitment strategy was reviewed and the following actions undertaken:

- The importance of positive attitudes between research and clinical team and clinical staff approaching potential participants was reaffirmed.
- A social media campaign including Facebook group for recruitment, trial twitter account and trial press release was investigated.

The trial team also considered that the conversion rate from screening notes to randomised participants may improve as the trial progressed due to improved confidence and experience of the team.

3.4.2 Second recruitment trigger point

By 31st December 2018 the aim was for 40% of participants (24 people) to have been randomised. By then the trial had randomised 19 participants and it appeared that recruitment was keeping up with the monthly proposed recruitment targets albeit still a month behind. The uptake rate had dropped further to 15% of those who were eligible and so the trial team investigated adding PIC sites. A preliminary search was undertaken at one potential GP PIC site, The Arnewood practice, which found 21 eligible participants out of their 13,000 patient list. With the acceptance rate at that time point of 15% the candidate hypothesised this would result in three recruits. The trial team therefore agreed in January 2019 to submit a substantial amendment to REC for the addition of further PIC sites with the aim to recruit 10 participants.

3.4.3 Third recruitment trigger point

The third trigger point was for 42 participants (70%) to have been randomised by 30th April 2019. Recruitment, however, had slowed down since January 2019 despite close liaison with the mental health teams who were providing referrals. The team were randomising around two people per month and a total of 28 participants had been randomised by the end of April 2019 rather than the proposed 42. The uptake rate remained lower than predicted at 16%.

50 letters were sent to patients registered at the Willow group GP practice, described in 2.7.3, and the candidate was awaiting responses from these. The major protocol amendment for the use of additional PIC sites was submitted on the 4th February 2018 but the REC committee was unable to keep to a 14 day turn around. Given delays in recruiting, the trial team agreed to extend recruitment until 31st October 2019.

3.4.4 Final recruitment

By July 2019 recruitment had increased. 34 participants were randomised and 4 more screening appointments were booked. Reasons for increased recruitment included financial incentives (£100) for mental health teams for each participant randomised, support from clinical management and results of the CRIS search. The candidate also believes that the latter, however, contributed to the overall acceptance rate dropping from 16% to 11% as people who have not been selected by clinicians as being likely to be interested in the study, were also now being approached.

PIC sites impact on recruitment

Once the trial received ethics approval to use PIC sites in August 2019, invitations were sent to all GP practices within West Hampshire and Southampton CCGs inviting them to take part in the study. Nine GP practices expressed initial interest and five signed up to take part. Two practices did not send invites to potential participants; one due to staff sickness and the other due to lack of time before recruitment closed. Three practices sent invitation letters to potential participants after undertaking a screen of their patient list. Solent GP practices (population of 18,000 patients) sent 37 letters on the 17th October 2019. Two Rivers practice (population 9,200) sent 10 letters on the 3rd October and a follow up text message on the 23rd October 2019. Park and St Francis surgery (population 16,892) sent four letters on the 17th September and text message reminder on the 3rd October 2019.

Table 8 Recruitment from PIC sites

	Randomised	Screening visit	Declined	No response
Two Rivers	1	1	3	6
Solent GPs	1	3	2	32
Park St Francis	0	0	1	3

3.5 Number approached

799 sets of patient notes were pre-screened for eligibility between 17 July 2018 and 31 October 2019. This was almost four times the number that was predicted (see Recruitment and retention 2.7). The breakdown of referrals and number of screening visits as a result of these referrals can be seen below in the table below.

Table 9 Breakdown of referrals and screening visits resulting from these

Types of referral	Number of potentially eligible participants identified (n)	Number who attended for a screening visit (n)	Percentage of screening visits from those identified (%)	95% CI
Self-referral	17	5	29.0	10.3 - 56.0
CRIS search	272	7	2.6	1.0 - 5.2
Willow group GP practice	53	1	1.8	0.1 - 10.1
Mental health team	406	38	9.4	6.7 - 12.6
PIC sites	51	4	7.8	2.2 - 18.9
Total	**799**	**55**	**6.5**	4.9 - 8.5

Out of the 799 individuals identified, 448 (56%) were confirmed to be eligible once their notes were reviewed by one of the trial team. 351 (44%) individuals, therefore, did not ultimately meet the inclusion and exclusion criteria. 127 (28%) of the 448 eligible people were uncontactable, despite attempting to contact them on three different occasions and sending a letter if the team were unable to get through on each of these attempts. 321 individuals were therefore invited to attend a screening visit (72% of those eligible).

55 individuals (17.1% of those invited) attended Moorgreen hospital for a screening visit. This figure does not include the 10 people who agreed to have a screening visit but who did not attend it, in most cases this was despite it being rearranged up to three times. The acceptance rate, as a proportion of all eligible participants, was therefore 12.2%.

3.5.1 Reasons why eligible candidates declined to take part

All eligible participants who were approached were asked if they were happy to share the reason why they did not want to take part. There was no onus on an individual to provide a reason. 269 individuals (33.7%) declined to participate and the trial team recorded contact with 154 of them on a paper CRF. 95 of these 154 individuals (62%) provided a reason. In order of frequency these were:

- Declined due to study specific medication/methods (n= 50)
    - Did not want to use/give injectable medication (n=20)
    - Too far to travel (n=9)
    - Too many study visits (n=7)
    - Did not want to potentially take a placebo medication (n=6)
    - Concerned about side effects (n=3)
    - Not interested in the study (n=2)
    - Concerned about what is in the medication/placebo (n=1)
    - Concerned that it is a drug used for people who have diabetes (n=1)
    - Did not want to have bloods taken (n=1)
- Declined for personal reasons (n= 36)
    - Did not feel that they needed to lose weight (n=11)
    - Prefer to do ‘naturally’, examples given as gym and weight watchers (n=8)
    - Not good time in their life to be taking part in a trial (n=3)
    - Burden of extra medication (n=3)
    - Concerned that being part of the trial would cause stress (n=2)
    - Moving out of the area (n=2)

- Planning pregnancy (n=2)
- Just started new medication so did not want to start another medication (n=2)
- Agoraphobia (n=1)
- Idea of being involved sounded overwhelming (n=1)
- Decided to start an alternative GLP-1 receptor agonist called exenatide (had a diagnosis of type 2 diabetes already) (n=1)

- Declined due to lack of interest in research generally (n=9)
  - Did not like idea of being in a trial (n=3)
  - Did not want to do research (n=3)
  - Family member not keen for them to be in a trial (n=3)

3.6 Rate of successful screens

85% of those who attended a screening visit were randomised. Eight potential participants failed screening visits for the following reasons:

- Not eligible (n=6)
  - Previous gastric band (n=1)
  - HbA_{1c} >8% (64 mmol/mol) (n=2)
  - ALT ≥2.5 times upper normal limit (n=1)
  - Psychosis diagnosis did not meet schizophrenia, schizoaffective disorder or first episode psychosis definition (n=1)
  - BMI <27 kg/m² (n=1)
  - BMI ≥ 27 kg/m² and < 30 kg/m² but no weight related consequence (n=1)
- Eligible but not randomised as individuals decided at end of screening visit not to take part (n=2)
  - On-going nausea so was concerned about side effect of the IMP (n =1)
  - Did not have support of family members (n=1)

3.7 Participant attrition rate

10 participants (21% of those randomised; 95% CI (0.11 – 0.36)) were not available for follow up as per the research protocol. In six of these cases the participant notified us that they wished to stop being part of the trial but in the other four cases the team were not able to contact the participants. Participant attrition was mainly in the intervention arm where four participants completely withdrew and three were lost to follow up compared with three complete withdrawals only in those on the placebo.

3.7.1 Reasons why participants completely withdrew from the research protocol.

Three of the six participants who withdrew from the study completely agreed to attend for a final visit. At this the participants was asked if they were happy to share the reason why they had decided to withdraw; all were happy to do so. Their reasons are listed below:

- Attributed new butterflies in their stomach to the study drug [034 in placebo arm]. Research staff were unable to elicit whether this was an epigastric experience or a delusion of infestation but the participant did not have a history of the latter and their mental health was stable at the time this was reported.
- They had not lost weight and were concerned that their new medication (prochlorperazine and omeprazole) may interact with the study drug [043 in intervention arm].
- Attributed new insomnia to the study drug [045 in placebo arm].

Participants who withdrew were also offered follow up interviews but none were available to do so. This as is discussed in Chapter 5.

3.8 Adherence to the investigational medicinal product

25 participants (53%) continued on their trial medication from baseline until V7. Twelve (48%) of these were in the intervention arm and 13 (52%) were on placebo. 12 participants (26%) withdrew from the trial medication but continued to attend study visits, five of these were in the intervention arm and seven were on placebo.

Adherence to the investigational medicinal product was defined as the number of empty cartridges returned at each visit by trial participants divided by the total number of cartridges prescribed (five per visit). Adherence was analysed both as a continuous variable where means (SD) scores are reported and by the number of participants using at least 70% of prescribed trial medication at 3 and 6 months. At visit 4 21 participants (45% of all randomised participants and 72% of those taking trial medication n=29) were using at least 70% of the trial medication. 9 (43%) of these were in the intervention arm and 12 (57%) were on the placebo. At visit 7 23 participants (49% of all randomised participants and 92% of those taking trial medication n=25) were using at least 70%, 11 (48%) of these were on the intervention and 12 (52%) on placebo. Two participants in the intervention arm were unable to titrate to the maximum dose of liraglutide. One reached a maximum tolerated dose of 1.2 mg daily and the other 2.4 mg daily.

Table 10 Adherence to trial medication at 3 months and 6 months

Variable	Intervention	Placebo	Overall	P-Value
Adherence to trial medication at 3 months [Mean(SD)]	0.8(0.2)	0.8(0.2)	0.8(0.2)	0.4973[a]
Adherence to trial medication at 6 months [Mean (SD)]	0.8(0.3)	0.8(0.1)	0.8(0.2)	0.7738[a]
Participants using at least 70% of prescribed trial medication [n (%)]				
3 months	9(64.3)	12(80.0)	21(72.4)	0.4270[b]
6 months	11(91.7)	12(92.3)	23(92.0)	0.5200[b]

a: Independent sample TTEST; b:Fisher's exact test

The results suggest high (>3.5) numbers of empty pens returned overall , by study arm and both at 3 and 6 months with no statistical significant difference by arms. Similar findings were observed with the proportion of those using at least 70% of prescribed trial medication.

3.9 The number of missing values, and the number of incomplete cases

Despite the Covid-19 pandemic at the end of the trial the candidate was pleased that all participants who remained enrolled in the trial were able to complete it, however, data were lost as a result of the fact that study visits for the two final participants became virtual rather than face to face during lockdown. This meant that if was not possible to collect any clinical data (apart from weight for participant 046 who had scales at home) for the two final study visits for participants 046 and 047.

Overall three participants who attended (face to face or virtual) appointments had missing data on weight at 6 months, two in the intervention arm and one in the placebo arm. Baseline characteristics of participants with missing weight data are described by arms and overall without any further analysis due to the small number of observations.

Table 11 Missing data overall and by arm, figures are numbers (%) unless otherwise specified

Variable	Study group (n=3)		Both overall
	Intervention; (n=2)	**Placebo; (n=1)**	
Age in years [Mean(SD)]	48.5(2.1)	53(0)	50(3)
Min - Max	47 - 50	53 - 53	47 - 53
Sex			
Female	1(50)	1(100)	2(66.7)
Male	1(50)	0(0)	1(33.3)
Ethnicity			

Caribbean, African, Other Black	0(0)	0(0)	0(0)
Indian, Pakistani, Bangladeshi, Other Asian	0(0)	0(0)	0(0)
Mixed White & Black Caribbean, White Asian, Other mixed	0(0)	0(0)	0(0)
Other Ethnic Group	0(0)	0(0)	0(0)
White British, Irish, Other	2(100)	1(100)	3(100)
Smoking status			
Current Smoker	0(0)	0(0)	0(0)
Never Smoked	0(0)	0(0)	0(0)
Previous Smoker	2(100)	1(100)	3(100)
Diagnosis of type 2 diabetes (yes/no)			
No	0(0)	0(0)	0(0)
Yes	0(0)	0(0)	0(0)
Time since diagnosis of diabetes if applicable [Mean(SD)]	0(0)	0(0)	0(0)
Diabetes treatment if applicable (DOSE_OF_METFORMIN)			
1000mg BD	0(0)	0(0)	0(0)
1000mg OD	0(0)	0(0)	0(0)
500gm BD	0(0)	0(0)	0(0)
500mg TDS	0(0)	0(0)	0(0)
Weight	80(0)	156.6(0)	118.3(54.2)
BMI [Mean(SD)] -Min - Max	33.9(0)	59.7(0)	46.8(5.4)
Waist circumference [Mean(SD)]	98(0)	158(0)	128(42.43)
Brief psychiatric rating scale (BPRS) [Mean(SD)]	56(0)	33(0)	44.5(16.26)
HbA_{1c} (mmol/mol) **[Mean(SD)]**	35(0)	44(0)	39.5(6.36)
Fasting plasma glucose (FPG) [Mean(SD)]	4.9(0)	4.8(0)	4.85(0.07)
Systolic blood pressure at baseline [Mean(SD)]	105(0)	153(0)	129(33.94)
Diastolic blood pressure at baseline [Mean(SD)]	76(0)	98(0)	87(15.56)
Lipids [Mean(SD)]			
Fasting Lipids - Cholesterol (mmol/l)	5.3(0)	6.6(0)	6.0(0.9)
Fasting Lipids - HDL cholesterol (mmol/l)	1.2(0)	2.3(0)	1.8(0.8)
Fasting Lipids - HDL cholesterol (mmol/l)	3.0(0)	3.8(0)	3.4(0.6)
Fasting Lipids - LDL cholesterol (mmol/l)	4.1(0)	4.3(0)	4.2(0.1)
Fasting Lipids - Non-HDL cholesterol (mmol/l)	2.4(0)	1(0)	1.7(1.0)

The number of participants with missing data for the other secondary outcomes at six months were as follows:

- Waist circumference (cm) = 5
- BPRS =2
- Systolic and diastolic blood pressure (mmHg) =6

- HbA_{1c} (mmol/mol) =13
- FBG (mmol/l) = 13
- Fasting Lipids - Cholesterol (mmol/l) =14
- Fasting Lipids - HDL cholesterol (mmol/l) =20
- Fasting Lipids - LDL cholesterol (mmol/l) =20
- Fasting Lipids - Non-HDL cholesterol (mmol/l) =14
- Fasting Lipids – Triglycerides (mmol/l) = 13

Chapter 4 **Secondary exploratory outcomes**

This chapter reports the secondary exploratory outcomes of the LOSE Weight study. The chapter is based on the following publication of which the candidate was first author and was published in January 2021:

The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomised double-blind placebo-controlled trial. Clare Alexandra Whicher, Hermione C Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Kandala Ngianga, Kerensa Thorne, Carolyn Asher, Robert C Peveler, Joanne McCarthy, Richard IG Holt. Diabetes, Obesity and Metabolism, 2021 https://doi.org/10.1111/dom.14334

The candidate completed all of the screening and randomisation visits. Follow up visits were predominately done by the research nursing team but all were overseen by the candidate throughout. The candidate oversaw the data collection throughout the trial. Data were physically collected by the candidate and the research team. Data were entered into the data management system by Jacqueline Williams and overseen by the candidate. The analysis of the data was done by the candidate and Associate Professor Kandala Ngianga.

4.1 Electronic database check and export

Before the database was locked 10% of participants were randomly selected using an online random number generator. For these participants their weight measurements, recorded at baseline, visit 4 and visit 7, were compared between the CRF and the REDCap database entry. No errors were found in the 10% sample. If more than a 2% error rate had been found then a data check of all data points would have been completed. The REDCap database was locked and exported on 17th July 2020.

4.2 Baseline characteristics

At baseline, the groups were largely balanced, however, the placebo group were on average 6.3 kg heavier, despite a higher proportion of men, who are on average heavier than women, in the intervention arm (62% vs. 39%) (Table 11). Mean age of participants was 43.9 years. Mean BMI was 39.3 kg/m^2 (29.4 – 59.7 kg/m^2) and the majority of participants were obese or morbidly obese rather than overweight. Most participants had an established diagnosis of schizophrenia or schizoaffective disorder. The participants reported mild-to-moderate psychiatric symptoms and

were prescribed a range of antipsychotic medications, including clozapine (n= 19; 19%) (Table 12). One participant, in the intervention arm, was taking three antipsychotic medications and six were taking dual antipsychotics and in the placebo arm three were taking two antipsychotic medications. In both arms, the remainder were taking one antipsychotic medication only.

Table 12 Baseline characteristics of study arms

Variable	Study Arm		
	Intervention (n=24)	Control (n=23)	P-value
Age (years)	42.7 ± 11.3 25.0 – 64.0	45.4 ± 10.7 21.0 – 63.0	0.554[t]
Sex			**0.036[c]**
Female	9 (38%)	14 (61%)	
Male	15 (62%)	9 (39%)	
Diagnosis			0.879
First Episode Psychosis	1 (4%)	1 (4%)	
Schizophrenia	15 (62%)	13 (56%)	
Schizoaffective disorder	8 (33%)	9 (39%)	
Ethnicity			0.325[c]

Other Ethnic Group	3 (13%)	6 (26%)	
White British, Irish, Other	21 (88%)	17 (74%)	
Smoking status*			0.412[c]
Current Smoker	13 (62%)	7 (32%)	
Never Smoked	5 (24%)	7 (32%)	
Previous Smoker	3 (14%)	8 (36%)	
Diagnosis of type 2 diabetes			0.287[c]
No	23 (96%)	20 (87%)	
Yes	1 (4%)	3 (13%)	
Height (m)	1.72 ± 0.13	1.71 ± 0.11	0.079[t]
	1.32 – 1.97	1.50 - 1.90	
Weight (kg)	111.4 ± 25.5	117.7 ± 23. 5	0.535[t]
	76.6 - 171.2	73.6 - 162.8	

Body mass index (kg/m^2)	37. 5 ± 6.9	41.0 ± 6.7	0.059[t]
	29.4 – 50.9	30.2 – 59.7	
Waist circumference (cm)	123.8 ± 20.1	130.6 ± 14.0	0.187[t]
	95.0 – 175.0	112.0 – 158.0	
Systolic blood pressure (mmHg)	130 ± 24	134 ± 15	0.086[t]
	93 - 197	113 - 169	
Diastolic blood pressure (mmHg)	92 ± 23	93 ± 7	0.537[t]
	68 - 174	81 - 112	
Brief psychiatric rating scale	38 ± 14	31 ± 9	0.076[t]
	21 – 80	18 – 51	
HbA_{1c} (mmol/mol)	37 ± 6	40 ± 5	0.166[t]
	25 - 49	31 - 47	
HbA_{1c} (%)	5.5 ± 0.6	5.8 ± 0.5	0.651[t]

	4.5 – 6.7	5.0 – 6.5	
Fasting plasma glucose (mmol/l)	5.2 ± 0.5	5.1 ± 0.7	0.771[t]
	4.5 – 6.0	3.9 - 6.6	
Fasting lipids (mmol/l)			
Total cholesterol	5.0 ± 1.0	5.0 ± 1.2	0.974[t]
	3.7 - 6.6	2.9 - 6.8	
HDL cholesterol	1.3 ± 0.3	1.4 ± 0.3	0.192[t]
	0.8 - 2.1	0.9 - 2.3	
LDL cholesterol	3.1 ± 0.8	2.7 ± 1.0	0.202[t]
	2.0 - 4.4	1.3 - 4.3	
Non-HDL cholesterol	3.7 ± 1.0	3.6 ± 1.1	0.711[t]
	1.6 - 5.7	1.7 - 5.1	
Triglycerides	1.8 ± 0.8	1.8 ± 0.8	0.965[t]

	0.8 - 3.6	0.9 - 3.7

t: Two independent sample T-TEST with equal variance; c: Chi-square Test

Data are mean ± SD; range or percentage. *Data are missing from 2 participants in the intervention arm and 1 in the placebo arm.

Table 13 Antipsychotic medication use in study arms

Medication	Liraglutide	Placebo	P-Value
Antipsychotic Medication	1 (4%)	2 (9%)	0.458
Aripiprazole	1 (4%)	2 (9%)	
Aripiprazole (IM)	0 (0%)	2 (9%)	
Clozapine	3 (12%)	6 (26%)	
Flupenthixol	4 (17%)	3 (13%)	
Olanzapine	2 (8%)	0 (0%)	
Paliperidone	4 (17%)	1 (4%)	
Quetiapine	1 (4%)	2 (9%)	
Risperidone	1 (4%)	2 (9%)	
Zuclopenthixol Decanoate (IM)	2 (8%)	1 (4%)	
Amisulpiride	1 (4%)	1 (4%)	
Multiple antipsychotic medication	5 (21%)	3 (13%)	0.321

Oral medication unless stated. IM: intramuscular

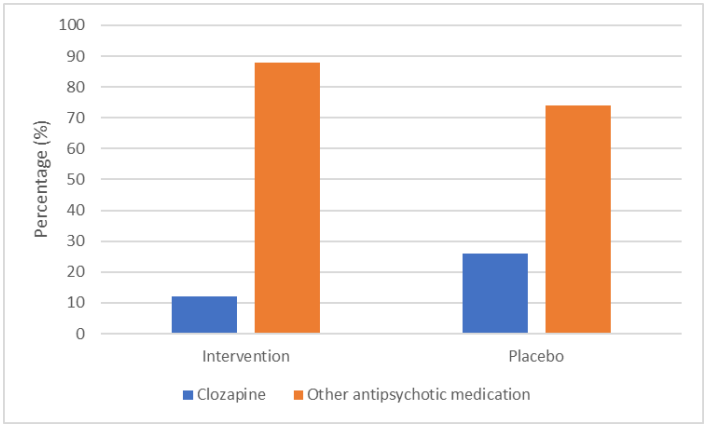


Figure 5 Percentages of participants on clozapine versus other antipsychotic medications

4.3 Secondary outcomes

15 intervention participants and 19 control participants were included in the final weight analysis. Imputation of data was not done as this was a feasibility trial and these analyses were looking at secondary exploratory outcomes. Since the differences for each variables were approximately normally distributed, paired sample t-test was used. After 6 months, participants in the intervention group lost a mean 5.7 ± 7.9 kg (95% CI -8.3 to -0.8 kg) in body weight while there was no weight change in the placebo group (0.3 ± 5.7 kg [95% CI -2.5 to 3.1 kg]). The estimated treatment difference between groups was −6.0 kg (95% CI: -10.8 to -1.3 kg; P = 0.015) (Table 13). There were statistically significant improvements in BMI, waist circumference and HbA_{1c} for participants treated with Saxenda®. There were also reductions in the BPRS and there is scope to explore the effects of study medication and placebo on the individual BPRS items, to determine whether weight loss is associated with a reduction in depression.

Table 14 Mean changes (95% CI) at 6 months for secondary exploratory outcomes

Change from Baseline to 6 months	Liraglutide (n=15)	Placebo (n=19)	Mean change between arms	P -value*
Weight in kilograms (kg)	**-5.7± 7.9**	**0.3 ± 5.7**	**-6.0**	**0.015**
	-10.1 to -1.4	**-2.5 to 3.1**	**-10.8 to -1.36**	
% weight	**4.5± 6.20**	**0.0 ± 4.2**	**-4.6**	**0.021**
	-8.3 to -0.8	**-1.9 to 2.1**	**-8.4 to -0.7**	
Body mass index (kg/m^2)	**-1.7± 2.6**	**0.0 ± 1.8**	**-1.76**	**0.028**
	-3.2 to -0.3	**-0.9 to 0.9**	**-3.31 to -0.20**	
Waist circumference (cm)	-5.3 ± 9.2	1.9 ± 4.6	**-7.2**	**0.008**
	-10.8 to 0.3	-0.4 to 4.2	**-12.3 to -2.1**	
Brief Psychiatric Rating Score	**-10.6 ± 12.1**	**-4.3 ± 8.8**	-6.3	0.088
	-17.6 to -3.6	**-8.4 to -0.1**	-13.6 to 1.0	
HbA_{1c} (mmol/mol)	**-3.3 ± 2.8**	0.3 ± 2.4	**-3.6**	**0.003**

	-5.2 to -1.4	-1.2 to 1.8	**-5.9 to -1.3**	
Fasting plasma glucose (mmol/l)	-0.2 ± 0.8	0.4 ± 0.9	-0.6	0.081
	-0.8 to 0.3	-0.2 to 0.9	-1.3 to 0.1	
Systolic blood pressure (mmHg)	-3 ± 14	-6 ± 17	3	0.600
	-12 to 6	-15 to 3	(-9 to 15)	
Diastolic blood pressure (mmHg)	2 ± 14	-2 ± 7	5	0.231
	-6 to 11	-6 to 1	-3 to 12	
Lipids (mmol/l):				
Total Cholesterol	-0.3 ± 0.6	0.0 ± 0.5	-0.3	0.198
	-0.8 to 0.1	-0.3 to 0.3	-0.8 to 0.2	
HDL cholesterol	0 ± 0.2	-0.1 ± 0.2	0.1	0.205
	-0.1 to 0.1	-0.2 to 0.0	-0.1 to 0.2	
LDL cholesterol	-0.2 ± (0.5)	0.1 ± (0.3)	-0.3	0.141

	-0.7 to 0.2	-0.2 to 0.3	-0.8 to 0.1	
Non-HDL cholesterol	-0.3 ± 0.6	0.1 ± 0.4	-0.4	0.071
	-0.7 to 0.1	-0.2 to 0.3	-0.8 to 0.0	
Triglycerides	0 ± 0.8	0 ± 0.4	0.0	0.942
	-0.5 to 0.5	-0.3 to 0.3	-0.5 to 0.5	

** Two Independent Sample T-Test P-value. Figures in bold are statistically significant*

4.3.1 Proportion of participants with 5% weight loss

53% of those who completed the trial on the trial medication in the intervention arm lost ≥5% of their body weight compared to 10% of the placebo participants (P = 0.007) (Table 15). This cut off was chosen as the license for Saxenda® supports its continuation if individuals have lost at least 5% of their initial body weight. Table 15 present the numbers and proportions of participants experiencing a weight loss of at least 5% from baseline to 3 months and 6 months. All eight participants who lost >5% of their body weight had done so by 3 months. Of the eight participants four (50%) lost >10% of their body weight.

Table 15 3 month and 6 month weight change of at least 5%

	Study arm		
Participants with ≥ 5% weight change	**Liraglutide**	**Placebo**	**P value**
3 month	8 (50%)	1 (5%)	**0.005***
6 month	8 (53%)	2 (10%)	**0.007***

* Chi-square Test, p value statistically significant at 5%. Data are number and percentage

4.3.2 Generalised linear regression model

A generalised linear regression model was used to account for baseline characteristics between groups and, once these were accounted for, treatment group was the only factor associated with weight change at 6 months.

Table 4. Unadjusted and adjusted generalised linear regression results for changes in body weight from baseline to 6 months (n=34)

Variable	Unadjusted analysis			Adjusted analysis		
	Estimated mean change	**95% CI**	**P -value**	**Estimated mean change**	**95% CI**	**P -value**
Age in years	-0.2	-0.0 to 0.4	0.075	-0.2	-6.0 to 6.7	0.067
Sex			0.942			0.352
Female	-0.2	-5.1 to 4.7		-4.8	-9.5 to 0.0	
Male	-2.5	-5.7 to 0.7		-5.4	-14.5 to 3.8	
Ethnicity			**0.028**			0.2666
Other Ethnic Group	2.1	-38 to 8.0		0.4	-6.0 to 6.7	
White British, Irish, Other	**-3.1**	**-5.8 to -0.3**			-14.5 to 3.8	
Sex * Ethnicity interaction						0.346
Other Ethnic Group & Female	NA	NA		4.7	-5.1 to 14.5	
White British, Irish, Other & Female	NA	NA		-5.4	-14.5 to 3.8	
Smoking status			0.353			
Current Smoker	-0.7	-5.0 to 3.6				
Never Smoked	-3.8	-9.3 to 1.8				
Previous Smoker	-0.7	-7.1 to 5.8				
Treatment			**0.002**			**0.002**
A	**-6.8**	**-11.2 to -2.5**		**-8.0**	**-12.2 to -3.7**	
B	0.3	-2.5 to 3.1		-5.4	-14.5 to 3.8	

Figure in bold means statistically significant associated with weight change at 6 months using 5% significant level.

4.4 Change in type or dose of diabetes medication

None of the four participants with a diagnosis of type 2 diabetes had any changes to the type or dose of their diabetes medication during their time in the trial. Of interest one participant (040) who did not have a diagnosis of type 2 diabetes was started on metformin during the trial by their psychiatrist. This participant was in the placebo arm.

4.5 Change in type or dose of antipsychotic medication

Overall there were 9 changes to antipsychotic medication during the trial. Three participants started or stopped an antipsychotic medication and six had a change in dose, but these were similar between arms.

Table 16 Antipsychotic medication changes during the trial

Variable	Intervention	Placebo	Overall
Changed antipsychotic medication (stopped/started)	2 (4%)	1 (2%)	3 (6%)
Changed antipsychotic medication dose	3 (6%)	3(6%)	6 (13%)
Daily antipsychotic medication dose reduced	3 (6%)	1 (2%)	4 (9%)
Daily antipsychotic medication dose increased	0 (0%)	2 (4%)	2 (4%)

4.6 Adverse events

4.6.1 Adverse events

One hundred AEs were reported during the trial; 56 in the intervention arm and 44 in the placebo arm. The most frequent adverse events were gastrointestinal, and these were more common (72% of those reported) in the intervention arm, in keeping with the known side effect profile of liraglutide. There was one case of gallstones in the intervention group but there were no episodes of pancreatitis or pancreatic cancer. Other adverse events were similar between groups and 65% of all reported adverse events were mild.

Table 17 Adverse events by organ system

Adverse Event	Liraglutide	Placebo
Gastrointestinal		
Vomiting	6 (11%)	3 (6%)
Nausea	7 (12%)	4 (9%)
Diarrhoea	9 (16%)	4 (9%)
Constipation	5 (9%)	2 (4%)
Dyspepsia	10 (17%)	0 (0%)
Gallstones	1 (2%)	0 (0%)
Blood in stool	1 (2%)	1 (2%)
Respiratory		

Upper respiratory tract infection	7 (12%)	12 (25%)
Asthma	0 (0%)	1 (2%)
Musculoskeletal	4 (7%)	2 (4%
Neurological	8 (15%)	7 (15%)
Dermatological	0 (0%)	1 (2%)
Other infection	1 (2%)	6 (13%)
Gynaecological	1 (2%)	1 (2%)
Haematological	0 (0%)	3 (6%)

Table 18 Severity of adverse events

Variable	Intervention	Placebo	Overall
Severity:			
Mild	39 (37%)	30 (29%)	69 (66%)
Moderate	15 (14%)	17 (16%)	32 (31%)
Severe	4 (4%)	0 (0%)	4 (4%)

4.6.2 SAE

There were five serious adverse events during the trial, four in the placebo group and one in the intervention group. In one case the participant was un-blinded at the time of the SAE. This participant was also withdrawn from the medication due to the nature of the SAE; being one of the exclusion criteria for the trial. Of note there were no SUSARs or SARs during the running of the trial.

Table 19 Details of SAEs

SAE number	Participant	Date	Description	Outcome	On IMP	Intervention or placebo arm	Un-blinded during trial	Withdrawn
1	106	22/09/2018	Found unconscious, admitted to intensive care	Recovered	No	Intervention	N/A	N/A
2	110	02/11/2018	Musculoskeletal chest pain, admitted to hospital.	Recovered	Yes	Placebo	No	No
3	110	17/11/2018	NSTEMI, admitted to hospital	Recovered	Yes	Placebo	Yes	Yes
4	111	20/11/2018	Self-harm	Recovered	Yes	Placebo	No	No
5	141	14/11/2019	Chest pain, admitted to hospital. Investigations for pulmonary embolism were negative	Recovered	Yes	Placebo	No	No

Chapter 5 **Qualitative outcomes**

The qualitative side of the LOSE Weight trial was led by Professor Barnard-Kelly who is trained and experienced in qualitative research. A specialist service, Medikin, was used to transcribe the interviews. The candidate was involved with all aspects of the qualitative work from designing the semi-structured interviews, consenting participants to take part in the optional interview, undertaking interviews both at the beginning and end of the trial and in the evaluation of the interview findings.

A qualitative results paper has been written by Professor Katharine Barnard-Kelly and the candidate (second author), which was submitted to Psychiatry Research on the 10th March 2021 and is currently undergoing peer review. The following members of the trial team have also contributed to the paper and are authors; Richard IG Holt, Hermione C Price, Peter Phiri, Shanaya Rathod, Carolyn Asher and Robert C Peveler.

5.1 Methods

Qualitative interviews with a sub-sample of Saxenda® treated participants provided data on the acceptability of the drug treatment and participation in the trial. Participants who were in the intervention arm and in the placebo arm were purposively sampled to recruit participants of different sex and ages.

Participants were invited to take part in the optional interview at the screening visit and consent obtained if they were willing to participate. The in depth interviews were conducted at baseline, shortly after the screening visit, and on completion of the trial. Semi-structured interview topic guides were designed which intended to elicit themes outlined in the existing published literature and explore more general open questions on the experience and acceptability of the treatments. Questions also explored expectations and their experience of taking part in the trial as well as broader experiences of attempted weight loss. The interviews were audio-taped and fully transcribed if participants gave permission at the time of the interview. One-to-one in depth semi-structured interviews were also held with a sub-sample of healthcare professionals delivering the intervention towards the end of the trial. The semi-structured interview scripts (baseline and follow-up) are attached as Appendix A and B.

Content and thematic analysis were used as per the National Centre for Social Research 'Framework' approach.[152] Two qualitative researchers led these analyses. A thematic analytical approach was used in which transcripts were cross-compared to identify issues and experiences that cut across different people's accounts and the underlying reasons for similarities and

differences in their experience and views. A coding framework was developed to capture key themes and each coded theme was subjected to further analyses to identify subthemes and illustrative verbatim quotes.

5.2 Results

In total 17 of 33 trial participants who consented to take part in the interviews were actually interviewed. The qualitative team were unable to make contact or arrange a time to do an interview with the remaining participants. Of these, 16 took part in baseline interview, nine completed both baseline and follow-up interview and one took part in the follow-up interview only. 12 of those interviewed (70.5%) completed the trial on the medication. This compares with 53% of all participants in the trial. Nine of those interviewed (53%) ultimately withdrawn from the medication which accounts for just over three quarters of those who withdrew from the medication overall. Of these nine, four were in the intervention arm and 5 were in the placebo arm. Mean interview duration was 13 minutes (range 5-37 minutes).No participants who completely withdrew from the trial were available for a follow up interview. Seven participants who were invited to take part in pre and post intervention telephone interviews did not consent to be contacted. A total of two HCPs who were delivering the intervention were also interviewed.

5.2.1 Content analysis

Table 20: Baseline interview responses (Yes/No) n=16

Numbers do not always total 16. Responses reflect unique codes, some participants gave more than one response; some participants either did not know or did not answer some questions.

Question	Yes	No
Have you tried to lose weight before taking part in the study?	13 (81%)	3 (19%)
Is there anything you are particularly optimistic about? - The potential to lose weight (n=9)	9 (56%)	2 (13%)
Is there anything you are particularly concerned or worried about? - Injecting (n=6) - Side effects (n=3)	9 (56%)	7 (44%)
Concerns about side effects? - Vomiting (n=1) - Diarrhoea (n=1) - Unsure (n=1)	3 (19%)	12 (75%)
Safety concerns? - Needle bending (n=1)	1 (6%)	14 (88%)
Do you expect any challenges in timing of doses? - Find it hard to stick to things (n=1)	1 (6%)	8 (50%)
Impact of timing on routine? - Need to take pen to work (n=1)	1 (6%)	9 (56%)

Table 21 Baseline interview responses (specific answers) n=16

Numbers do not always total 16. Responses reflect unique codes, some participants gave more than one response; some participants either did not know or did not answer some questions.

Question	Responses	Frequency
First, please tell me why you chose to take part in this study?	Put on lots of weight/am overweight - Due to medication - Due to hospital stays	8 (50%) 5 (31%) 1 (6%)
	Offered to take part/it was recommended by a healthcare professional	6 (38%)
	To lose weight	5 (31%)
	To benefit other people and me in the future	4 (25%)
	Give it a go/why not	2 (12%)
Have you tried to lose weight before taking part in the study? If yes could you tell me a little bit about that experience?	Altered diet - Due to joining a commercial weight loss programme	9 (56%) 4
	Increase in exercise	5 (36%)
	Healthcare professional recommended it	4 (25%)
	It was working	4 (25%)
	Commercial weight loss programmes too expensive to keep up a membership	2 (12%)
What are your expectations going into the study?	It was explained well, I know what to expect	4 (25%)
	No expectations	3 (19%)
Is there anything you are particularly optimistic about?	The potential to lose weight	7 (44%)
	I've already started, it's going okay	2 (11%)
Is there anything you are particularly concerned or worried about?	I'm not worried	6 (33%)
	Injecting	5 (28%)
	Side effects - Such as vomiting - Such as diarrhoea	3 (17%) 1 1
Any concerns about side effects?	I'm not worried	9 (50%)
Do you expect any challenges in timing of doses?	Same time everyday	2 (11%)
Do you expect any challenges in impact on routine?	Same time everyday	4 (22%)
Anything else?	Can I expect a difference in my mental health?	2 (11%)

	Information all clear, no concerns	2 (11%)

Table 22: Follow up interview responses (Yes/No) n=10

Numbers do not always total 10. Responses reflect unique codes, some participants gave more than one response; some participants either did not know or did not answer some questions.

Question	Yes	No
Did you lose any weight?	5(50%)	4 (40%)
Were your expectations met?	2 (20%)	2 (20%)
Anything unexpected?	2 (20%)	7 (70%)
Change in diet or exercise? - Trying to keep to smaller portions (n=4) - Eating healthier (n=4)	6 (60%)	3 (30%)
Did you feel safe when taking liraglutide?	7 (70%)	2 (20%)
Was there anything you were particularly concerned or worried about? - The size of the needle (n=1)	1 (10%)	4 (40%)
Any side effects? - Sickness (n=2) - Diarrhoea (n=2) - Constipation (n=2) - Extreme stomach pain (n=2)	8 (80%)	5 (50%)
Any additional stress? - Stressed about travel not being in my control (n=1) - Due to side effects (n=2)	3 (30%)	2 (20%)
Did taking liraglutide impact on your everyday living or daily routine in terms of additional burden or benefit? - Side effects were a burden (n=3)	3 (30%)	6 (60%)
Did you experience any challenges in timing of doses? - Forgetting (n=3) - Fitting injections around work (n=1)	4 (40%)	5 (50%)
If a similar clinical trial were to be conducted, would you recommend it to a friend if they met the inclusion criteria?	9 (90%)	0 (0%)

5.2.2 Thematic analysis of participants

Four main themes were identified from the participants' interviews and these are now discussed in detail below.

5.2.2.1 Medication associated weight gain

Several participants reported considerable weight gain associated with medications they are taking, for example:

> 'Ever since being diagnosed with mental health, all sorts of medications made me put on weight. I'm not happy with my weight' [002].

> 'I want to lose weight. I'm fed up of looking fat. When I came in here [Ravenswood house] two years ago I was 12 stone and I went up to 21 stone at my heaviest' [011].

> 'I need to lose weight … it was dreadful. My medication doesn't help' [012].

> 'I've been going [to Slimming World] for 18 months … it worked for a while but the medications I'm on make me hungry' [013].

> 'I'm fat … I've had a problem with my weight for 4-5 years, it's linked to my medication' [015].

> 'I've seen different healthcare professionals about it [being overweight] but they just tell you the same things' [021].

For some participants, this was associated with reduced motivation and despondency as illustrated by the following verbatim:

> 'I went to the gym but there's no point trying. It's a waste of time. Then I get less motivated, I'm not very motivated as it is, so it was really hard. Like fighting an uphill battle' [001].

> 'I went to weightwatchers and it didn't work … so many different diets!' [010]

> 'I've tried not eating … eating healthy … exercise … I just can't lose it' [016]

5.2.2.2 Quality of Life impact

Several participants commented that there had been an improvement in their quality of life due to the study, including a positive impact on family relations. One participant said that their daughter mentioned their weight loss quite a bit and is now able to put her arms around them which she could not do before as her hands could not touch. Another participant reported that their family were no longer nagging them about food, and told them they were looking good again, as well as saying that the participant is much nicer to be around as they are mentally in a better place.

> 'I can walk properly again with improved mobility. I have better breathing … my mood is improved' [021].

> 'It's been life-changing, a brilliant experience. Before, I was in crippling pain and couldn't walk even short distances so was isolated further and further. Now I can walk to the corner shop. I'd do it all again tomorrow' [024].

> 'I felt better when my clothes were getting looser, it kind of put me on a bit of a buzz. My daughter noticed it, mentioned it quite a bit. She could put her arms around for a cuddle. When I was bigger, she couldn't as her hands couldn't touch but now she can which is nice' [007].

> 'I dropped two clothes sizes, I'm feeling better physically and mentally' [024].

In the next two examples the respondents acknowledge impact on quality of life and family noticing changes

> 'My family says I'm nicer to be around … mentally I'm in a better place …. My mum's stopped nagging about food and acting like the food police' [021]

> 'My family noticed my weight loss … told me I'm looking good again. I'm up and about more, engaging with life more, not drowsy all day, wasn't sleeping all day, it's a big big help, it's lovely' [021]

Quality of life for some participants was also reportedly improved directly due to the weight loss. Participant 024 who dropped two clothes sizes described their experience in the study as life changing as they are feeling better physically and mentally, stating that previously they would not have been able to walk short distances such as to the corner shop.

5.2.2.3 Study support and participation

A common theme spoken about by participants was the positive trial support. On the whole participants felt well supported by the staff who were described as having explained information really well (n=7). These two quotations typify responses:

> 'I felt supported, I didn't feel abandoned at all' [026].

> 'Information and advice were brilliant, I knew what to expect… I always had five minutes to ask any questions' [021].

Furthermore, participants said that the information sheets were good and they found them useful (n=8).

'The information sheet was quite concise, it was pretty good. No jargon' [013].

'It was explained really well. I felt I got a lot of support, felt very supported' [003].

Whilst all participants interviewed reported being pleased that they had participated in the study, it is clear that some who did not lose any weight were disappointed. Each of these participants assumed they were in the control group, i.e. receiving the placebo. Despite this disappointment, they did not regret their participation.

5.2.2.3.1 Text messages

Text message reminders were a key theme of trial support highlighted by participants (n=6). They reported that they which helped them remember to do the injections daily. Three participants reported issues with forgetting to take their injections on occasion, however the text messages were a useful reminder. Although not every participant needed the reminders, they were still useful; for example, the following participants said,

'the messages set routine, [020]

and another said that

'the text messages everyday helped because they get unsure if they have taken something or not' [013].

One participant who did not need the reminders still described them as a

'good back up plan' [026].

5.2.2.4 Practical Aspects

Despite clinic attendance being described as okay (n=3), two participants found the journey to appointments problematic because of the additional stress of not being able to control taxi timings and waiting for their taxi if it was late. One participants suggested booking the taxi 20-30 minutes earlier to reduce this burden.

One participant withdrew because unfortunately the staff where he was an inpatient incorrectly put his trial medication in the fridge.

'It was going well until 6 weeks ago. I think they had started to put the medication in the fridge as the pens were cold when the nurses gave them to me and then it was harder to inject. Then I started getting pains in my tummy when injecting, they've got better now but I had bruises and lumps. I was upset about the bumps in my stomach' [011]

Unfortunately the healthcare team did not contact the trial team about this development and the participant had withdrawn from the medication by the time of the participant's next trial visit. The participant had been having a positive experience of being in the trial up until then but unfortunately could not be persuaded to restart the trial medication once the storage error had occurred.

> 'I liked taking them, felt hopeful would lose weight and look better. I think I was losing weight so that was positive and to start off I looked forward to giving the injection; I felt I was doing something positive' [011].

5.3 Process evaluation

Two healthcare professionals who were responsible for delivery of the pilot study, including the candidate, were interviewed by Professor Barnard-Kelly on the 25th February 2020. Both were involved from the start of the pilot study and were involved with design and set up, recruitment, intervention delivery and follow-up.

Professor Barnard-Kelly reported that both described recruitment to be challenging, reflecting the ultimate failure to recruit the intended numbers of participants. Having said that they also believed the intervention was feasible if delivered as part of routine care. A particularly positive and rewarding experience reported was the dramatic weight loss that some participants experienced and the visible positive impact on their quality of life. The nature of dose delivery, i.e. injection therapy was seen as a downside by one HCP who felt this was a factor affecting recruitment and a stressor for some participants. No safety concerns were identified by either healthcare professional, with no concerns regarding timing or doses, impact on daily living or adherence to the treatment regime.

5.4 Discussion

19 individuals took part in the interviews in total. Of the participants this represents over a third (36%) of those randomised in the LOSE Weight pilot study. Participants were representative of study participants, reflecting both intervention and control arms, as well as those who continued to the end of the study and some that chose to discontinue the medication early. 63% who reported weight loss were in the intervention arm and had taken > 70% of their trial medication. The interviews also provided context and depth of understanding to their participation in the trial but also allowed the team insight into their often complex lives. As one participant noted:

> 'Effects every area of one's life, having mental health problems' [007]

Weight loss can be very difficult, particularly in this population due to the obesogenic nature of medications and often sedentary lifestyles [1]. The majority of patient participants interviewed had tried to lose weight previously (81%) and by the nature of being eligible to take part in the study remained overweight or obese despite this. Unsurprisingly, therefore, many participants reported having become despondent with their weight loss attempts and were increasingly less motivated to keep trying to lose weight. Being disheartened by previous attempts at losing weight may have contributed to some acting as passive bystander in their quest for weight loss. Participant 003 reported they withdrew from the medication as their GP had said to stop it, rather than choosing to themselves. They reported burping as a side effect but had lost 6 stone at the time of withdrawal. Another reported the positive impact of the trial is that their wife, who had also attended trial appointments, is now buying more fruit and vegetables.

The nature of drug delivery, namely injection therapy, was perceived to be a barrier to recruitment. Having had an injection pen available for potential participants to see and hold when initially approached about the trial could have improved recruitment. A concern was that potential participants could have thought that the injections would be similar to depot injections, with a much larger needle. This could, understandably, be off-putting for many. Participants reported being pleasantly surprised by the injection device and only one participant expressed concern regarding injections, namely that the needle may bend but did not experience such an event. Despite reservations by some participants about the injections before the study (n=5) most of those who completed the trial reported no challenges in timing or administration of the injections. Three participants were concerned before the study started about potential side effects of vomiting and diarrhoea. On completion of the trial, side effects of constipation, diarrhoea, and vomiting and stomach pain were each reported by two participants. Of the five participants that reported these side effects one withdrew from the medication but the others completed the study on the intervention or placebo. All participants who were asked would recommend a similar clinical trial, if it were to be conducted, to a friend.

Evidence shows that almost half of appointments for mental healthcare users can be missed [153]. The most common reasons for missed appointments included forgetting, work commitments, no transportation and financial constraints. The participants in this trial reported a high attendance at study appointments, with healthcare professionals commenting on their high level of attendance and commitment to attend also. Practical issues around timing of transport were reported by a minority of participants however these did not deter full involvement in the study. Text message reminders in healthcare services have received much attention [154]. A systematic literature review reports that text messages appear to be an effective reminder to improve appointment attendance and medical engagement. Such messages have demonstrated

benefits and these benefits are clearly experienced by the current population. Text reminders in the current study were reported to be useful and reassuring by participants, although not always necessary.

The quality of life benefits associated with successful weight loss were considerable and life-changing for some participants. It is crucial to balance the demands of additional medication with potential benefit. The results show that participants did not find the injections to be burdensome and easily accommodated them within their usual daily routine. Supported weight management, such as that delivered in the pilot study, appeared to be well-received and acceptable as an intervention by the interviewed participants. The two healthcare professional involved in the trial also believed the intervention could theoretically be delivered as part of routine care. While this was a pragmatic trial the candidate is also aware that trial conditions are often not transferrable to acute practice. The candidate therefore believe it would now be of interest to interview mental healthcare professionals to elicit their perceptions of pharmacological interventions as part of their care coordinating role in their current workload. How much specialist knowledge they feel they would need and their views on patient selection would also be important to elicit.

Key strengths of the current study include conducting interviews both at baseline and follow-up, with a broad range of participants taking part at both or either time points. This enabled the capture of a broader range of views. Similarly, conducting interviews with healthcare professionals delivering the study provided valuable data on feasibility of delivery of the intervention in routine clinical care and the experiences of delivering as well as receiving the intervention. The study was limited by challenges in recruitment and the fact that the team were unable to interview any participants who had withdrawn completely from the study and the views of the participants interviewed may not be generalisable to all participants in the study. In terms of data saturation, it is not possible to say this was reached. The consequences of weight loss or not were very personal and extremely impactful for some participants, both physically and emotionally. Whilst there were key themes with several participants reporting similar things, the inclusion of saturation in this context might be misconstrued that future participants would have nothing new to add, which is unlikely to be the case.

In conclusion Saxenda® appears to be an acceptable therapy for obesity in this population with limited side effects in those interviewed. The perceived negatives of self-injection were vastly outweighed by the weight loss. Both participants and researchers involved in the pilot study were also satisfied with the research protocol. The quality of life benefits realised by several intervention participants reinforce the biomedical benefits of achieved weight loss. Future research could consider whether a cross-over design may improve recruitment, retention and

participant satisfaction. From this qualitative data the candidate believes that despite many despairing about their weight and ability to lose weight this intervention in some cases did change how they felt about this which in turn determined their actions and behaviour.

Chapter 6 **Discussion**

This chapter discusses the results, the strengths and limitations of the trial and what impact the findings of the LOSE Weight study could have on research in this area. The chapter is based on the following publication, which was published in January 2021, of which the candidate was first author:

The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomised double-blind placebo-controlled trial. Clare Alexandra Whicher, Hermione C Price, Peter Phiri, Shanaya Rathod, Katharine Barnard-Kelly, Kandala Ngianga, Kerensa Thorne, Carolyn Asher, Robert C Peveler, Joanne McCarthy, Richard IG Holt. Diabetes, Obesity and Metabolism, 2021 https://doi.org/10.1111/dom.14334

Results of the study were submitted for publication in a peer reviewed journal, as seen above, and will also be submitted for presentation at national and international scientific, medical and nursing conferences (International Conference of the Royal College of Psychiatry, World Psychiatric Association, and European Congress of Obesity).

Ms Asher, the PPI representative of the TMG, supported the candidate in organising a meeting at the end of the trial to share the final results with participants, patients and the public. Given the Covid-19 pandemic this was a virtual meeting and 14 participants expressed an interest in attending. Three participants joined the online meeting. Results will also be shared with participants in the trust PPI magazine.

6.1 Primary outcomes

This is the first trial to assess the use of the GLP-1 receptor agonist, liraglutide at the licensed dose for the treatment of overweight and obesity, in people with SMI. The study successfully collected data on recruitment, eligibility, consent, attrition and adherence to the study medication.

Recruitment for this trial proved more challenging than initially expected and was stopped for pragmatic reasons, in agreement with the TSC, after a three-month extension to the recruitment period during which 47 participants had been randomised. The number of case notes that had been pre-screened for eligibility was almost four times the number predicted and the acceptance rate was lower than estimated. Southern Health was a study site for the STEPWISE study, which evaluated the use of a group-based structured education lifestyle intervention to support weight loss in people with SMI [155]. In the STEPWISE study, the research team screened 180 people for

eligibility, invited 101 people to take part and recruited 55 people over an 8-month period. As the inclusion and exclusion criteria were similar between the studies, the candidate had expected a similar rate of recruitment for the current study. The time commitment between the studies was broadly comparable and so the likely reason for the difference is the use of an injectable medication. While the main documented reason as to why eligible candidates declined to take part was the study specific medication or protocol, only a minority of potential participants actually declined because of stated concerns about the liraglutide. From the trial's qualitative data only one participant reported a concern with injecting (the size of the needle) and the candidate therefore speculates whether the rate of uptake would have been higher if potential participants were able to see the device and small needle size when the study was first being discussed with them. This is because many people with SMI's experience of injectable therapies is with depot intramuscular antipsychotics which are deep intramuscular injections using much larger needles A full-scale trial will need to account for this and consider ways of reducing the injectable barrier while remembering that, although willingness to take part in research is strong, 60% of the general population report they would be prepared to take part in a clinical trial, the reality is that between 10-23% of the population actually do [156].

While the acceptance rate was lower than predicted it was higher than that in one of the major clinical trials, the US Diabetes Prevention Programme, which largely underpins the concept that lifestyle interventions are an effective method of preventing type 2 diabetes. 2.5% of those screened made up the 3819 participants (158,777 were screened). In fact the candidate believes it was encouraging that this study was acceptable to 1 in 8 people as current lifetime participation in UK trials is similar [156]. The candidate therefore believes the findings are likely to be representative of a reasonable proportion of this population, which is important to avoid selection bias.

Whilst the research team had good working relations with a number of the mental health teams and a small network of professionals who were enthusiastic about the study, there were also other teams who were more difficult to engage. This may, in part, be due to the fact that SHFT is geographically spread out and teams often do not work closely with one another. The trial team, therefore, screened many notes through CRIS. As 38% of these however, did not have their BMI or weight and height recorded on Open RiO, it is likely that a number of potentially eligible participants were never identified. The possibility of also using primary care data to check if weight and or BMI is recorded in those missing from OpenRIO could be investigated for a definite trial.

In addition, the trial experienced a number of issues which are ultimately also likely to have impacted on recruitment. One was the delay in ethics approval between February, when the substantial amendment for PIC sites was submitted to REC, and August 2019 when it was granted. While the number of participants randomised from primary care was low this was actually due to the fact that it was not part of the original recruitment strategy and ethical approval was then delayed. It would, therefore, still be worth considering recruitment from this setting going forward. Ten GP practices expressed an interest in taking part but only three practices managed to screen and send letters within the remaining timeframe available. From these practices three participants were recruited and the candidate therefore hypothesises that, if there had not been the significant delay in obtaining approval for PIC sites, a further six participants could have been recruited from the remaining practices. There was also a high turnover of staff working on the study which meant that the candidate spent a considerable amount of time upskilling new staff. This time could have been spent supporting the recruitment process. It is recognised that if research staff are embedded into clinical teams this can have a positive impact on recruitment but this is much less likely to happen with a high staff turnover [157].

Text messaging should also be incorporated into recruitment strategies. Using a combination of strategies concurrently, for example both telephone and text messaging, has consistently proven to increase recruitment rates [157] and may have supported the trial team in making contact with the 28% who we were uncontactable by telephone call and letter. Calling from withheld and private numbers may also have been a barrier in terms of making contact with potential participants. An analysis of trials funded by two large UK agencies indicated that 45% of trials failed to meet their recruitment target and 46% had to extend the study duration in order to meet the targets [158]. This highlights the importance of doing a pilot trial so that large scale trials can be planned with preliminary data and experience from the pilot.

The screening to randomization rate (5.9%) was lower than that seen in the other two GLP-1 receptor agonist studies in this patient population that reported their randomisation rate (Larsen et al 48% and Siskind et al 22%). In these studies, as well as this trial, the main reason for non-participation was ineligibility [132, 133]. The CODEX study was also unable to reach its initial recruitment target, ultimately randomising 28 participants from a target of 60 participants [132].

In contrast to the difficulties in recruitment, once an individual was recruited, retention and adherence to medication were in line with expectations. Analysis of the attrition rates in previous studies of pharmacological treatments of obesity, including liraglutide, shows that around a third of individuals do not complete the study, which is consistent with the 78% completion rate in our study [125, 159]. Both arms of the trial were as likely to stay on their prescribed medication until

study completion and treatment adherence in other trials was ~70%, which again is similar to this trial [160]. This is encouraging as it supports the notion that participants in general gained confidence in their ability to self-administer. This could also reflect that those who remained in the trial were the most motivated to lose weight and supports the fact that attendance and completion is frequently positively correlated with weight loss outcomes.

Retaining participants in obesity trials is challenging because they are aware and demotivated if they do not lose weight. Dropout rates and have been reported to be as high as 80% [160]. If the treatment is ineffective, participants may be unwilling to continue treatment, particularly if they are experiencing medication adverse effects. While complete withdrawals from the trial were the same in both arms, four participants were lost to follow up in the trial and these were all in the intervention arm. The attrition rate was therefore greater in the intervention arm as was seen in both the Larsen et al. study and the SCALE Obesity and pre-diabetes trial [125, 133]. For the latter this was reported to be related to a greater number of withdrawals due to adverse effects (9.9% vs. 3.8% intervention and placebo respectively). A review of retention rates for single and multicentre randomised control trials funded and published by the UK's National Institute for Health Research Health Technology Assessment Programme found that the median retention rate was 89% [161]. This is in line with the SCALE Obesity and prediabetes trial where 87% remained in the trial and 69% of those randomised completed 56 weeks of treatment (71% in the Saxenda® group and 64% in the placebo group) [125]. A strength of the SCALE Obesity and prediabetes trial was reported to be the low attrition rate in comparison to other weight loss studies. While studies involving participants with SMI report attrition rates between 25-60% [162] the results of this study suggest there are minimal differences between people with SMI and the general population in this regard.

6.2 Secondary exploratory outcomes

The study also provided useful pilot data about the potential clinical effectiveness of Saxenda® in the management of obesity in people with schizophrenia and schizoaffective disorder.

6.2.1 Baseline characteristics

At baseline, the groups were largely balanced; however, the intervention group were on average lighter which was surprising as there was also a higher proportion of men in this arm. Given the small sample size, this was likely due to chance but that it is also worth highlighting that weight loss is generally considered easier in those with a higher BMI and therefore this may have reduced any observed treatment difference between the intervention and control group. While it is

notable that those recruited into the trial were very obese, this was not surprising to the candidate as it is in line with those recruited to STEPWISE and the SCALE Obesity trial [103, 125]. Similar numbers of men and women were recruited to the trial;, however, as described above, there was an imbalance in sex between the two groups. This was also likely due to chance given the small numbers and randomised controlled design of the study and notes that sex is known to be a natural confounder.

Participants had similar smoking rates to previous publications of people with SMI [108]. This did not include participants who reported vaping rather than smoking. The candidate recorded these participants as previous smokers to ensure continuity. Less than 10% of participants had type 2 diabetes, which is slightly lower than that seen generally in people with SMI, but could be explained by the fact that only those with an HbA_{1c} <64mmol/mol and on certain oral medications were eligible to take part. Encouragingly mean HbA_1 of participants was in the normal range. On a similar note mean cholesterol levels and systolic BP of participants were also satisfactory at 5mmol/mol and 132mmHg respectively despite participants elevated BMI's which reflects the age of participants.

By design, the trial team aimed to include a broad representation of people with schizophrenia, schizoaffective disorder and first-episode psychosis, although those with high levels of psychiatric symptoms were excluded. People with first episode psychosis, however, only made up 4% of those randomised. This compares to 15% of those in the STEPWISE trial. It is possible that Saxenda® could have been even more effective during early psychosis, when weight gain is most rapid, however, the candidate hypothesises that taking part in a clinical trial which involves an IMP rather than a lifestyle intervention would be more difficult during the acute phase of psychosis. As such the candidate believes it would be reasonable to not include people with first episode psychosis in a definitive trial. Most participants in fact had a long history of established psychiatric disorder and a fifth were taking clozapine, a second-line antipsychotic medication, the majority of whom were in the placebo group. All of those on olanzapine were in the intervention group and therefore the candidate feels that the spread of the most obesogenic antipsychotic medications can be considered reasonable.

6.2.2 Body weight and other secondary exploratory outcomes

Despite the low numbers who completed the study on the medication, there was a clinically significant treatment effect on weight in those who completed treatment with Saxenda®. A greater proportion of participants who completed the trial lost at least 5% of their body weight if

they were in the intervention rather than placebo arm. This effect size and SD of the change in weight can now be used to inform a power calculation for a fully powered RCT.

The weight reduction in this pilot trial was greater than the weight loss seen in the other GLP-1 receptor agonist studies in this population and was almost comparable with the 5.7% – 8.0% weight loss seen in the SCALE phase III clinical trial programme [125, 163-166]. In the SCALE Obesity and Prediabetes trial, whose participants were most similar to our study, those treated with the liraglutide 3.0 mg group lost a mean 8.4 kg of body weight after 56 weeks of treatment, compared with 5.7 kg in our study after 6 months of treatment [125]. In addition to the presence of a SMI, there are other important differences in the participant characteristics between the studies. Baseline mean BMI was higher in the SCALE Obesity and Prediabetes trial (38.3 kg/m^2) and 78% of participants were female.

Consistent with our trial, weight loss in the other GLP-1 receptor agonist trials in people with antipsychotic induced weight gain was also associated with reductions in HbA_{1c} and improvement in cardiometabolic measurements (waist circumference and cholesterol levels) in the GLP-1 receptor agonist groups [134]. The reduction in HbA_{1c} is particularly relevant in potential reduced risk of diabetes development, and consequent cardiovascular disease. Whether the established benefits of liraglutide treatment for CVD can be extended to people with SMI remains unknown. BPRS scores reduced in both arms but there was a greater numerical score reduction in the intervention arm. The reduction may suggest improved psychological wellbeing with weight loss. Given the BPRS measures a number of clusters of symptoms including psychotic, anxiety and mood related it would have been of interest to see if these reductions were generally related to one of these areas. The candidate hypothesises that the Hawthorne effect may explain the reduction seen in the placebo arm.

Despite limitations in interpreting mathematical models the GLR model was consistent that there was no other major effect on outcome than the treatment. Given the wide range of antipsychotic medication use and the small numbers of participants, it was not possible to do further sub-group analysis according to the antipsychotic treatment being used. Change in smoking rates were not included in the SAP and therefore not analysed. This could be considered in a definitive trial as smoking cessation can be associated with changes in weight. Finally, once all participants were un-blinded the candidate was able to see that none of the SAEs seen in the trial were due to Saxenda®. While not statistically significant, the candidate also believes that it was reassuring that no major adverse events, including those predicted in this group of the population, were seen in the intervention arm.

6.3 Significant events

6.3.1 Eligibility

A number of additional events also occurred during the running of the trial and will be discussed here. Regular and thorough monitoring was carried out throughout the running the trial. In general minor errors were picked up with the exception of two queries regarding the eligibility of participants who had been randomised into the trial. In the first scenario, participant 029, had a diagnosis of schizoaffective disorder but also had a diagnosis of psychotic depression historically (psychotic depression or mania was an exclusion criteria). The case was therefore discussed at the TSC where it was agreed to keep the participant in the trial. Professor Dickens commented that at a point in time the diagnosis may have look like psychotic depression but longitudinally more likely to be clear that it was schizoaffective disorder. A corrective actions and prevention form was completed by the candidate with the plan to discuss any similar scenarios with Professor Rathod before randomisation. For a definitive trial the exclusion criteria should be changed to a solo diagnosis of psychotic depression.

In the second scenario participant 042 had taken insulin in a previous pregnancy 2 years earlier. The candidate discussed this with the CI as current or previous use of incretins or insulin was also an exclusion criteria. As the CI had never envisaged that temporary use during a pregnancy would be an exclusion criteria and in retrospect noted that the exclusion criteria should have worded as

> *Current or previous use of incretin based therapies (GLP-1 receptor agonist or DPP-4 inhibitors) or **current use of** insulin*

The CI recommended going ahead and recruiting her with a trial file note explaining the above. The participant attended a screening visit and was consented and subsequently randomised into the study. The participant then, however, changed their mind and did not attend the randomisation visit and so did not go on to take part in the trial. This episode was picked up during a monitoring visit and a query was raised as this was a deviation from the study protocol. This was again discussed with the TSC and sponsor. The TSC felt they were well positioned to give a view on whether this constitutes a serious breach according to the MHRA regulations. Their view was that the safety of the individual concerned was not put at risk, and the integrity of the trial was not undermined and therefore did not constitute it a serious breach. The sponsor's investigation into the incident revealed this was a single episode, recruitment at site had stopped when the incident was discovered (so there cannot be a reoccurrence) and agreed that the safety of the individual was not compromised and no participant data will be used in the study. The investigation into the incident and agreed actions were documented in site file.

Recruiting ineligible people to a trial is negative in many ways. Participants can be exposed to unnecessary risk, they may have to be withdrawn against their wishes, their data would be unusable or require additional analyses and ultimately it could affect the outcome of the trial and possibly mislead future care. Both scenarios discussed above were due to the wording of the protocol not being clear-cut rather than a desire from the trial team to change the exclusion criteria. This is one of the reasons for running a pilot trial so that issues such as these can be worked through. For a definitive trial it could also be worth considering whether it would be beneficial to have two people confirming eligibility.

6.3.2 SAEs

Overall these pilot data support Saxenda® as being a safe and well-tolerated medication. The candidate, however, believes two SAE's warrant further discussion. Participant 010 was withdrawn from the medication after a SAE of a myocardial infarction. This was because one of the exclusion criteria for prescribing Saxenda® is a myocardial infarction in the previous 180 days. For the candidate this was an interesting situation as Saxenda® has been reported to reduce the risks of CV events which the study population are known to be at risk of, especially if they have had a previous event. This event was also a useful learning opportunity for the candidate. When the participant was admitted to hospital the cardiology team asked for the patient to be urgently un-blinded which the candidate did. On discussing this SAE at a later date with the TSC they felt that this was unnecessary as it would not have impacted on the patient's management. Going forward from that point in the trial the candidate would have discussed any further un-blinding requests with a principal investigator and have a higher threshold of when to consider un-blinding necessary. Of note this was the only un-blinding request during the trial.

On 7 October 2019 participant 031 reported feeling suicidal after her son was abusive towards her. She reported this event at her next trial appointment but that she was also now not feeling suicidal. Given one of the exclusion criteria was mental illnesses that could seriously reduce their ability to participant in the trial, including significant suicidality the decision was made to withdraw her from the trial after unsuccessful attempts to contact their CCO over a 48 hour period. The CCO then made contact with the candidate and confirmed the participant's suicidal thoughts were short lived and that they had documented that she was not suicidal in OpenRIO and that her risk of self-harm was low. Of interest the mental health team were very keen for the participant to stay in the study. The case was therefore discussed at the next TMG meeting and all, including Professor Rathod (psychiatrist), were in agreement that the participant could restart the medication.

6.3.3 Individual funding requests

The candidate applied for five individual funding requests (IFRs) on behalf of participants that lost at least 5% of their initial body weight by the end of the trial. This cut off was chosen in line with the license for supporting the continuation of Saxenda®, although it is worth noting the general population are assessed after a 12 week time period where as in the trial the participants had a 6 month time period. The trial team and REC felt this was appropriate as it is known that weight loss in this population is harder than in the general population [103]. All but one of the IFRs were actually for participants who had lost >10% of their body weight. The IFRs were submitted to West Hampshire and Southampton CCGs and were all approved on the proviso that the participants continued to maintain their weight loss or lost further weight. From NICE's review into the use of Saxenda® in the NHS for the management of obesity [130] only 2 out of the 5 participants who the candidate applied for on-going funding would have met these criteria had they been in place at the time. The additional challenges regarding weight in the context of antipsychotic medication use is not included in the criteria which the candidate considers an omission.

6.3.4 Covid-19

In March 2020, with the escalating novel corona virus 2019 (Covid-19) situation, the candidate made suggestions to the TMG which were agreed to be appropriate. At that point in the trial only one participant was left on the trial medication with two others remaining in the trial but off the medication. On 12th March the introduction of a screening phone call was brought into place prior to any study visits. This was to ensure that research participants were well to protect other trial participants as well as staff. No visits were affected as a result of this. A NSA was submitted on 20th March 2020 and is summarised in 2.2.2. It was also agreed by the TMG that if a participant become unwell the trial team would have a low threshold to stop the medication given the small risk of tachycardia if not on placebo. From a staffing point of view there were a number of the trial team trained to be able to do visits/telephone calls and the candidate was fully set up to work from home (so could do telephone appointment this way also). Participants 046 and 047 therefore had their final visits as telephone calls. For V7 for 046 they were able to provide a weight measurement for the team to record using home scales (as per NSA) but unfortunately this was not possible for participant 047. With hindsight if the candidate had been aware of this they could have arranged for some scales to be delivered to the participant.

6.4 Strengths and limitations of the trial

Key strengths included the randomised placebo controlled design of the clinically relevant trial in a vulnerable under treated population, the retention rate, zero errors in the database check, the joint mental and physical health team working and impact the intervention made to a number of the participants, especially the ones who lost more than 10% of their body weight. As judged by the baseline characteristics, the trial recruited a broad representative group of people with SMI taking a range of different antipsychotic medications. The trial team also maintained the double blind throughout the trial, including during statistical analysis, apart from for one participant as discussed previously in 4.6.2 . The consistency of the key trial members, including a dedicated TSC, from inception to close out of the study could also be noted as an asset of the trial. While the TMG remained consistent throughout the trial the original statistician left in August 2019. The SAP that the original statistician and candidate developed remained largely the same and standard parametric and nonparametric tests were used depending on data distribution. The SAP did not, however, include any plan for imputation of data and therefore observed data estimand analyses were done rather than ITT analyses. These differences were discussed at the final TSC meeting in September 2020 which included an external senior statistician on the panel and felt to be reasonable as this was a feasibility study.

This study facilitated joint mental and physical health team working which had not been seen in the SHFT R&D team previously. At the outset of the study there had been some barriers and while turnover of staff in general was a limitation, in this regard, it was an opportunity for new team members to work on the study which they did enthusiastically. This enabled progressive joint working with the mental health team in the department that will hopefully continue going forward.

Limitations include the failure to reach the planned sample size, which led to some imbalance in baseline characteristics, and the fact that data were not collected on 42% of those approached to take part in the study who did not have a screening visit organised. Reason why they did not wish to take part were therefore not considered in the analysis. Data from the final participants were missing because the trial had to stop with the introduction of Covid-19 restrictions.

Other limitations include the exclusion of non-English speakers. In order to have a fully representative sample allowance for interpreters and extra time for trial appointments would be recommended for the fully powered trial. Another limitation was that BMI was not adjusted for the Asian population of the sample and are known to have weight related consequences at a lower threshold. Finally the travel budget only supported people to come from a certain radius

around Southampton and if there were no financial limits then this would not have been a barrier to taking part in this study.

The participant groups were not homogeneous as they were on a range of different antipsychotic medications and in some cases multiple antipsychotic medications. Given the small sample size trial arms were not matched or adjusted to take this into account. Conversely, however, if the trial had only included participants on particular antipsychotic medications then results would not have been relevant to many people with SMI. Some participants were also on antidepressants and anxiolytics which may have also affected the secondary exploratory outcomes looked at. Additional potential confounders may also not have been considered. While reasonable efforts were made to ascertain reasons for complete withdrawal from the study none of these participants ultimately took part in an exit interview, despite being invited to, which could have provided valuable insights. Another limitation is that best practice requires the BPRS to be carried out independently by two people, however, this was not feasible in this pilot due to staff work load. It would have also lengthened each participants visit by a further 10 minutes but could be considered, for future studies if not felt to cause unreasonable additional burden for trial participants. The merits of other psychiatric scales, such as CGI-S and PANSS, could also be discussed but are more time consuming and require baseline knowledge of the condition and participant. The BPRS has the 6 schizophrenia specific items from the PANSS and while we acknowledge that the PANSS may be superior to the BPRS in clinical research on schizophrenia, and that most BPRS items are not interchangeable with identically named PANSS items, we believed that the BPRS met our study objectives. A further limitation is the lack of a formal assessment of diet and physical activity before and during the trial. However, given our experience during the STEPWISE trial with a similar patient group, the candidate does not believe that weight change is likely to be attributable to the provision of standardised lifestyle advice [103].

The trial did not allow for any data collection after cessation of the trial medication to observe what happened to weight post-treatment cessation. Whilst the candidate hypothesises that it is likely that participants in the intervention arm re-gained at least some of the weight they lost, hence the indication for life-long Saxenda® when prescribed, even short term weight loss can have a positive impact on health. Finally the trial was funded by the investigational drug manufacturer and this could lead to potential bias. In order to mitigate against this bias, the trial was sponsored by SHFT, which had the responsibility for the initiation, management, conduct, analysis, reporting and publication of the trial. Although Novo Nordisk Ltd provided support financially and the product for the trial, they were not involved in the conduct, management and delivery of the trial. Additionally, the initial idea, rationale and design for the trial came from the

Chief Investigator. Nevertheless, the results of this study would need to be confirmed in a fully powered investigator-led trial.

6.5 Comparison with findings from other studies

Overall this pilot suggested greater weight loss than that seen in the 16-week trial of daily subcutaneous liraglutide (maximum dose 1.8mg) and 24-week trial of weekly exenatide LAR in people with SMI. Of note Larsen et al did a modified ITT analysis and CODEX did an ITT analysis with imputed data using last observation carried forward. The candidate's findings were also comparable with the SCALE Obesity & pre-diabetes trial where participants in the Saxenda® group lost a mean 8.4±7.3 kg of body weight after 56 weeks of treatment [125]. Baseline mean BMI was higher in the SCALE trial (38.3kg/m^2) and 78.5% of participants were female. Weight loss in all of these trials was also associated with reductions in HbA_{1c}. In Larsen et al. and SCALE there was also a greater reduction in cardiometabolic parameters (blood pressure and cholesterol levels) in the liraglutide group [125, 133].

The screening to randomization rate in this trial was lower than that seen in the other two trials which also demonstrated weight loss (Larsen et al 48% and Siskind et al 22%). In all three studies the main reason for not taking part was not being eligible. The Siskind et al. study aimed to include 60 participants in their protocol publication but ultimately randomised 28 participants. Prior to recruiting participants, the authors reviewed the rates of obesity, diabetes and poorly controlled diabetes among people on clozapine at their clinical service and realized they would be unable to meet their recruitment targets and the protocol was therefore adjusted. A benefit of the candidates pilot trial compared to the Larsen et al. study, as discussed in 1.6.4, was that the inclusion criteria was wider, the latter only included participants who had prediabetes in addition to overweight or obesity on clozapine or olanzapine which limited the results generalizability.

Table 23 Comparison of LOSE Weight feasibility trial vs. SCALE and other GLP-1 receptor agonist trials in people with SMI

Trial and location	LOSE Weight UK	Liraglutide 1.8mg (Larsen)[133] Denmark	CODEX (Siskind) [132] Australia	Exenatide LAR (Ishøy) [131] Denmark	SCALE Pre Diabetes and Obesity [125] Worldwide
Screening to	6%	48%	22%	69%	45%

randomisation rate					
Participants	47	103	28	45	3,731
Placebo controlled	Yes	Yes	No (usual care)	Yes	Yes
Timeframe	6 months	16 weeks	6 months	3 months	56 weeks
Primary endpoint	Pilot	Glucose	>5% weight loss Pilot	Body weight	Body weight >5% or >10% weight loss
Antipsychotic medication	All	Clozapine or olanzapine	Clozapine	All	N/A
Baseline age (years)	43	42	Not reported	35	45
Baseline weight (kg)	115	102	105	117	106
Male	51%	58%	55%	50%	22%
Baseline BMI kg/m^2	39	33	35	38	38
Completed	79%	93%	100%	88%	87%
Weight loss intervention arm (kg)	-5.7	−5.3	−5.3	-2.24	-8.4
Other reductions	HbA_{1c} Waist circumference	Glucose tolerance Systolic BP LDL	HbA_{1c}	None	Hba1c FBG BP TC
Psychiatry score	BPRS	CGI-S/GAF	BPRS	None	N/A

used					

6.6 Impact for a fully powered RCT

Confirming screening, enrolment and dropout rates were important aims of the study and by executing this there are now data available to inform a fully powered RCT. The qualitative data collected also enabled the candidate to have an insight into how the thoughts of participants taking part drove their behaviour. This data would also be essential in designing a fully powered RCT.

A power calculation to calculate the number of participants needed has been calculated from the effect size and SD of the change in weight analysed. A sample size of 60 participants in each group (120 participants in total) will have 90% power to detect a difference in mean weight of 6.4kg using a two independent sample t-test with a 5% significance level. Assuming one in four participants were enrolled (supported by the pilot study), 144 participants would be included, allowing for an attrition rate of 20% (please adjust where possible).

While baseline data of those who were randomised has been analysed these characteristics have not been compared with those who declined to take part in the study. Age and sex of all participants approached has been documented and therefore could be looked at to further inform the recruitment strategy.

As in 6.3.1 two exclusion criteria would need be updated for a fully powered trial to reflect the learnings discussed.

- *Current or previous use of incretin based therapies (GLP-1 receptor agonist or DPP-4 inhibitors) or* ***current use of*** *insulin*
- A **solo** diagnosis or tentative diagnosis of psychotic depression or mania.

A TMG could also consider whether to only include those on a limited number of antipsychotic medications to reduced influences of differential effects. Further consideration may also be taken on how best ensure that the exclusion criterion '*Mental illnesses that could seriously reduce their ability to participate in the trial, including significant suicidality*' remains from a safety point of view but does not preclude potential participants who may be at the greatest need from taking part in a future RCT. As antipsychotic drugs are prescribed for patients with conditions other than schizophrenia-related disorders, for example in augmentation treatment of depressive illness and

in acute mania, the study design could also be adopted to explore antipsychotic-related weight gain in these conditions.

From a SAP point of view there would need to be a plan regarding imputation of data at the design stage of the trial as these results suggest there would again be a reasonable attrition rate and loss of data. The candidate would suggest last observation carried forward and this should be stated in the SAP. In this pilot study that would have provided 3 month data for four of the participants. Sensitivity analyses would also be needed to confirm that any findings were robust.

For a future definitive trial the following findings from this study could be taken into account in order to ensure a definitive RCT could recruit and retain the necessary participants

- From the secondary exploratory outcomes the effect size and SD of the change in weight for the intervention group could inform a power calculation to allow an appropriate number of participants to be recruited in order to have sufficient statistical power.
- 56% of people with schizophrenia, schizoaffective disorder or FEP would be eligible to take part in the study. This is lower than the 70% predicted at the outset of the trial.
- 17% would be willing, once invited, to take part in the study.
- 85% of participants who attend for a screening visit would be randomised.
- 79% of the randomised participants would complete the 6 month study and 97% of these would complete the trial on the medication.
- 21% of the randomised participants would withdraw completely or be lost to follow up. This is similar to the predicated dropout rate at 6 months of 15% to 20%.

A number of factors are likely to have impacted recruitment in the pilot trial and while the candidate recognises that recruitment to trials is complex the candidate also believes the following additional suggestions could benefit a future trial:

- Researchers embedded in clinical teams or establishing research champions within clinical teams.
- Identify clinicians who are not bought in on the importance of the research and potential of the intervention with the aim to explore and challenge these beliefs.

Both of these strategies would focus on engaging teams in research and promoting study participation. By being part of the team researchers or champions could identify how recruitment would function best within that setup. Their presence would serve as a regular reminder and allow direct participant referrals. The single most influential factor in enrolling participants in clinical trials has been reported to be physician influence. A review of UK psychiatry healthcare professionals found that 17% thought it was not part of their role to provide advice about weight

[167] despite national guidance stating that 'the secondary care team maintains responsibility for screening and monitoring metabolic risk factors for the first twelve months or until the condition has stabilised – whichever is longer' [68]. Reasons from mental health professionals for this discrepancy included 57% being worried about treating obesity and type 2 diabetes or a lack of incentive. If clinicians working with people with SMI do not feel, at least in part, responsible for the physical health of this population then the candidate hypothesises that they will be less motivated to recruit people into a trial such as this one.

Identifying sites which could support the suggestions described above would be preferable to needing a large number of sites which would require considerable co-ordination. From the positive uptake seen by adding PIC sites, despite this being for a short period of time, primary care services would-also be avenues worthy of consideration to be part of the recruitment strategy. The majority of participants reported finding the text message reminder service beneficial. Going forward text messaging could also be incorporated into recruitment strategies. A combination of strategies concurrently, for example using telephone and text messaging, has consistently found to increase recruitment rates [157] and may have supported the trial team to make contact with the 28% who we were uncontactable by telephone call and letter. A dedicated TMG and TSC would also be strongly recommended.

An array of mitigating actions could also be considered to support a high retention and adherence rate. The SELECT trial looking at cardiovascular outcomes with a novel GLP-1 receptor agonist (discussed in 6.7) is using methods such as a patient app and 'Barriers and Motivations' interview at the screening visit. The latter looks at why participants are wanting to take part in the first place. The idea is to help investigators identify and manage potential barriers to adherence early in the study, so the participants can be supported in addressing these before they are at risk of prematurely discontinuing medication or withdrawing. If a participant is considering withdrawing from the study investigators can also look back at the motivations comments made in this interview and discuss with participants if these are still relevant [168].

6.7 Implications for future research

While this research contributes to the development of effective weight management intervention programmes for people with SMI several key research questions regarding the use of injectable weight loss medications remain for this patient population. Although encouraging, the results of this study would need to be confirmed in a fully powered trial. As far as the candidate is aware the only other data regarding the use of Saxenda® in SMI is a retrospective review published in February 2021. This looked at 16 patients with obesity with schizophrenia or bipolar disorder who

were treated with 3.0 mg of liraglutide for 16 weeks [169]. Findings were in line with the candidates results.

While studies such as this can struggle to recruit to target on time, especially in hard to reach populations, the candidate believes this highlights the need to share learnt experiences for other researchers to consider when planning future studies in this area. This study highlights the need to scrutinize the method of estimation of eligible participants, use a lower acceptance rate if using an investigational product rather than lifestyle intervention and note the importance of healthcare professionals' opinions on trial intervention effectiveness and perceived burden of trial involvement on recruitment.

While the healthcare professionals interviewed as part of this study believed that the intervention was feasible to be delivered as part of routine care, the practicalities of how best to do this remain uncertain. How to identify those who are sufficiently motivated to benefit most from an injectable weight loss intervention would be valuable in order to inform how this treatment could be delivered. Ambivalence is recognised to undermine behavioural change and of those identified in the qualitative interviews, as having tried multiple approaches previously, none went on to lose >10% of their body weight (four were in the intervention arm). While these are very small numbers and it is possible that they ultimately still had hope that an alternative strategy could be beneficial to them it would be of interest to explore whether these previous setbacks impacted their response. While inclusion criteria stipulated a minimum of one month on antipsychotic medication additional studies are warranted on whether Saxenda® or other GLP-1 receptor agonists can prevent obesity at antipsychotic medication commencement. The possibility of co-administration with Saxenda® to ameliorate this could also be explored.

Although liraglutide 3.0 mg daily is currently the only licensed GLP-1 receptor agonist for the treatment of obesity, there are on-going studies of other GLP-1 receptor agonists for this indication. Since this protocol was designed a once weekly GLP-1 receptor agonist, semaglutide (trade name Ozempic®), has been developed and brought to the market. Semaglutide 1 mg, a once weekly GLP-1 receptor agonist, has been shown to lead to significantly greater weight loss than that seen with liraglutide 1.2mg daily (diabetes dose) in people with type 2 diabetes in the SUSTAIN-10 trial (-5.8 vs 1.9 kg) [170]. A phase 2 study of semaglutide 2.4 mg once weekly demonstrated a mean weight loss of up to -13.8% for those treated with semaglutide [171] and five phase III studies are now on-going as part of the Semaglutide Treatment Effect in People with obesity STEP programme as a medication for obesity treatment for those with established CVD [172]. The use of a once weekly preparation may appeal to those who declined to take part in this study because of the need for daily injections with Saxenda®. A once weekly preparation may also

allow the injections to be administered by healthcare professionals where necessary. The PIONEER clinical trials for oral semaglutide support the use as a treatment for type 2 diabetes and it was accordingly approved by the FDA in 2020. If oral semaglutide is also efficacious for overweight and obesity it may prove to be a better option for people with or without SMI who find daily or weekly injections unfeasible, however, the dose needed may be uneconomical. Long trial run in time can result in the loss of relevance as practice may have moved on by the time a trial is published. While the option of an oral tablet or weekly injection would be valuable additions to the weight loss medications repertoire these are not currently licensed in the UK and accordingly this is important research to demonstrate the potential for use of overweight and obesity medication that is available at the time of writing for people with SMI

Further research about lifestyle interventions suitable for people with SMI are also needed. Dietary interventions, to date, in people with SMI have tended to focus on either low fat diets, healthy eating or prescribed calorie daily calorie reductions of 500-600 kcal/day. A randomised, placebo-controlled, double-blinded trial investigating the efficacy of dietary fibre and probiotics alone and in combination to reduce metabolic side effects induced by atypical antipsychotic medications is currently in process [173]. While studies using a low-calorie 'total diet replacement' in the wider population have demonstrated significant improvements to people's health (average weight losses of 10 kg at one year) there have been no studies using this approach among people with SMI. Qualitative research has shown that total diet replacement is easier to follow than first thought with social and clinical support identified as essential to success. What few data exist within the area of SMI and bariatric surgery suggests that there is comparable weight loss and complication rates, however, these individuals required more postoperative support.[174, 175] While large long-term studies identifying both how SMI predicts the outcome of bariatric surgery and the outcome of SMI following surgery are needed the candidate believes other issues would also need to be tackled as otherwise this intervention would likely to remain uncommon regardless. Conflicting views on clinical matters and ambiguity over roles (i.e. who would refer for bariatric surgery) can result in inertia. A review of UK psychiatry healthcare professionals found that 17% thought it was not part of their role to provide advice about weight [167] despite national guidance stating that 'the secondary care team maintains responsibility for screening and monitoring metabolic risk factors for the first twelve months or until the condition has stabilised – whichever is longer' [68]. Reasons from mental health professionals for this discrepancy included 57% being worried about treating obesity and a lack of incentive. Many healthcare professionals may be unfamiliar with the notion of metabolic risk and the importance of assessing and treating this. Appropriate agreement about clinical responsibility is needed to ensure joint working across mental and physical as well as primary and

secondary care teams. The ability for healthcare providers to share core information is also currently often lacking and access to healthcare settings can be perplexing for people with SMI.

Ultimately while the optimal weight management of people with SMI remains uncertain it is likely to include a multimodal approach tailored to an individual's needs. Further research is therefore needed to establish the most effective combination.

Finally, further work is needed to cement the importance of physical health research in people with mental health illness as the candidate considers stigma around the latter to still be a factor for both patients and healthcare staff. By adding to the body of work in this, at times neglected, area the candidate hopes this work supports the stance that research questions in this area are vital to improve care and consequently outcomes. The candidates also hopes that others doing research in this area will recognise the important of joint working of physical and mental health research staff such as there was in this pilot study. Supporting the perception that this is beneficial could be a step in the right direction to break down barriers that can currently exist between physical and mental healthcare providers.

6.8 Conclusion

Obesity adversely affects the physical health, quality of life and psychological well-being of people with SMI. This pilot study explored the feasibility and practical issues of conducting a future definitive randomised controlled trial evaluating weight change with liraglutide up to 3.0 mg daily in people with overweight or obesity with SMI and provided data to estimate important parameters to help its design. This research will contribute to the development of effective weight management intervention programmes for people with SMI and supports the potential of injectable GLP-1 receptor agonists, at an overweight and obesity dose, as an acceptable and effective weight loss medication in this group of people.

More research is now needed to develop and evaluate novel clinical innovations to prevent weight gain and better support those with mental illness. The candidate believes people with mental illness should be included in appropriate trials to reduce the risk of widening health inequality and hopes that trials such as this one will support this stance. Obesity and mental illness can both be challenging lifelong conditions but opportunities exist to improve the current situation for this potentially vulnerable and high-risk group. Achieving parity of esteem between mental and physical health is a worldwide priority if we wish to improve life-expectancy and quality of life in people with SMI.

Appendix A Interview guide for start of trial

Why have you chosen to take part?

Have you tried to lose weight before?

Can you tell me about your expectations of the trial?

Do you have any safety concerns?

Do you think injections will impact your daily life?

Anything else you wish to share or discuss?

Appendix B Interview guide for end of study

How did it go?

Thanks, could you tell me a bit about some of the specifics of taking part?

Could you please tell me about your experience of taking Saxenda®?

Did you feel safe when taking Saxenda®?

Did taking Saxenda® impact on your everyday living or daily routine in terms of additional burden or benefit?

Was there anything unexpected about taking Saxenda® that you experienced during the trial?

If a larger clinical trial were to be conducted, along the lines of this pilot study, would you recommend to a friend that they participate if they met the inclusion criteria?

Is there anything else at all that I should have asked you or that you would like to tell me about your experience of taking part?

Appendix C Statistical analysis plan

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INTRODUCTION

LOSE. Weight is a double blind randomised pilot study investigating the use of once daily liraglutide (maximum dose 3.0mg) subcutaneous injection in comparison to placebo in people with obesity or overweight with schizophrenia, schizoaffective disorder or first episode psychosis. It aims to explore the feasibility and practical issues of conducting a future definitive randomised controlled trial (RCT) evaluating weight change with liraglutide in people with overweight or obesity with severe mental illness. This feasibility trial will estimate important parameters to help its design.

OBJECTIVES

Primary Objective

The primary objective of the trial is to gather data on feasibility for a fully powered trial, as follows:

a. Time to reach recruitment target.
b. The number of eligible participants required to be screened in order to reach recruitment target. Key characteristics and reasons for not joining the trial will be recorded, in line with the CONSORT criteria for clinical trials.
c. To estimate participant attrition rate.
d. To estimate adherence to the investigational medicinal product.

Secondary exploratory outcomes

To estimate effect size and standard deviation (SD) of the change in weight at 26 weeks in order to inform a power calculation for a fully powered RCT based on this feasibility pilot study.

The secondary objective is to test the null hypothesis that there is no difference in weight loss between treatment groups. Changes in waist circumference, body mass index, fasting plasma glucose, HbA1c, blood pressure, lipid profile at 12 and 26 weeks will also be assessed for statistical significance.

TRIAL METHODS

Trial design

The trial is a single centre, double blind, randomised, placebo-controlled trial. Treatment allocation is a 1:1 ratio. Participants are randomised to either liraglutide (maximum dose 3.0mg) or matched placebo control.

Randomisation

Each randomisation is via simple randomisation with permuted block size. The randomisation process is described in full within the clinical trial protocol.

Sample Size

This study is a pilot trial aiming to explore feasibility, practical issues of conducting a future definitive trial and estimate important parameters to help its design. In this regard, sample size is based on the need to estimate study parameters within a reasonable degree of precision rather than on hypothesis testing. Simulation work by Sim et al (2012) recommended a minimum of 50 participants (25 per group) in order to achieve pilot/feasibility objectives [139]. Assuming a dropout rate at 6 months of between 15% to 20%, we will need to recruit at least 60 participants (30 per group) to provide robust estimates that will inform the design of the definitive trial.

In a pilot trial looking at the use of liraglutide (maximum dose 1.8 mg) of 214 potential participants assessed for eligibility 103 were randomised. Of the 111 excluded 86 actually did not meet final inclusion/exclusion criteria, 23 declined to participate and 2 had too severe degree of mental illness to participate. [133] However, in a similar study, the use of exenatide LAR in people with schizophrenia, out of 123 potentially eligible participants only 28 were randomised with 63

declining to participate [132] . We used these data to estimate our screened to randomised rate (see table below).

Interim analysis

This study focusses on the feasibility of recruiting from this patient population for a fully powered RCT. The recruitment rate will be reviewed at 12 weeks post study start (i.e. 24/9/18) compared to the planned trigger points in the table below and the recruitment strategy revised if necessary. No serious adverse outcomes are anticipated associated with use (or not) of the trial medication; therefore no interim statistical analysis is planned regarding safety, however the trial steering committee will review all SAEs regularly.

Data quality control

Data will be recorded via paper CRFs and entered by a dedicated member of staff onto an electronic data management system which applies appropriate range and format checks on entry.

STATISTICAL PRINCIPLES

Statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

Analysis populations

The data will be analysed based on the intention-to-treat population; all randomised participants, regardless of their eligibility, according to the treatment they were randomised to receive will be included. Due to the feasibility nature of this study a per-protocol analysis will not be necessary.

Screening data and participant flow

Key characteristics and reasons for not joining the trial will be recorded for all participants screened. A CONSORT diagram will be used to summarise the number of participants who were:

- Estimated number of eligible participants in the recruitment area (from a Current Research Information System (CRIS) search of the Southern Health database)
- Pre-screened for eligibility via medical notes
- Invited for screening visit; accepted and not accepted*
- assessed for eligibility at screening visit; eligible and not eligible*
- eligible and randomised

- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- Randomised and included in the primary analyses

*reasons will be provided.

Baseline participant characteristics

Participants will be described with respect to age, gender, ethnicity, smoking status, diagnosis of type 2 diabetes (yes/no), time since diagnosis of diabetes if applicable, diabetes treatment if applicable, type of psychiatric diagnosis and time since this diagnosis, type of antipsychotic medication, weight, BMI, waist circumference, brief psychiatric rating scale (BPRS), HbA1c, fasting plasma glucose (FPG), lipids, systolic and diastolic blood pressure at baseline, both overall and separately for the two randomised groups.

Categorical baseline data will be summarised by numbers and percentages. Continuous baseline data will be summarised by mean and SD if data are normal or median and IQR if data are skewed. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

ANALYSIS

Outcome definitions

e. Time to reach recruitment target is defined as the time from first participant screened to randomisation of the 60th participant.
f. Number of participants required to be screened in order to reach recruitment target is defined as the number of participants attending a screening visit.
g. Participant attrition rate is defined as the number of participants not available for follow-up at the final study visit as per the research protocol.
h. Adherence to the investigational medicinal product is defined as the number of empty cartridges returned at each visit by trial participants divided by the total number of cartridges prescribed. Adherence will be analysed both as a continuous variable and by the number of participants using at least 70% of prescribed trial medication over 12 weeks and 26 weeks.

Appendix

Analysis methods

Analysis of primary objectives

d. Time to reach recruitment target will be reported as a number (in weeks). The mean number of participants recruited per week will also be presented with 95% confidence interval

e. Number of participants required to be screened: the rate of successful screens will be evaluated as the number of participants randomised divided by the number of participants screened; presented as proportion with 95% CI.

The following will be analysed at 12 and 26 weeks, both overall and within treatment group:

f. Participant attrition rate: will be evaluated as the number of participants not available for follow-up, divided by the number of participants randomised; presented as proportion with 95% CI.

- Adherence to the investigational medicinal product – (defined as the proportion of medication used by each person ranging 0-100%)
    - Either mean (SD) or median (IQR) adherence will be presented as appropriate
    - Number of participants using at least 70% of prescribed trial medication with 95% CI

Analysis of secondary exploratory outcomes

Changes in weight (defined as weight in kilograms (kg) at 3 or 6 months minus weight in kg at randomisation), BMI, waist circumference, brief psychiatric rating scale (BPRS), HbA1c, fasting plasma glucose (FPG), lipids, systolic and diastolic blood pressure, and adherence to randomised treatment (including the effect of the using the optional text messaging reminder service or not), type of diabetes medication, change in type or dose of diabetes medication, type of antipsychotic medication, change in type or dose of antipsychotic medication between the two treatment groups will be reported using mean (SD) or median (IQR) according to the distributions, and compared statistically using either paired t-test or Mann-Witney U test. The number of participants experiencing a weight loss of at least 5% from baseline to 12 weeks and 26 weeks will also be reported and tested for significance.

We will then use a generalised linear model (GLM) adjusted for baseline in order to compare the change in body weight between the two groups at 26 weeks. This will be done

3. Unadjusted for covariates
4. Adjusted for any covariates that are significantly different between the two treatment groups in the univariate analysis described above

Missing data

Analysis will be completed using list wise deletion of missing data.

Participants with and without missing data will be compared for differences in demographic and physiological data where possible, by looking at appropriate summary statistics with statistical tests, as follows:

- Mean (SD) with t-test or Median (IQR) with Mann-Whitney test for continuous data
- N (%) with either chi-squared test or Fisher's Exact test for categorical data

Differences between the participants will be taken into account in deducing the feasibility of a full study.

Harms

The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

Statistical software

The analysis will be carried out using IBM SPSS Statistics 19. Other packages, such as R, may be used if necessary.

Appendix

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