TRIAL PROTOCOL

IIH-Advance

A phase III multi-stage randomised controlled trial to determine the effects of weight loss, induced by Tirzepatide, in adults with active idiopathic intracranial hypertension

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: **1.0**

Version Date: **03 September 2025**

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

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This project is funded by the Sir Jules Thorn Charitable Trust. The views expressed are those of the authors and not necessarily those of the Sir Jules Thorn Charitable Trust.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	IIH-Advance
Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
CI name:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the IIH-Advance trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the IIH-Advance trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, the principles of Good Clinical Practice (GCP), and the Data Protection Act 2018 and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_25-056
ISRCTN reference number	< ISRCTN reference number >
IRAS reference number	347499

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Non-Independent Members	
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ABBREVIATIONS

Abbreviation	Term
AUDIT	Alcohol Use Disorders Identification Test
BCTU	Birmingham Clinical Trials Unit
BES	Binge Eating Scale
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSRI	Client Service Receipt Inventory
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EDC	Electronic Data Capture system
EQ-5D-5L	EuroQol 5-Dimension 5-Level
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP-1	Glucagon-Like Peptide-1
GLP-1R	Glucagon-Like Peptide-1 Receptor
HADS	Hospital Anxiety and Depression Scale
HIT-6	Headache Impact Test-6
HRA	Health Research Authority
ICF	Informed Consent Form
ICP	Intracranial pressure
IIH	Idiopathic intracranial hypertension
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISI	Insomnia Severity Index
MD	Mean Deviation
Mg	Milligram
MHD	Monthly Headache Days
MHRA	Medicines and Healthcare products Regulatory Agency

NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCT	Optical coherence tomography
OSA	Obstructive Sleep Apnoea
PIS	Participant Information Sheet
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
REC	Research Ethics Committee
REGI	University of Birmingham Research Ethics, Governance and Integrity team
RNA	Ribonucleic Acid
RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SF-36	Short Form 36
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment Scale

DEFINITIONS

Month – in IIH-Advance, defined as 28 days

Trial Office – the trial management staff at Birmingham Clinical Trials Unit responsible for the day-to-day management of the trial

Trial Researcher – the research nurses and doctors responsible for day-to-day delivery of all participant-facing aspects of the trial

Trial Doctor – a subset of Trial Researcher, a medically qualified doctor responsible for clinical oversight of participants during the delivery of the trial

TRIAL SUMMARY

Idiopathic Intracranial Hypertension (IIH) is a condition characterised by elevated intracranial pressure. It occurs primarily in women of childbearing age with obesity. The elevated brain pressure drives papilloedema with ensuing chronic disabling headaches and risk of visual loss (which can be severe and permanent). There is no licenced pharmacological treatment for IIH so management of IIH is challenging.

Previous studies using diet or bariatric surgery to induce weight loss have demonstrated significant improvement in IIH by reducing intracranial pressure and subsequently papilloedema and headaches. However, weight loss attained through dieting is challenging to achieve and maintain. Weight loss achieved by bariatric surgery is invasive and is not appropriate for all. Hence there is a need to identify a safe, acceptable and effective method to lose and maintain weight and consequently induce IIH remission.

The advent of the new class of anti-obesity drugs targeting the Glucagon-like peptide-1 receptor (GLP-1R) is an important opportunity as this class of drugs is thought to be safe and effective. Tirzepatide, a glucose-dependent insulinotropic polypeptide and GLP-1R agonist, is a highly effective drug in this class.

However, there is uncertainty about the use of anti-obesity drugs in the context of IIH. The amount of weight loss needed and the ability of anti-obesity drugs to generate sufficient weight loss to induce remission in IIH is not known. Additionally, the impact of weight regain (that can occur when anti-obesity drugs are stopped) on disease activity is not well described. This trial sets out to answer these questions.

Title

A Phase III multi-stage randomised controlled trial to determine the effects of weight loss, induced by Tirzepatide, in adults with active idiopathic intracranial hypertension: IIH-Advance.

Aim

The aim of the trial is to evaluate the clinical impact of weight change induced by Tirzepatide in IIH.

Primary Objective

To evaluate the effect of weight loss induced by Tirzepatide plus standard of care over 6 months in patients diagnosed with IIH compared to standard of care only through the evaluation of the proportion of patients with resolution of papilloedema, measured by Optical Coherence Topography scan (OCT).

Trial design

A pragmatic phase III single-centre 2-arm parallel group multi-stage randomised controlled trial.

Participant population and sample size

86 adults with active IIH.

Setting

Participants will be recruited through direct patient-initiated contact with the trial researchers. The intervention will be self-administered at participants' homes, and papilloedema measured by OCT at a third-party high street optician, Specsavers.

Eligibility criteria

Inclusion:

- Confirmed diagnosis of IIH as defined by the IIH consensus criteria.
- Age ≥ 18 years.
- No evidence of sight threatening papilloedema requiring urgent surgical intervention.
- Presence of papilloedema in at least one eye measured by OCT Retinal Nerve Fibre Layer.
- Body Mass Index (BMI) greater than or equal to:
    - 30.0 kg/sqm or

- 27.0 kg/sqm with IIH associated with increased weight or
- 27.0 kg/sqm and of South Asian, Chinese, other Asian, Middle Eastern, Black African or African Caribbean ethnicity*.

- At least one self-reported unsuccessful dietary effort to lose body weight.
- Able to provide informed consent.

*Self-reported ethnicity according to the 2021 UK government census.

Exclusion:

- Previous bariatric surgery within the last 3 months or intention to undergo bariatric surgery during the trial.
- Previous surgery for IIH including optic nerve sheath fenestration, CSF shunting procedures, sub-temporal decompression and venous stenting.
- Using glucose-lowering medication.
- Currently taking or has received a GLP-1R agonist for any indication in the last 4 weeks.
- Previous or current pancreatitis.
- Contraindication to Tirzepatide (e.g. previous or current medullary cancer, history of multiple endocrine neoplasia, active gall stones).
- Current eating disorder requiring hospital intervention or treatment.
- Is unable to self-administer (or administer with carer support) the trial medication.
- Females of child-bearing potential only:
  - Pregnant. Note: Spot urine test will be performed before randomisation to rule out pregnancy in females of child-bearing potential
  - Not willing to take highly effective contraceptive measures during the study intervention period AND for 5 weeks following the last trial medication dose
  - Not willing to stop breastfeeding once randomised into the trial

NB: Highly effective contraceptive measures are listed in **section 4, Eligibility**.

Interventions

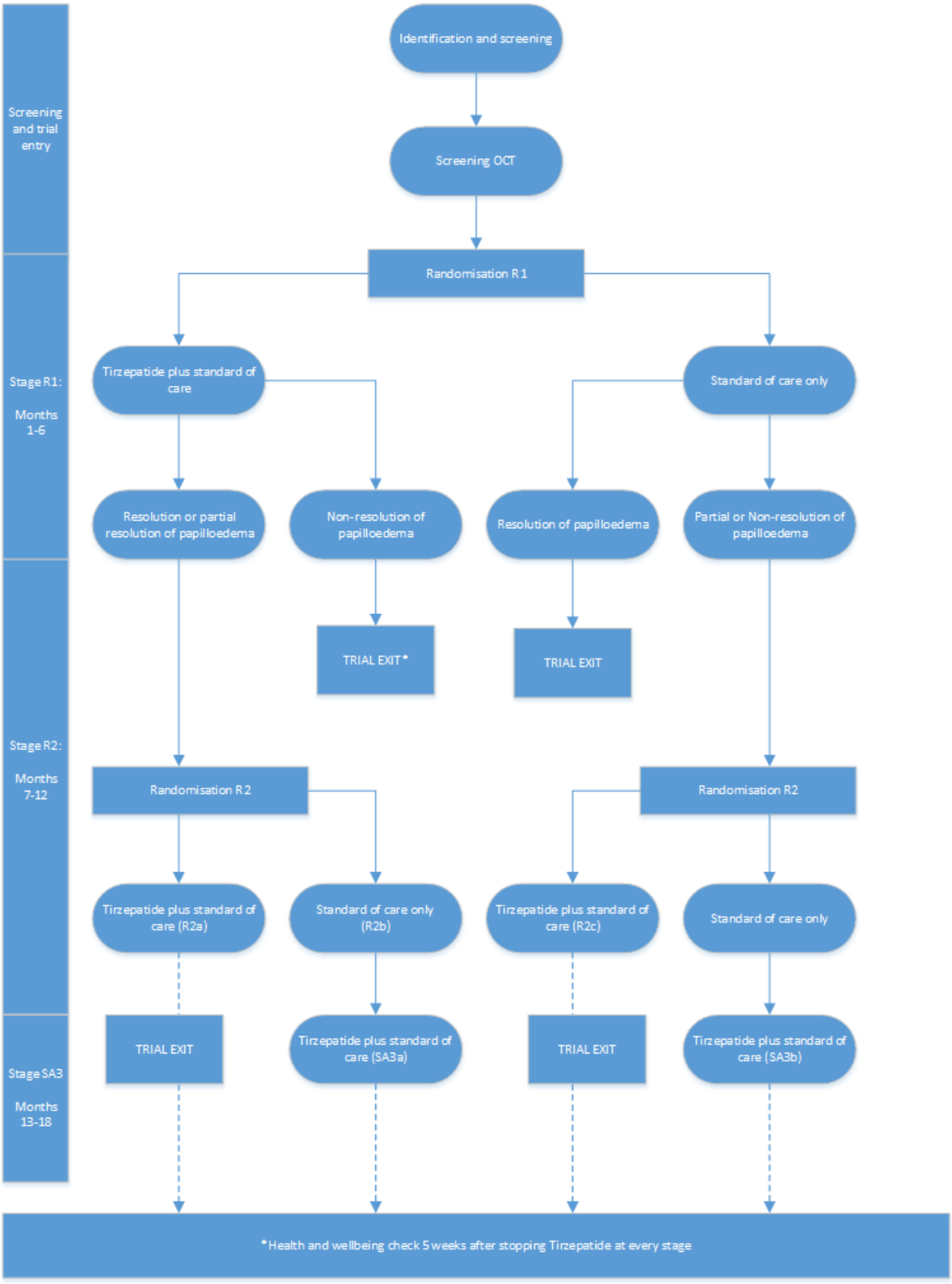
Tirzepatide once weekly via a subcutaneous injector pen plus standard of care vs standard of care alone.

Outcome measures

Primary Outcome:

- Resolution of papilloedema, as measured by OCT at 6 months post-randomisation

FIGURE 1: TRIAL SCHEMA



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1. Background and rationale

1.1. Idiopathic Intracranial Hypertension (IIH)

IIH, also known as benign intracranial hypertension or pseudotumour cerebri, is a condition of unknown aetiology characterised by elevated intracranial pressure (ICP) and papilloedema[1]. IIH is a condition found primarily in obese women (90%), causing disabling daily headaches and visual loss. Although IIH is classified as a rare disease, the incidence of IIH is rising in line with global obesity rates (incidence in women of 3.5 per 100,000 in 2002 rising to 7.7 per 100,000 in 2016). The costs associated with caring for patients with IIH are high and rising (£462 million/year in the National Health Service (NHS) predicted by 2030[2]).

Although IIH is 'idiopathic' and the underlying cause is not fully delineated, there is increasing evidence that it is a disease of metabolic dysfunction[1]. Patients with IIH have central adiposity[3], altered adipocyte metabolism (with a unique transcriptional profile primed for weight gain)[4], insulin resistance[5] and androgen excess[6], which results in a doubled risk of cardiovascular disease beyond that driven by obesity[7].

IIH can cause considerable disability. The elevated ICP in IIH drives papilloedema (swelling of the optic nerve), which can cause blindness. Visual loss occurs in more than 90% of cases[8] and can be severe and permanent in up to 25% of cases[9]. Headache is a prominent, disabling symptom, affecting over 90% of patients[10–12]. These headaches, which significantly impair quality of life[12,13], are primarily associated with raised ICP[14] and exhibit a migraine-like phenotype in more than 90% of cases[14].

1.2. Current therapy for IIH

Consensus treatment guidelines for managing IIH have been developed and standard of care for IIH in the UK largely follows these guidelines[15]. Weight management advice is central, with recommendations for a low-calorie diet and increased exercise. Regular visual monitoring is required. Headache management is key and may be required even after ICP is controlled. Pharmacological treatments are limited. The most used drug, acetazolamide, is used off-label and has demonstrated efficacy[15–18] but is hindered by side effects (48% discontinuation rate)[19]. Other drugs may be used to lower ICP (amiloride, topiramate, furosemide, spironolactone)[20] but they have questionable clinically meaningful efficacy as well as prevalent side effects[21]. Surgical interventions aimed at reducing ICP are typically a last resort, primarily employed in emergency situations to preserve vision. These procedures are associated with a high failure rate and frequent complications[22].

The lack of effective therapies in IIH has been emphasised by patient groups. A priority-setting exercise conducted with IIH patients (utilising the James Lind methodology) identified that research into understanding weight loss in IIH was a top priority[23].

1.3. Weight loss

A significant association exists between IIH and obesity[26]. A 5% weight gain has been linked to the development of IIH and to the recurrence of the condition[24]. Weight loss has been shown to be the only condition modifying treatment[25,26]. However, the degree of weight loss needed to achieve remission is unclear. Diet-induced weight loss of 15 % has been shown to significantly reduce ICP and is associated with remission[26]. However, the probability of attaining a normal body weight for those with an initial body mass index (BMI) >35 Kg/m^2 is 1 in 70[27], and most patients regain weight over a 2- to 5-year period[27]. Furthermore, one- to two-thirds of individuals who diet often regain more weight than they initially lose[28]. Weight regain is increasingly recognised as a physiological homeostatic response, with evidence that following dieting, there is an increase in hunger, a reduction in satiety-related hormonal signals, and a decrease in energy expenditure[29–32]. Obesity is now recognised by the World Health Organization (WHO) as a chronic relapsing disease[33].

Long term weight loss (25-30%) can be achieved with bariatric surgery[34]. The role of bariatric surgery in IIH has been evaluated in a randomised controlled trial where it was found to significantly reduce both weight

and ICP over 12- and 24-month periods[25]. A correlation was also observed between the amount of weight loss and the reduction in ICP. Weight loss of 24% was associated with IIH remission, defined as an ICP of ≤25 cmCSF[35]. It was noted that those with a higher starting weight needed to lose more weight to achieve remission. Sustained weight loss of this magnitude is unlikely to be achieved with diet alone.

1.4. Health care cost

Given the substantial healthcare costs associated with IIH, the identification of cost-effective treatment strategies is highly desirable[2,36]. Bariatric surgery-induced weight loss in patients with IIH has been demonstrated to be a cost-effective intervention but involves risk and may not be suitable for all[37,38].

1.5. Anti-obesity drugs

1.5.1. Glucagon-like peptide-1 receptor agonists

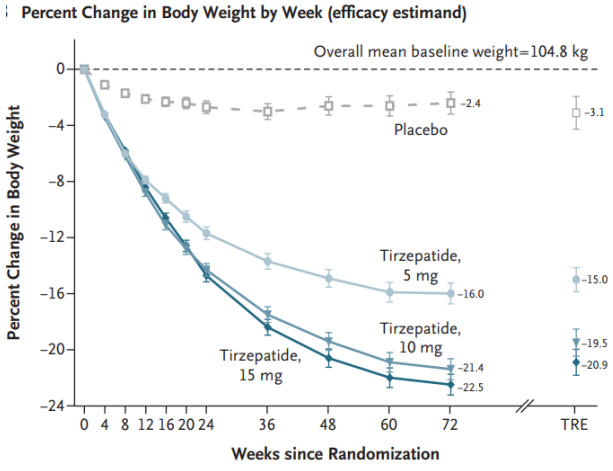
Pharmacological approaches to managing obesity have significantly advanced with the development of therapies targeting the glucagon-like peptide-1 (GLP-1) receptor. GLP-1 is an incretin hormone involved in regulating insulin release and glucose homeostasis[39]. Drugs targeting the GLP-1 receptor (GLP-1R) were initially developed for diabetes (for example, Exenatide, Lixisenatide, Albiglutide, Dulaglutide, Liraglutide and Semaglutide)[40]. However, the actions of GLP-1R agonists extend beyond glucose regulation, as they have been shown to suppress appetite, leading to their use as anti-obesity agents.

1.5.2. Tirzepatide and weight loss

As of 2025, there are three GLP-1R agonists approved for treatment of obesity (Liraglutide, Semaglutide and Tirzepatide). Superior to Semaglutide in head-to head randomised controlled trials[41], Tirzepatide is the most effective GLP-1R agonist, leading to 14% weight loss by 6 months and 19-20% weight loss by 12 months[42]. Weight loss increases with duration and dosing, and by 18 months, a decrease of 15% in body weight was noted on a 5mg dose, -19.5% on a 10mg dose and -20.9% on a 15mg dose. Weight loss plateaus after 60 weeks.

Tirzepatide was licenced and approved for use by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2023 for weight loss and weight management in adults aged 18 and over[43]. It is in routine use in the NHS and will be widely used in primary care in the NHS from 2025[44]. It is prescribed as a weekly injection under the skin of a patient's stomach area, thigh or upper arm. The starting dose of Tirzepatide is 2.5mg once a week for four weeks, increasing to 5mg once a week. The dose may then be increased in at least 4-week intervals up to the maximum dose of 15mg once weekly. Tirzepatide has a similar side effect profile to other incretin (GLP-1R) therapies with mild to moderate transient gastrointestinal events noted, particularly during dose escalation[45]. Tirzepatide is used routinely around the world with a wealth of available safety data from both clinical trials and real-world experience.

Figure 2: Percent change in body weight according to weeks since randomisation[42]



1.5.3. Weight regain

Obesity is a chronic relapsing disease and discontinuing anti-obesity treatment leads to weight regain. Weight regain is observed following the cessation of all anti-obesity medications[46–49]. Following discontinuation of Tirzepatide, patients have been noted to regain 14% of body weight over a year[50]. It is not known if the benefits of weight reduction are maintained. It is not known if weight reduction, even if temporary, can lead to a lasting remission of IIH. It is not clear if weight regain will have a deleterious effect on IIH or if the condition will remain in remission. Hence, this trial will also evaluate withdrawal of treatment in relation to the degree of lasting benefit and the extent of recurrence rate of papilloedema.

1.5.4. GLP-1 in IIH

Data from an open-label study has shown the ability of GLP-1R agonists to drive weight loss, improve headache outcomes and reduce acetazolamide dose in patients with IIH[51].

1.6. Trial rationale

The optimal method to achieve and maintain weight loss and disease remission in IIH is not known. This trial will use the anti-obesity drug Tirzepatide to induce weight loss and thereby potentially improve IIH symptoms. Furthermore, the trial will evaluate the potential impact of weight maintenance and weight regain on IIH.

1.6.1. Justification for participant population

We will recruit adult patients with active IIH, meaning they will have papilloedema, or optic nerve swelling, a marker of raised ICP which can be measured non-invasively. Active papilloedema is necessary to enable measurement of this outcome as a measure of disease activity using optical coherence tomography, (OCT).

Participants will be required to have raised BMI and self-reported as having failed previous dietary weight loss attempts to be eligible for the trial in keeping with NHS recommendations for use of anti-obesity drugs (NICE guideline NG246)[52].

Participants will be identified through direct contact from interested patients rather than recruitment through NHS clinics, which will help ensure our results will be representative of the broader United Kingdom (UK) population with IIH.

1.6.2. Justification for design

IIH-Advance will be split into 3 stages of randomisation and treatment to enable assessment of different objectives (see section 2). These will each last 6 months for a total maximum trial duration of 18 months per participant. It is expected that enough weight loss will be achieved in 6 months of treatment with Tirzepatide for papilloedema to resolve; changes in papilloedema, headache and quality of life measures have been observed in other IIH trials over 6 months[17]. The trial design is described in full in section 3.

1.6.3. Justification for choice of intervention

Weight loss is the only proven condition modifying treatment[25,26]. We are choosing to induce weight loss through treatment by Tirzepatide, chosen over other GLP-1R agonists as it has a suggested greater efficacy compared to Semaglutide[41]. In the original paper regarding the efficacy of Tirzepatide, the mean reduction in body weight of patients who received Tirzepatide was 14% at six months[42]. It is anticipated that the patients who receive active treatment as part of IIH-Advance will experience a similar weight loss. Given the patient population recruited to IIH-Advance is similar to the population who were recruited to IIH:WT[25](which itself is more similar to the Wilding *et al.* population[59] where a larger reduction in body weight was seen), we assume an anticipated 14% body weight loss in the active arm of IIH-Advance.

1.6.4. Justification of choice of primary outcome

Papilloedema is a sign of raised ICP[53], and changes in papilloedema are used in IIH trials to assess improvement in disease activity[14,17,19]. OCT imaging provides a reliable objective measurement[17,19].

Papilloedema is a clinically important measure used to monitor IIH improvement and deterioration. It is widely accessible, easily measurable and therefore internationally relevant. As an objective measure, papilloedema is more reliable than headache and quality of life measures which may be prone to a placebo response.

OCT evaluates the optic nerve, including retinal nerve fibre layer (RNFL) thickness and optic nerve head volume, which reflect papilloedema severity. Measures of the ganglion cell layer thickness indicate axonal loss. Optic nerve head loss correlates with visual field sensitivity loss[54], and RNFL changes correlate with visual field perimetric mean deviation[55]. OCT measures of the macular volume have been shown to predict axonal loss of the optic nerve[56]. Ganglion cell volume has been shown to significantly correlate with the Humphrey visual field mean deviation[57] which indicates the ganglion cell layer can be measured to reflect visual function. In other neurological diseases OCT has also been found to measure neuronal loss and correlate with visual loss[58].

2. Aims and Objectives

2.1. Main trial objectives

2.1.1. Primary Objective

To evaluate the effect of weight loss induced by Tirzepatide plus standard of care over 6 months in patients diagnosed with IIH compared to standard of care only through the evaluation of the proportion of participants with resolution of papilloedema, measured by OCT (Randomisation phase R1; see **section 3.1.1** below).

2.1.2. Secondary Objectives

To determine the effect of weight loss induced by Tirzepatide plus standard of care over 6 months in patients diagnosed with IIH compared to standard of care on change in:

- Clinical outcomes: Papilloedema, headache, weight and BMI
- Patient-centred outcomes: Health- and vision- related quality of life, binge eating, alcohol use, anxiety and depression, tolerability of weight loss in IIH driven by Tirzepatide determined by all cause discontinuation
- Service use outcomes: Service use, absenteeism and presenteeism, medication use (use and dose of acetazolamide or other ICP lowering drugs)

2.1.3. Exploratory objectives

At 12 and 18 months, for primary and secondary outcomes and assessed in a subset of participants:

- In those participants whose IIH responds to weight loss driven by Tirzepatide, to determine the recurrence effect of stopping Tirzepatide on IIH (Randomisation phase R2b; see **section 3.1.2**)
- In those participants whose IIH responds to weight loss driven by Tirzepatide, to evaluate the maintenance effect of Tirzepatide on IIH (Randomisation phase R2a; see **section 3.1.2**)
- To determine the effect of a delayed start of weight loss, driven by Tirzepatide, on IIH (Randomisation phase R2c, Single arm phase SA3; see **section 3.1.3**)
- To determine the effect on weight change from restarting Tirzepatide (Single arm phase SA3a; see **section 3.1.3**)

An exploratory translational sub-study will determine the effect of weight loss, driven by Tirzepatide, on biomarkers of inflammation, hormonal changes and metabolism.

An exploratory sleep sub-study will evaluate the effect of weight loss, driven by Tirzepatide, on sleep, the circadian cycle and daytime activity.

An optional qualitative sub-study will explore the experience of weight management strategies and services for people living with IIH.

3. Trial design and setting

3.1. Trial design

IIH-Advance is a pragmatic, phase III, single-centre, unblinded, 2-arm, parallel group, multi-stage randomised controlled trial of patients with active IIH. The trial will compare participants expected to achieve significant weight loss (driven by Tirzepatide, an anti-obesity drug) with participants receiving standard of care. IIH-Advance is not a Clinical Trial of an Investigational Medicinal Product. Tirzepatide is currently used in the NHS as an anti-obesity medication; IIH-Advance is examining the effect of weight loss on IIH linked to obesity, rather than the efficacy or safety of Tirzepatide.

There will be 3 stages to the trial.

3.1.1. Stage RI

In the first stage, R1, 86 people with IIH will be randomised in a 1:1 ratio to either Tirzepatide with standard of care or standard of care alone for 6 months. The primary outcome is resolution of papilloedema, with those participants in whom there is resolution of papilloedema classed as responders and those with partial resolution of papilloedema classified as partial responders for the purposes of re-randomisation.

3.1.1.1. Objective of stage R1

This stage will meet the primary objective of evaluating the effectiveness of weight loss driven by Tirzepatide plus standard of care compared to standard of care in patients with active IIH.

3.1.2. Stage R2

After 6 months, stage R1 will end and participants will have a 6 month follow up appointment. Their papilloedema will be reviewed and they will be re-randomised and enter stage R2 if they could still potentially benefit from Tirzepatide:

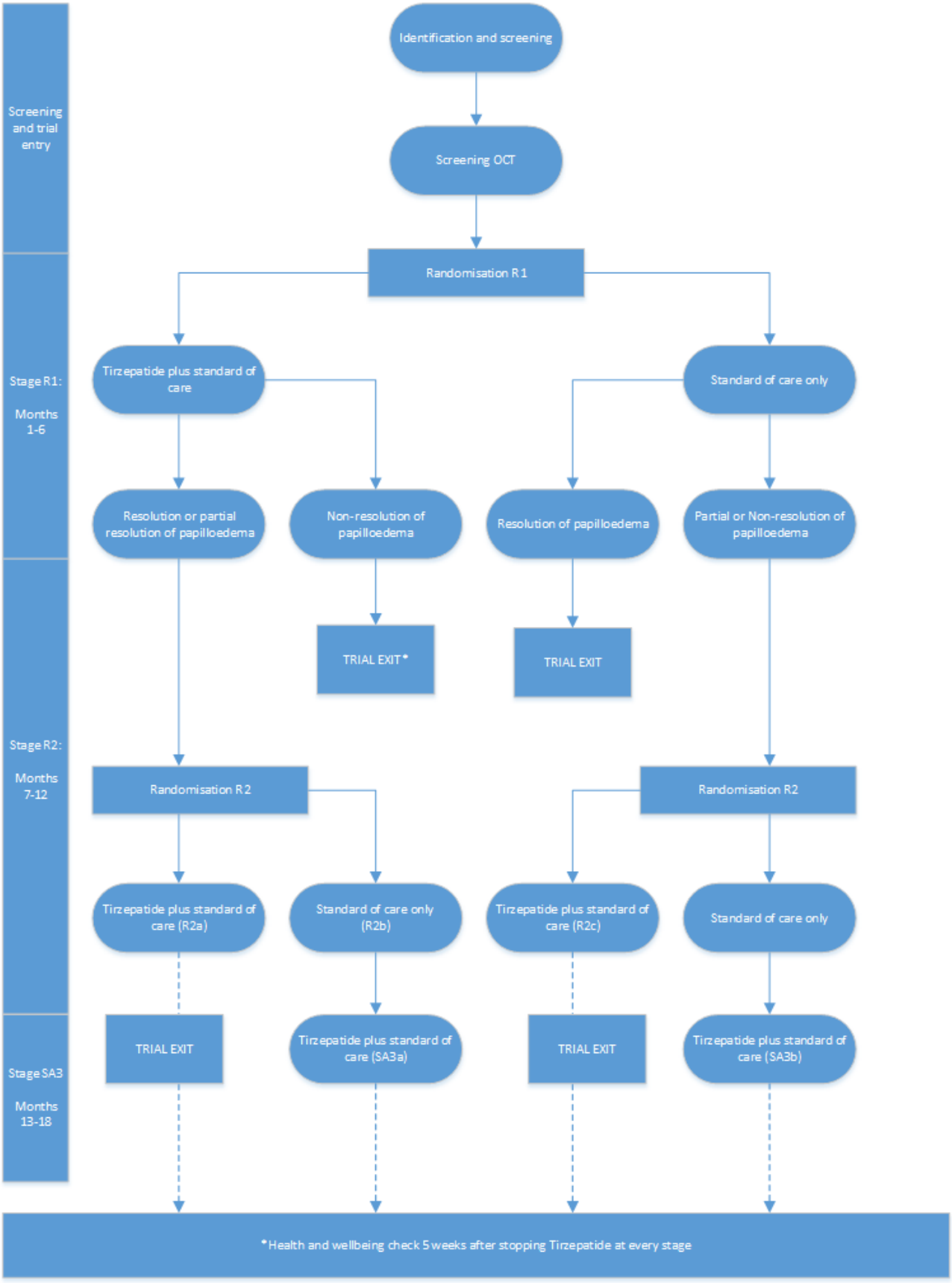
- Participants who have resolution or partial resolution of papilloedema as measured by OCT after 6 months of treatment with Tirzepatide plus standard of care will be randomised again to either Tirzepatide plus standard of care vs standard of care. This will allow evaluation of the maintenance of effect compared to those who discontinue treatment at 12 months. Discontinuing will enable evaluation of the impact of drug cessation on weight change and its impact on IIH at 12 months, compared to those continuing Tirzepatide plus standard of care.
- Participants who have no resolution of papilloedema as measured by OCT after 6 months of treatment with standard of care will be randomised again to either Tirzepatide plus standard of care or standard of care for 6 months. This will allow evaluation of the effect of delayed initiation of weight loss induced by Tirzepatide for 6 months on IIH, again at 12 months, compared to standard of care.

Participants will not be randomised again if they are unlikely to benefit from Tirzepatide:

- Participants who have no resolution of papilloedema after 6 months of Tirzepatide plus standard of care will not be eligible to be re-randomised as their IIH symptoms are unlikely to benefit from a second 6-month course of treatment.
- Participants who have resolution of papilloedema after 6 months of standard of care will not be eligible to be re-randomised as their IIH symptoms would not benefit from weight loss and starting Tirzepatide.

Participants who receive Tirzepatide in stage R2 will leave the trial after this 6 month treatment period.

Figure 3: Trial Schema



3.1.2.1. Objective of stage R2

The purpose of stage R2 is threefold, meeting the secondary objectives of evaluating:

- The maintenance of effect (by continuing Tirzepatide) (R2a),
- The lasting benefit and extent of recurrence rate of papilloedema upon treatment cessation (R2b)
- The effect of delayed start to weight loss (R2c)

3.1.3. Stage SA3

After 12 months, stage R2 will end and participants will have a 12 month follow up appointment. Their papilloedema will be reviewed. Participants who received standard of care during stage R2 will be offered a 6 month open-label treatment phase with Tirzepatide in the third stage, SA3:

- Participants who received standard of care only during Stage R2 will be offered Tirzepatide plus standard of care for the final open label 6 month period of the trial (SA3) to ensure that all participants can potentially benefit from the expected weight loss benefits of the treatment.
- If participants receiving standard of care during stage R2 only have resolution of papilloedema at 12 months, they will be offered the final 6 month open label period, which will contribute towards investigating the maintenance of weight and disease remission.

3.1.3.1. Objective of stage SA3

This stage will also enable the evaluation of the exploratory objectives:

- Evaluating re-occurrence of response to weight loss at 18 months (SA3a).
- Evaluating occurrence of response to weight loss at 18 months for those not treated with Tirzepatide previously (SA3b).

3.1.4. Trial exit at all stages

In all stages, participants who receive Tirzepatide will have a final well-being follow up appointment with the trial researcher 5 weeks after the last dose of the drug, which completes their involvement in the trial.

3.2. Trial setting

Participants from across the UK will be recruited through direct patient-initiated contact with the Trial Researchers (**section 5**). The intervention will be delivered to participants' homes and papilloedema measured by OCT at a third-party high street optician, Specsavers UK. Outcome measures will be collected directly via participant reported outcome measures administered online (secure link sent via email or SMS), and by video calls between the participant and Trial Researchers.

3.3. Sub-studies

- A mechanistic sub-study will collect biofluids (saliva, blood, 24-hour urine and stool) for evaluation of weight-loss related changes in liver function, diabetic status, hormones, markers of inflammation, pain chemicals involved in headache, and micoRNA. Stool samples will be collected to evaluate the gut microbiome. Samples will be collected at baseline, 3 and 6 months. Please see **section 17** for full details.
- A qualitative sub-study will conduct two focus group discussions with main trial participants to explore acceptability of weight management strategies and the experience of people living with IIH and their weight management discussions with healthcare professionals. Please see **section 18** for full details.
- A sleep sub-study will use a wearable device to explore IIH, weight loss, and the circadian cycle and daytime activity.

3.4. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: higher than the risk of standard medical care.

Tirzepatide is being used in its licenced indication and IIH-Advance's monthly follow up schedule will monitor participants more closely than the NICE guidance, which will also come into effect for a UK-wide NHS primary care roll out of self-administered Tirzepatide treatment in 2025, recommends ("monthly initially, then every 3 months")[44]. However, it is recognised that monitoring of metabolic parameters such as HbA1c (if diabetic) or lipids will not be carried out by the IIH-Advance team and clinical oversight (provided by the trial doctors supervised by a consultant neurologist and a consultant endocrinologist) will be at a further remove than it might otherwise be in the NHS. For this reason we class the trial as slightly higher than the risk of standard of care.

4. Eligibility

4.1. Inclusion criteria

- Confirmed diagnosis of IIH as defined by the IIH consensus criteria[15].
- Age ≥ 18 years.
- No evidence of sight threatening papilloedema requiring urgent surgical intervention.
- Presence of papilloedema in at least one eye measured by OCT RNFL.
- BMI greater than or equal to:
    - 30.0 kg/sqm or
    - 27.0 kg/sqm with IIH associated with increased weight or
    - 27.0 kg/sqm and of South Asian, Chinese, other Asian, Middle Eastern, Black African or African Caribbean ethnicity*.
- At least one self-reported unsuccessful dietary effort to lose body weight
- Able to provide written informed consent.

*Self-reported ethnicity according to the 2021 UK government census.

4.2. Exclusion criteria

- Previous bariatric surgery within the last 3 months or intention to undergo bariatric surgery during the trial.
- Previous surgery for IIH including optic nerve sheath fenestration, CSF shunting procedures, sub-temporal decompression and venous stenting.
- Using glucose-lowering medication.
- Currently taking or has received a GLP-1R agonist for any indication in the last 4 weeks.
- Previous or current pancreatitis.
- Contraindication to Tirzepatide (e.g. previous or current medullary cancer, history of multiple endocrine neoplasia, active gall stones).
- Current eating disorder requiring hospital intervention or treatment.
- Is unable to self-administer (or administer with carer support) the trial medication.
- Females of child-bearing potential only:

- Pregnant. Note: Spot urine test will be performed before randomisation to rule out pregnancy in females of child-bearing potential
- Not willing to take highly effective contraceptive measures during the study intervention period AND for 5 weeks following the last trial medication dose
- Not willing to stop breastfeeding once randomised into the trial

4.3. Contraceptive measures

Highly effective contraceptive measures include:

- Combined hormonal contraception associated with inhibition of ovulation:
  - Oral, intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral, injectable or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

If a hormonal method of birth control is selected then patients must have been using this method at least 28 days prior to drug administration, or be abstinent, or utilise a barrier method of contraception until the selected hormonal method has been in place for the 28 day period.

If using an oral contraceptive it is advised to switch to a non-oral contraceptive method or add a barrier method of contraception upon initiating Tirzepatide (for 4 weeks), or after each dose escalation (for 4 weeks)[45] (see section 7.2.4).

Female participants of childbearing potential will be screened with a urine pregnancy test, which must be negative no more than 7 days before randomisation.

The selected method of birth control should continue in use for at least 5 weeks post-dose of study medication.

4.4. Co-enrolment

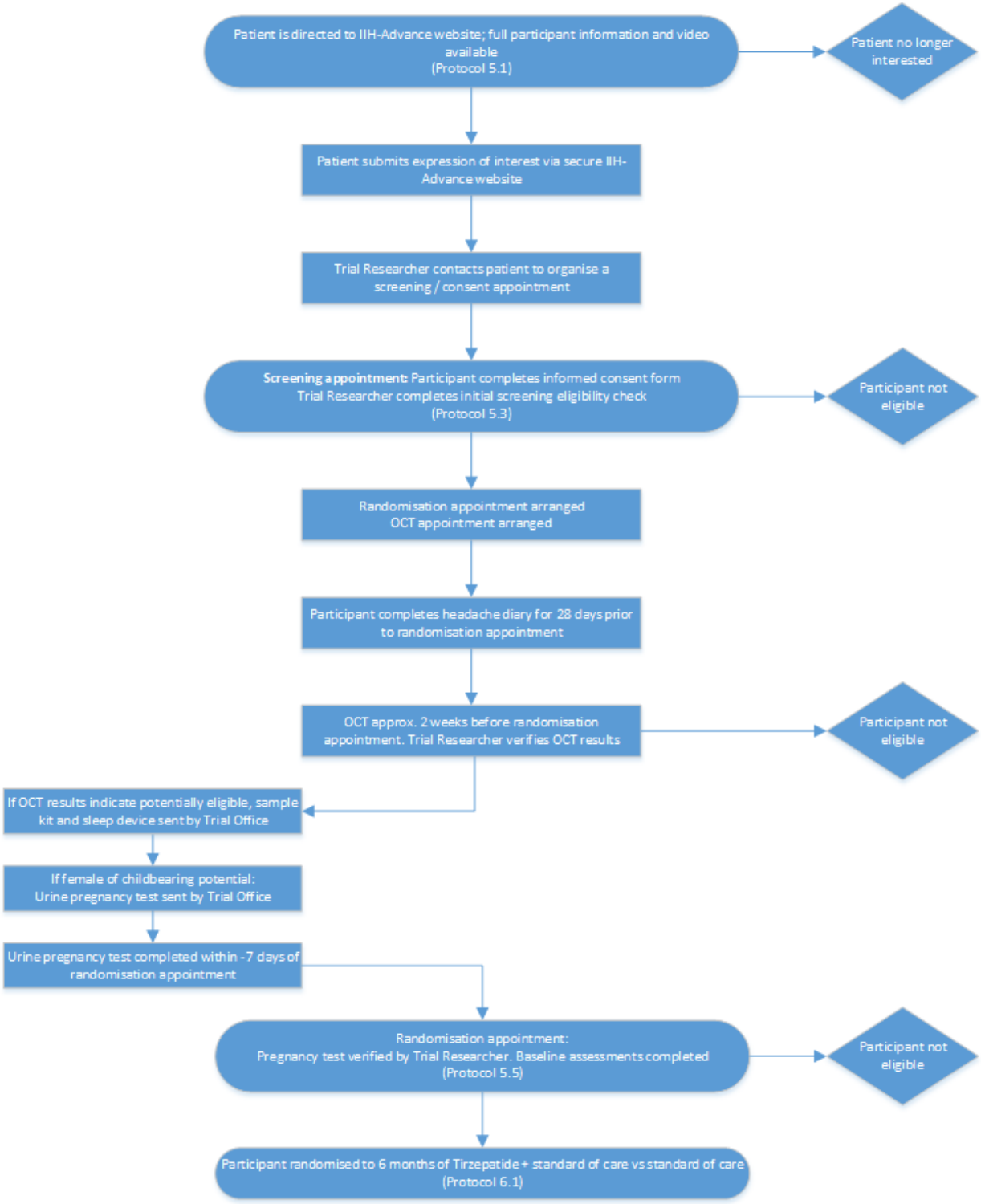
Participants in IIH-Advance can participate in any observational study. Co-enrolment in other trials can be considered after discussion with the Chief Investigator (CI) or in their absence a medically qualified member of the Trial Management Group (TMG).

5. Identification, Screening, and Consent

5.1. Identification

Potential participants will self-identify by first contacting the IIH-Advance Trial Office via the IIH-Advance website. Health care professionals can also contact the IIH-Advance Trial Office with potential participant details at the request of the participant. Potential participants will be made aware of the trial via advertisements on social media. Social media platforms that may be used will include Facebook, Instagram, Threads, Twitter, Bluesky, Youtube, HealthUnlocked, LinkedIn, Reddit and Tiktok. The charity IIH UK will be contacted with a request to feature the trial on the charity website; they have indicated their support for the trial. Local radio and other media will also be considered. Potential participants will initially be directed to a public facing trial website as described below.

Figure 4: Trial entry process



5.2. Patient information

Materials for IIH-Advance are largely digital, and the use of paper will be kept to a minimum. The IIH-Advance trial is dependent on high-quality information being presented to potential participants in a clear and efficient way. We will use a Research Ethics Committee (REC) approved multimedia website with images and animations to provide an overview of the trial, supported by trial materials presented in an abbreviated format. The IIH-Advance animation video will be designed to provide a clear and efficient

method of explaining the trial to potential participants and will be presented prior to consent, along with the accompanying Participant Information Sheet (PIS).

The trial website will also host videos instructing participants on how to take the sub-study samples, and how to administer Tirzepatide.

5.2.1. Potential participant expressions of interest

The website will include the function for a potential participant to express their interest with the Trial Office via a secure University of Birmingham hosted webform. The webform will perform a basic screening function (e.g. correct age range) and then all appropriate expressions of interest received will be reviewed by a Trial Researcher, who will respond to the potential participant. This response may be an explanation of why the potential participant is unsuitable for IIH-Advance, a request for clarification, or an invite to an initial online appointment with the Trial Researcher to discuss the trial. The webform will include an explanation of what personal data is being collected at this stage and how it will be used and managed.

5.3. Consent

It is the responsibility of the CI to obtain informed consent for each participant prior to performing any trial related procedures. This task can be delegated by the CI to other suitable trained Trial Researchers, if this responsibility has been documented in the trial delegation log. Obtaining consent will be undertaken remotely and will use electronic online consent forms.

Potential participants who have expressed their interest in the trial and may be eligible will be invited to attend an online appointment with a Trial Researcher via the Trial Researcher's secure NHS video call facility. The Trial Researcher will make sure the patient has received the patient information (PIS and video) before discussing the trial.

If the patient is interested in entering the trial, informed consent will be sought. The CI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the potential participant. They will also explain that participation is voluntary and that they are free to decide to take part and may withdraw from the trial at any time. The potential participant will be given the opportunity to ask questions, and given sufficient time and opportunity to read the PIS and to discuss their participation with others outside of the site research team. This may include returning to a later appointment to continue the consent process. The patient will be reminded that even if they undergo screening there is no obligation to continue.

If the potential participant then wishes to participate in the trial, they will be asked to electronically sign and date the latest version of the electronic Informed Consent Form (ICF) using the UoB developed and hosted IIH-Advance electronic data capture system (EDC). The CI or delegate will then sign and date the electronic ICF. A copy of the completed ICF will then be emailed to the participant. Participants will consent to their email address being stored for this purpose. At this point, the participant will be registered into screening and will be assigned a trial number. If the participant does not proceed beyond screening, then their email address will be removed from use, but may still exist within the backups of the EDC.

Should participants wish to do so, they can receive a printed copy of their ICF instead. Participants will consent explicitly to their identifiable details (name and address) being stored and transferred to the trial pharmacy if required for distribution of intervention as well as Specsavers UK as required for facilitation, completion and report of OCT assessments.

To mirror what would be expected in an NHS patient's notes, details of the consent discussions will be recorded in the participant's trial EDC notes. This will include date of discussion, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received.

5.4. Screening arrangements

Once the participant has consented to enter the trial, they will be asked for their height and weight and will be asked to provide a letter from a medically qualified healthcare professional confirming their diagnosis of IIH. The participant will be advised these letters may be accessed from the NHS app. If the participant does not have access to the NHS app, a copy of their last clinic letter will be accepted. This letter must be dated within the last 12 months. It will be recorded on the EDC that a letter has been seen by the Trial Researcher doing the screening the provenance of the letter, and that the letter confirms the diagnosis of IIH.

If the details supplied thus far meet the eligibility criteria (age, BMI and IIH diagnosis), then an OCT scan to confirm the eligibility criteria of active papilloedema will be arranged by the Trial Office with their preferred Specsavers. The ICF will have a statement for the participant to acknowledge that their personal data will be shared with Specsavers as required to arrange OCT and report on scans.

The participant will be asked to complete a 28-day headache diary on a recommended third-party mobile app of their choice, such as Headache Pro, Migraine Buddy or Migraine Insight. Commonly used in routine practice in NHS headache care, this will be used as an aide-memoire to complete headache outcomes with the Trial Researcher at later visits. Participants will be asked to detail the monthly headache days, monthly migraine days, monthly analgesic days and monthly headache severity at each follow up assessment.

Anonymised details of all patients (including OCT measurements if the potential participant progresses to this stage) who approach the Trial Office to discuss participant in the trial will be recorded on the IIH-Advance Participant Screening Log in the Trial Master File (TMF).

5.5. Screening results

Once the OCT scan has been completed, the OCT measurements will be sent from Specsavers UK to the Trial Office. Only trial number and OCT measurements will be transferred from Specsavers UK to the Trial Office. This report will then be stored as source data and reviewed by a Trial Doctor as per the inclusion criteria.

If the OCT results meet the inclusion criteria, the participant will be invited to attend a baseline appointment by video call. The potential participant will be sent a trial sample kit and a sleep actigraphy device. If female of childbearing potential, unless they have documented hysterectomy, bilateral salpingectomy or oophorectomy, or have a confirmed postmenopausal state, the potential participant will be sent a urine pregnancy test by the Trial Office. This will be performed by the participant at home. This must be negative within 7 days before eligibility is confirmed and randomisation occurs.

The OCT will not be reviewed clinically by Specsavers. If the screening OCT shows any evidence of sight-threatening papilloedema requiring urgent surgical intervention when reviewed by a Trial Doctor then the participant will be informed and onwards care pathways initiated; they will not enter IIH-Advance.

5.6. Main Trial Entry

At the baseline appointment, if the potential participant has been sent a urine pregnancy test as described in **section 5.5** above this must be negative and shown to the researcher at the beginning of this appointment with a confirmation of the date it was performed. After confirming that the participant is willing to continue, the full baseline tests as per the assessment schedule (**section 10**) will be completed and they will be randomised into the trial (**section 6**).

At each visit, the participant's willingness to continue in the trial will be ascertained and documented on the appropriate case report form (CRF). Throughout the trial, the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue they

will be re-consented, which will be documented as per an original consent. The participant's right to withdraw from the trial will remain.

5.7. Optional consent points

There are an exploratory sample sub-study and a sleep sub-study in IIH-Advance which will not be optional consent points. However, the below three points will be optional consent points:

5.7.1. Long term follow up

We will also add an additional statement to the ICF for the participant to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g. Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other central UK NHS bodies. The participant will acknowledge that they understand that the Trial Office might send their name, address, date of birth and NHS number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

5.7.2. Qualitative sub-study

An additional statement on the ICF will ask participants if they consent to be approached about the possibility of participating in the qualitative sub-study.

The qualitative researcher will have limited access to the database permitting only access to the details needed to organise sub-study visits for those participants who consent to this contact. Potential participants will be contacted directly by the qualitative researcher (and offered a PIS for the sub-study) to talk through what participation in a sub-study interview would involve. Consent into the sub-study will be taken by the qualitative researcher, prior to the interview.

The qualitative sub-study will have a separate consent process, detailed in **section 18**.

5.7.3. Long term qualitative follow up

An additional statement on the ICF will ask participants if they consent to be contacted up to 10 years after the end of their trial participation about the possibility of participating in a long term follow up qualitative sub-study to explore post-trial changes in their experience of weight management strategies and related healthcare professionals in the NHS. This sub-study will be carried out under a separate protocol/ethical approval.

6. Randomisation

Once informed consent is obtained and eligibility confirmed, the participant and researcher should complete all baseline assessments (**section 9**) before proceeding to randomisation.

6.1. Randomisation

Randomisation will be provided by BCTU using a secure online system (available at *<insert web address>*), thereby ensuring allocation concealment. Unique log-in usernames will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the IIH-Advance Delegation Log. These log-in details must not be shared with other staff and in no circumstances should staff access the system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. In the

event of the online system not being available, the Trial Office should be contacted Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and UoB closed days.

Participants will be randomised one or two times during the study, depending on their response to the allocated arm.

6.2. Initial randomisation (R1)

All participants will be randomised 1:1 to receive either Tirzepatide plus standard of care or standard of care. This stage will last 6 months as per **section 3.1.1**.

6.3. Second randomisation (R2)

A second stage of randomisation will commence for participants who were:

1. Allocated Tirzepatide in R1 and showed a response or partial response
2. Allocated Standard care in R1 and showed partial or no response

These participants will be randomised 1:1 to receive either Tirzepatide plus standard of care or standard care. This stage will last 6 months as per **section 3.1.2**.

6.4. Final treatment allocation (SA3)

After this second 6 month treatment period, those participants allocated standard of care at R2 will enter the open label stage and receive Tirzepatide for a final 6 months as per **section 3.1.3**.

6.5. Randomisation process

All questions and data items on the Randomisation Form must be answered prior to a participant being randomised into the trial. Following randomisation, a confirmatory email will be sent to the randomising Trial Researcher, the IIH-Advance trial mailbox, and the nominated participating Specsavers UK store. The email will include the date of randomisation, trial number, and name of nominated participating Specsavers UK store. Specsavers will be asked to arrange the next OCT scan appointment in 6 months' time.

6.5.1. Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either Tirzepatide or standard of care. The randomisation process for initial randomisation R1 will use a minimisation algorithm to ensure balance in the treatment allocation for the following variables:

- Baseline acetazolamide status (currently taking, yes/no)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.6. Blinding

IIH-Advance is an unblinded trial. It is not possible to perform a blinded controlled trial of Tirzepatide due to the extent of weight loss expected[42] even if a placebo injection was introduced as a control arm. The primary outcome will be based on the objective measurement of RNFL by OCT as output by the OCT machine operated by Specsavers' staff blinded to a participant's allocation.

6.7. Informing the participant's GP and other parties

If the participant consents, the participant's GP will be notified that they are in the IIH-Advance trial at each stage they are allocated to Tirzepatide plus standard of care, using the IIH-Advance GP Letter. This will be sent to the participant's GP directly from the IIH-Advance Trial Office after each appropriate randomisation phase.

7. Trial Intervention

7.1. Trial intervention and dosing schedule

The trial intervention in IIH-Advance is Tirzepatide, self-administered weekly via a subcutaneous injector pen, plus standard of care (see Section 1.2). The dose will escalate over the 6-month intervention period in accordance with the dosing schedule detailed in the Summary of Product Characteristics for Tirzepatide and summarised below, although titration can be individualised according to patient tolerability. This titration should be followed each time the intervention is being introduced. At each timepoint that Tirzepatide is to be prescribed, the trial doctor will check the current dose is tolerated, and if so prescribe the next planned dose.

Please note that, since Tirzepatide is supplied in weekly injector pens, a month in IIH-Advance will be defined as 28 days.

- Month 1 dose 2.5 mg
- Month 2 dose 5 mg
- Month 3 dose 7.5 mg
- Month 4 dose 10 mg
- Month 5 dose 12.5 mg
- Month 6 dose 15 mg

If allocated to receive Tirzepatide, participants will be trained how to administer the drug. As per routine practice within the NHS and the wider NHS primary care use of Tirzepatide, a video instructing how to self-administer the injection will be shown to participants and then discussed with the Trial Researcher before any self-administration; this video will be available at all times through the IIH-Advance website.

7.2. Drug interaction or contraindications

7.2.1. Permitted medications/interventions

Other than the randomised allocation (and therefore with reference to **section 7.2.2** below), treatment as usual as per local practice (including weight management or weight loss regimes) will continue.

7.2.2. Prohibited medications/interventions

Any medication which is contraindicated in people taking Tirzepatide according to the British National Formulary will be prohibited, if appropriate according to the participant's allocation. Glucose-lowering medications are prohibited as per the eligibility criteria.

7.2.3. Pregnancy

Tirzepatide is contraindicated in pregnancy due to the lack of data in humans to determine the risk of birth effects, miscarriage, or other adverse outcomes. Tirzepatide is not recommended in women wanting to become pregnant and should be discontinued for one month before a planned pregnancy. If a participant becomes pregnant whilst allocated to Tirzepatide, they will be instructed to immediately stop taking it.

7.2.4. Contraceptives

Administration of a combination oral contraceptive in the presence of a single dose of Tirzepatide (5mg) led to a small reduction in combination oral contraceptive efficacy in normal weight women, but this was not considered to be clinically relevant and the Summary of Product Characteristics does not suggest adjustment of the dose of combination oral contraceptive is needed. In women with a high BMI, there is no data and reduced efficacy of oral contraceptives cannot be excluded. If using an oral contraceptive it is advised to switch to a non-oral contraceptive method or add a barrier method of contraception upon initiating Tirzepatide (for 4 weeks), or after each dose escalation (for 4 weeks)[45] .

7.3. Intervention modification or discontinuation

It is expected that there may be cases where Tirzepatide is less well tolerated in terms of side effects. In this case, on discussion between participant and Trial Doctor, a dose may be reduced or held at the previous month's dose as required. The reason should be noted on the EDC Medication Form.

7.4. Intervention supply and storage

Tirzepatide will be prescribed by a Trial Doctor, using an online pharmacy (this will be QuickMeds unless there is an exceptional issue that would require moving to an alternative pharmacy to maintain drug supply). QuickMeds are a registered pharmacy (9012521) and a manufacturer-recommended (Eli Lilly) local supplier[59]. A trial-specific section of the secure QuickMeds prescribing portal will be set up for Trial Doctors to prescribe in a process similar to prescribing in private practice.

Tirzepatide will be prescribed in accordance with the recommended dosing schedule, with modification or reduction as agreed between clinician and participant depending on tolerability. The medication will be dispensed and dispatched as per usual practice from QuickMeds once the online prescription is completed. A monthly repeat prescription will only be issued if the participant attends and completes the monthly follow up appointment to ensure safety and compliance.

No clinical trial specific pharmacy requirements of the drug intervention including supply, storage, labelling, drug accountability and destruction will be needed. The participant will be advised that Tirzepatide needs to be stored in their refrigerator and that after use the self-injector pen should be kept for visual inspection. Responsibility for drug dispensing will lie with QuickMeds pharmacy.

7.5. Adherence

During each monthly follow up appointment, the participant will be asked to produce the Tirzepatide pens prescribed over the last month, where they will be visually inspected for adherence by the Trial Researcher. Visual confirmation of used doses via the indicator window on the pen will be recorded on the EDC.

7.6. Standard of care

We are evaluating the impact of weight loss from Tirzepatide plus standard of care against current NHS practice (standard of care). Standard of care is described in the IIH guidelines (see also **Section 1.2**) and in medically treated patients encompasses giving dietary advice on weight loss, with or without the use of off label drugs which may lower ICP (for example, acetazolamide, frusemide, topiramate, amiloride and spironolactone)[15]. In patients with sight threatening IIH, a surgical intervention could be used to save vision (CSF shunting, optic nerve sheath fenestration and venous sinus stenting)[15].

8. Outcome Measures

8.1. Main trial outcomes

8.1.1. Primary outcome

Resolution of papilloedema, as measured by OCT at 6 months post-randomisation.

8.1.2. Secondary outcomes

All secondary outcomes measured at 6 months post-randomisation unless stated otherwise:

- Clinical outcomes:
  - Change in papilloedema as measured by OCT
  - Headache: Monthly headache days (MHD), Monthly migraine days, Headache responder rate (≥50% reduction in MHD), Monthly analgesic days and Monthly headache severity (numerical rating scale lowest 0-10 highest).
  - Headache disability (using the Headache Impact Test-6 (HIT-6))

- Weight and BMI

- Patient-centred outcomes:
  - Quality of Life (QoL) measured using the 36-item short form survey (SF-36) summary score, physical component score and mental component score
  - QoL measured using the EQ-5D-5L
  - Vision related QoL measured using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) plus the 10-item supplement
  - Binge eating measured using the Binge Eating Scale (BES)
  - Alcohol use measured using the Alcohol Use Disorders Identification Test (AUDIT)
  - Anxiety and depression measured using the Hospital Anxiety and Depression Scale (HADS)
  - Tolerability of weight loss in IIH driven by Tirzepatide as determined by all cause discontinuation at 6, 12 and 18 months
- Service use outcomes:
  - Service use (doctor attendance, hospital attendance, days in hospital, lumbar punctures, brain imaging scans) (as recorded by Client Service Receipt Inventory (CSRI))
  - Medication use (use and dose of acetazolamide or other ICP lowering drugs)
  - Absenteeism and presenteeism measured using the Work Productivity and Activity Impairment (WPAI) Scale

8.1.3. Exploratory outcomes

All exploratory outcomes measured at 12 and 18 months from baseline unless stated otherwise and assessed in a subset of participants:

- Clinical outcomes:
  - Resolution of papilloedema as measured by OCT
  - Change in papilloedema as measured by OCT
  - Headache: Monthly headache days, Monthly migraine days, Headache responder rate (≥50% reduction in MHD), Monthly analgesic days and Monthly headache severity (numerical rating scale lowest 0-10 highest).
  - Headache disability (using the HIT-6)
  - Weight and BMI
- Patient-centred outcomes:
  - Quality of life (QoL) measured using the SF-36 summary score, physical component score and mental component score
  - QoL measured using the EQ-5D-5L
  - Vision related QoL measured using the NEI-VFQ-25 plus the 10-item supplement
  - Binge eating measured using the BES
  - Alcohol use measured using the AUDIT
  - Anxiety and depression measured using the HADS
- Economic outcomes:
  - Service use (doctor attendance, hospital attendance, days in hospital, lumbar punctures, brain imaging scans) (as recorded by CSRI)
  - Medication use (use and dose of acetazolamide or other ICP lowering drugs)

- Absenteeism and presenteeism measured using the WPAI

- Sleep outcomes:
  - Sleep, circadian cycle and daytime activity will be evaluated at baseline, 3 and 6 months using wearable device actigraphy data and the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Berlin questionnaire and STOP-Bang sleep apnoea screening questionnaire

Exploratory mechanistic outcomes

- Blood, saliva, 24-hour urine and stool samples will be collected at baseline, 3 and 6 months for later analysis for miRNA biomarkers, steroid metabolomics, protein biomarkers, inflammatory markers and Calcitonin Gene-Related Peptide, and rRNA sequencing to analyse gut microbiome changes.

Exploratory sleep sub-study outcomes

- Sleep, circadian cycle and daytime activity will be evaluated at baseline, 3 and 6 months.

Qualitative sub-study outcomes

A qualitative sub-study will answer the following research questions:

- What is the experience of weight management services and strategies for people with IIH?
- What should an optimal IIH weight management service look like?

8.2. Justification of key secondary and exploratory outcomes

8.2.1. Headache

Headache is the primary presenting symptom in IIH[2]. The condition causes significant morbidity, with headaches being a major contributor to reduced QoL[12,13]. Headache in active IIH is closely linked to elevated ICP, with improvements in severity and frequency observed following CSF removal, shunt placement, or weight loss[60–62]. Studies show a significant correlation between changes in ICP and headache severity or frequency[14]. The IIH Weight Trial indicated that reducing ICP through weight management led to improvements in headache outcomes[25].

The American Headache Society and International Headache Society recommend using headache outcomes derived from a 28-day diagnostic diary to assess treatment. This diary tracks headache frequency, severity and acute analgesic medication use.

8.2.2. Monthly headache days

Monthly headache days (MHD) will include all headache days, defined as those with an onset, continuation or recurrence of any severity or phenotype of headache and lasting at least 30 minutes or which require acute headache analgesia in a month (28 days).

8.2.3. Monthly migraine days

Monthly migraine days indicate the mean number of days a month (28 days) where a migraine or probable migraine is present. Migraine is diagnosed by the International Classification of Headache Disorders 3rd edition beta[63]. In IIH, headaches are migraine-like but cannot fulfil the full criteria for migraine as a secondary cause is present. However, for the purposes of classification in this trial we will use the International Classification of Headache Disorders definitions for migraine and probable migraine.

8.2.4. Headache responder rate

Headache responder rate (≥50% reduction in MHD from baseline) is the proportion of participants achieving at least 50% reduction in the number of MHD. This is clinically relevant as it is used as an empirical review for continuing or discontinuing headache therapy[64]. As a sensitivity analysis, we will appraise the proportion of participants achieving at least a 30% reduction in the number of MHD.

8.2.5. Headache severity

Some treatments may not reduce MHD, but can improve severity, leading to functional benefits and reduced disability, which is clinically relevant[65]. Headache severity is assessed by an 11-point Numeric Rating Scale (0 = no pain and 10 = most severe pain). The monthly headache severity is calculated as the mean severity with the denominator as the number of MHD.

8.2.6. Monthly use of acute headache rescue medications

Up to 48% of IIH patients experience medication overuse headaches and this can exacerbate the headache burden[66]. Acute headache analgesic use reflects treatment inefficacy and is a helpful secondary outcome. Reduction in analgesic days is linked to IIH clinical remission[26]. We will measure the number of days per month that acute headache analgesic medication is used.

8.2.7. Headache disability

The Headache Impact Test-6 (HIT-6) is a 6-item self-report tool used to assess the disability and impact of headaches on daily life, including areas such as work, social activities, and relationships. Responses are rated on a 5-point scale, with higher scores indicating greater impact. The total score categorises the severity of headache-related disability as mild, moderate, or severe.

8.2.8. Absenteeism and presenteeism

The Work Productivity and Activity Impairment (WPAI) Scale is a widely used, validated tool for assessing the impact of health conditions on work productivity and daily activities[67]. It measures both absenteeism (time missed from work) and presenteeism (reduced productivity while at work), as well as overall activity impairment. It is widely used in headache studies to understand the significant impact of headaches on work productivity and daily activities[68,69].

8.2.9. Quality of life in IIH

IIH negatively affects quality of life; primarily driven by headaches[12,13,24]. Measures of vision (the visual field) correlate with quality of life[70]. While there is no IIH-specific quality of life measure, most trials in IIH use the 36-item Short Form (SF-36) health survey, which correlates with changes in ICP[13,14,17,19,70]. The EQ-5D-5L is used for cost-effectiveness assessments lacks sensitivity compared to the SF-36 for IIH[19,71]. The National Eye Institute Visual Function Questionnaire-25 and 10-item supplement assesses visual-related quality of life and is linked to visual field improvements[70,72,73], with the 10-item neuro-ophthalmic supplement discriminating in a prior IIH trial[17].

8.2.10. Binge eating

Binge eating can influence weight gain. Approximately 7.5–30% of obese individuals seeking treatment have binge eating disorder or subclinical binge eating[74]. The validated Binge Eating Scale (BES) can be used to identify binge eaters[75,76], and has proven effective for both diagnosis and treatment monitoring[75]. Individuals with BES scores <18 are classified as non-binge eaters.

8.2.11. Alcohol use disorders identification test

The Alcohol Use Disorders Identification Test (AUDIT) is a tool developed by the WHO to identify individuals at risk for alcohol use disorders. It consists of 10 questions that assess alcohol consumption, drinking behaviours, and alcohol-related problems. The scoring ranges from 0 to 40, with a score of 8 or more suggesting hazardous or harmful drinking.

8.2.12. Hospital Anxiety and Depression Scale

IIH can significantly impact mental health leading to depression (42%) and anxiety (47%)[77]. The Hospital Anxiety and Depression Scale (HADS) is a widely used self-report questionnaire designed to assess levels of anxiety and depression in non-psychiatric hospital patients. The items are scored on a 4-point scale, yielding scores for both subscales, with higher scores indicating greater severity of symptoms. The HADS is

valued for its simplicity, ease of administration, and ability to distinguish between anxiety and depression, making it a useful tool in clinical and research settings, particularly in medical populations where somatic symptoms may overlap with psychological distress.

8.2.13. Exploratory sleep outcomes

Obesity significantly alters sleep patterns, increasing the risk of sleep disturbances such as obstructive sleep apnoea (OSA). Sleep has not been studied in IIH, but OSA is a known complication in IIH[78]. GLP-1R agonists have been shown to reduce weight and so improve OSA[79]. Additionally, GLP-1R agonists have also been shown to increase non-rapid eye movement sleep in rodents which may contribute to the overall positive effects on health which can be observed in these drugs[80]. We will evaluate the effects of weight loss driven by GLP-1R agonist Tirzepatide on sleep and how this might impact headache and mental health outcomes.

9. Trial procedures

9.1. Screening assessment (Month -1)

Following consent, participant contact details including telephone number will be collected. Email address will be collected during the consent process.

Participants will then be asked to provide a letter from an NHS medical professional confirming a diagnosis of IIH (correspondence may be available on the participant's NHS app). This will be reviewed by the research medical team to confirm a diagnosis of IIH. Where the correspondence is unclear, further documentation may be requested. Confirmation from a private health care provider will be considered on a case-by-case basis by the CI.

The participant will be asked to provide their height and weight. BMI will be calculated by the EDC.

A provisional baseline appointment may be arranged and Trial Office will liaise with Specsavers and the participant to arrange an OCT scan at a participating Specsavers UK store of the participant's choice. The resulting report (comprising solely of TNO and RNFL measurements) will be sent by email to the Trial Office and entered onto the EDC to allow a Trial Researcher to determine participant's level of papilloedema is sufficient to meet the trial eligibility.

If the participant is potentially eligible to continue into the trial on review of the OCT scan, then a baseline appointment will be arranged/confirmed.

Capillary (finger prick) blood, saliva, 24-hour urine and stool collection kits will be posted to the home address of the participant and information will be provided for collection. A video describing how each sample is collected, stored and posted will be shared with the participants and be available on the IIH-Advance website. Electronic scales and a paper tape measure will be provided to participants by post. A wearable device to capture exploratory sleep actigraphy data for 2 weeks will be provided to participants by post, and a link for an accompanying sleep diary, to be completed daily for 2 weeks, will be provided. This link will direct the participant to a subsection of the secure trial-specific EDC. If the participant is female of childbearing potential, the Trial Office will post a urine pregnancy test. This should be completed by the participant up to 7 days before the baseline assessment. The participant will provide the date the urine pregnancy test was completed at the baseline appointment.

It will be attempted to review OCT scans and post sample kits, sleep devices and pregnancy tests more than 2 weeks before baseline wherever possible.

9.2. Baseline visit (Month 0)

The baseline visit will take place via video call and last approximately 60-90 minutes. During this visit, full eligibility for randomisation will be confirmed by the Trial Doctor who will also ask the participant to

verbally confirm that they are happy to continue. Participant medical history, relevant current medications and demographic information including ethnicity and gender will be collected by the researcher.

The baseline 28-day headache diary will be reviewed, so the trial researcher can record the monthly headache days, monthly migraine days, monthly analgesic days and monthly headache severity.

The following validated questionnaires will be completed by the Trial Researcher reading out the questions and recording the participant's answers onto the EDC:

- Headache disability questionnaire (HIT-6)
- SF-36 v2
- EQ5D-5L
- NEI-VFQ-25 with 10 Item Neuro-Ophthalmic Supplement
- Binge eating questionnaire (BES)
- Alcohol intake questionnaire (AUDIT)
- Hospital Anxiety and depression Scale (HADS)
- CSRI
- Work Productivity and Activity Impairment (WPAI) Scale
- Pittsburgh Sleep Quality Index (PSQI)
- Insomnia Severity Index (ISI)
- Berlin questionnaire
- STOP-Bang sleep apnoea screening questionnaire

Once all baseline assessments are complete, the researcher will randomise the participant as per **section 6**.

9.3. Monthly follow up visits (month 1-5, 7-11, and 13-17)

Monthly after randomisation the participant will be invited to attend a video call with a trial researcher to review weight, headache, and intervention compliance. These video calls will last approximately 30-60 minutes and include:

Researcher collection of:

- Weight (as demonstrated during the videocall or by photograph of the provided scales)
- Visual inspection of Tirzepatide pen (if participant randomised to receive Tirzepatide)
- Concomitant medications
- Participant's monthly headache history
- Postage of sample collection kit to participant (prior to months 3 and 6)
- Postage of exploratory sleep wearable device (months 3 and 6)

Participant completion of:

- CSRI
- HIT-6
- Blood, saliva, 24-hour urine and stool samples (sent prior to months 3 and 6)
- Two weeks of exploratory sleep wearable device actigraphy collection, two weeks of daily sleep diary (months 3 and 6)

9.4. Review and treatment allocation visit R2 (month 6)

With sufficient notice before the 6 month time point, an OCT scan will be arranged at a participating Specsavers UK store of the participant's choice, to be completed <2 weeks before the 6 month time point.

Then, at 6 months, a full review as per the baseline visit as detailed in **section 9.2** (minus height, demographics and medical history) will be carried out.

Once the OCT scan has been analysed by the trial researcher and all month 6 assessments have been completed, participants will be classed as responder, partial responder or non-responder.

- Responders to standard of care will leave the trial.
- Non-responders to Tirzepatide will proceed to their final follow up visit (**section 9.6**).
- Responders and partial responders to Tirzepatide, and partial and non-responders to standard of care will be re-randomised into R2 as per the R1 randomisation method in **section 6**.

9.5. Review and open-label single-arm stage (SA3) (month 12)

At 12 months after randomisation R1, the participant will attend a 6 monthly review with full assessments as per baseline as above, with OCT scan arranged for two weeks prior.

- Participants who received Tirzepatide at R2 will proceed to their final follow up contact (**section 9.6**).
- Participants who did not receive Tirzepatide at R2 will receive 6 months of open-label Tirzepatide and continue with monthly follow up appointments as per **section 9.3**.
- At 18 months a full review as per the baseline visit as detailed in **section 9.2** (minus height, demographics and medical history) will be carried out.

9.6. Follow up (final dose of Tirzepatide + 5 weeks)

Five weeks after their final dose of Tirzepatide (whenever this occurs for each participant), all participants will be invited to attend a short follow up call, where a health and wellbeing check will be carried out as per recommended routine practice when losing weight using Tirzepatide. They will then leave the trial.

9.7. Unscheduled OCT visits

If there is deterioration (or suspected deterioration) of visual function, additional OCT visits should be scheduled with Specsavers to ensure the participant's ongoing visual health, as would be recommended in routine NHS practice. If required, an urgent referral to the NHS will be arranged and Tirzepatide halted.

10. Schedule of assessments

Table 1: Schedule of Assessments (Researcher completed)

			R1				R2		SA3		Follow up
Visit	0	1	2-3	4	5-6	7	8-12	13	14-18	19	
	Screening	Baseline/ Randomisation	Months 1-2	Month 3	Months 4-5	Month 6	Months 7-11	Month 12	Months 13-17	Month 18	5 weeks after stopping intervention
Visit window (days)	(-14)	(+14)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)
Eligibility check		x				x		x			
Valid informed consent	x										
OCT Imaging	x					x		x		x	
Ophthalmic review		x				x		x		x	
Medical, IIH and ophthalmic history*		x									
Concomitant medication		x	x	x	x	x	x	x	x	x	
Demographics		x									
Randomisation		x				x					
Height	x										
Weight and BMI	x	x	x	x	x	x	x	x	x	x	
Urine pregnancy test		x				x		x			
Safety and adverse events check			x	x	x	x	x	x	x	x	x
Fit and well check											x
Trial medication training		x				x		x			
Trial medication dispensing		x	x	x	x	x	x	x	x	x	
Trial medication adherence			x	x	x	x	x	x	x	x	

*assessed by Trial Doctor

NB: OCT imaging performed at local participating Specsavers UK store

Table 2: Schedule of Assessments (Participant completed)

			R1				R2		SA3	
Visit	0	1	2-3	4	5-6	7	8-12	13	14-18	19
	Screening	Baseline/ Randomisation	Months 1-2	Month 3	Months 4-5	Month 6	Months 7-11	Month 12	Months 13-17	Month 18
Visit window (days)	(-14)	(+14)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)	(+/-7)
CSRI		x	x	x	x	x	x	x	x	x
Headache Diary		x	x	x	x	x	x	x	x	x
HIT-6 questionnaire		x	x	x	x	x	x	x	x	x
WPAI		x				x		x		x
SF-36		x				x		x		x
EQ5D-5L		x				x		x		x
NEVI VFQ-25		x				x		x		x
Binge Eating Questionnaire		x				x		x		x
AUDIT		x				x		x		x
HADS		x				x		x		x
PSQI		x				x		x		x
ISI		x		x		x				
Berlin Questionnaire		x		x		x				
STOP-Bang		x		x		x				
Research biological sample collection		x		x		x		x		x
Sleep / activity tracker (2 weeks prior)		x		x		x				

11. Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a particular aspect of the trial. The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) will be entered onto the Participant Change of Status Form on the EDC. Participants can change their level of participation without giving a reason.

11.1. Specsavers follow up

If a participant fails to attend 3 consecutive OCT appointments they will be removed from further follow up at Specsavers. If the participant can then be contacted by the IIH-Advance trials team, is keen to re-engage and is happy to remain in the research study an OCT appointment will be re-booked.

12. Adverse Event Reporting

12.1. Definitions

Table 3: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	N/A	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death

		Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	N/A	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

12.2. Adverse event recording – general

The recording and reporting of adverse events will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in **Table 3: Adverse Event reporting definitions** in **section 12.1**.

It is routine practice in NHS research to record adverse events in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and of causality (relatedness) in relation to the intervention in accordance with the protocol. We will therefore mirror what would be expected in an NHS participant's notes; a notes field will be created on the eCRF for each follow up assessment to serve the function of medical notes. The trial researcher will review all potential AEs with participants at each appointment and record the discussions, including an evaluation of these events.

12.3. Adverse event reporting in IIH-Advance

The reporting period for adverse events in IIH-Advance will be from the day of randomisation until the end of follow up (i.e. 5 weeks after the last dose, if having taken Tirzepatide). The safety profile for this trial population and rapid weight loss regimens are well characterised so a strategy of targeted reporting of adverse events will not affect the safety of participants: only Serious Adverse Events (SAEs) will be reported.

12.4. Serious Adverse Advents reporting in IIH-Advance

For all SAEs, the Trial Researcher must do one of the following:

1. **Record safety reporting-exempt SAEs** in the EDC notes field notes but **not report** them to the Trial Office on an SAE form as per **Section 12.4.1** Serious Adverse Events not requiring reporting to the Trial Office.
2. **Report SAEs to the Trial Office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per **Section 12.4.2** Serious Adverse Events requiring non-expedited reporting to the Trial Office.

3. **Report SAEs to the Trial Office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per **Section 12.5** SAE Reporting process.

12.4.1. Serious Adverse Events not requiring reporting to the Trial Office

The following will not be considered critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation
- General hospital attendance lasting less than 24 hours
- Hospitalisation for routine treatment or monitoring of IIH, not associated with any deterioration in condition or trial procedures
- Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study
- Admission to a hospital or other institution for general care (not related to IIH or trial intervention), not associated with any deterioration in condition or trial procedures

All events which meet the definition of serious must be recorded in the participant notes field on the EDC as per adverse events in **section 12.2** , including the causality and severity, throughout the participant's time in the trial, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

12.4.2. Serious Adverse Events requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition) and the SAE may be known. That is, such events are protocol-defined as "expected" (see **Section 12.5.2**). Such events should still be recorded by the trial team in the participant's notes field on the EDC, and reported to the Trial Office on the trial specific SAE form **within 4 weeks of becoming aware of the event**. These events do not require expedited reporting (i.e. immediately on becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. These are:

- Hospitalisation due to exacerbation of IIH
- Hospitalisation for treatment of IIH

12.4.3. Serious Adverse Events requiring expedited reporting to the Trial Office

All SAEs not listed in **Sections 12.4.1** and **12.4.2** must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

12.5. SAE Reporting process

To report an SAE to the Trial Office, the trial researcher must complete the trial specific SAE form on the EDC. The completed form should be submitted to the Trial Office in accordance with the timelines given in **Sections 12.4.2** and **12.4.3**.

To report an SAE, complete the SAE eCRF on the Electronic Data Capture System.

Where an SAE form has been completed initially by someone other than a medically qualified researcher, the electronic SAE form must be reviewed and approved by a medically qualified researcher to confirm the causality and severity assessments. When an SAE form has been entered onto the EDC, it will be allocated a unique reference number.

12.5.1. Assessment of causality of an SAE

When completing the SAE form, a Trial Doctor (i.e. a medically qualified researcher) will be asked to define the nature of the seriousness and causality of the event.

In defining the causality, the Trial Doctor must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table 4: Categories of causality**, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered by the assessing medically qualified researcher to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and safety reporting-exempt SAEs in the source data.

Table 4: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will alert the CI or delegate(s) who will independently* review the causality of the SAE. An SAE judged by the assessing Trial Doctor or CI (or delegate) to have a reasonable causal relationship ("Related" as per Table 4: Categories of causality) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the Trial Doctor will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the assessing Trial Doctor's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the assessing Trial Doctor, an independent clinical causality review will be performed.

12.5.2. Assessment of expectedness of an SAE by the CI

The CI or delegate will also assess all related SAEs for expectedness with reference to the criteria in **Table 5: Categories of expectedness**.

Table 5: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or rapid weight loss regimens.
Unexpected	An adverse event that is not consistent with known information about the trial related procedures or rapid weight loss regimens.

The CI or delegate will undertake review of all SAEs and may request further information from the assessing Trial Doctor for any given event to assist in this. If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

12.5.3. Provision of SAE follow up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow up information should be provided using the SAE reference number provided by the Trial Office.

12.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and Sponsor within 15 days of being notified.

12.7. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

13. Data Handling and Record Keeping

13.1. Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. To allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

In IIH-Advance, all trial data is being collected on the electronic CRFs on the EDC, therefore the electronic CRFs will be considered as source data. The exception will be for the OCT scans, where the source data will be the output report provided by and retained by Specsavers UK, and the original clinical letter stating the participant has IIH, which will remain with the participant.

Table 6: Source data in IIH-Advance

Data	Source
Participant Reported Outcomes	Obtained by participant direct entry, or interview directly with the participant for entry onto the EDC. The electronic CRF is the source data.
Height, weight	Obtained by interview directly with the participant for entry onto the EDC. The electronic CRF is the source data.
OCT Scans	The source is the original scan saved as an electronic file and stored by Specsavers UK in line with their usual processes. A report of this scan will be sent to the IIH-Advance trial team where it will be stored securely on University of Birmingham (UoB) research servers.
Clinical event data	Obtained by interview directly with the participant or by remote inspection of the participant's clinical letters for entry onto the EDC. The electronic CRF is the source data.
Recruitment	The original record of the randomisation on the electronic CRF is the source.

Change of Status	The change of status form on the electronic CRF is the source data. This form will be completed by Trial Researchers directly onto the EDC.

13.2. Case Report Form completion

The electronic CRFs will include (but will NOT be limited to) the following Forms (see **Table 7: Case Report Forms in IIH-Advance**).

Table 7: Case Report Forms in IIH-Advance

Form Name	Schedule for submission
ICF and Screening CRF	At the point of the consent / screening visit
Randomisation CRF	At the point of randomisation
Baseline and follow up CRFs including participant reported outcome measures	As soon as possible after each follow up assessment time point
Serious Adverse Event CRF	If expedited: submitted within 24 hours of research team becoming aware of event If non-expedited: submitted within 2 weeks of research team becoming aware of event
Change of status CRF	As soon as possible after the point of reduced participation or death

In IIH-Advance electronic CRFs will be used, and the relevant forms should be completed for each individual participant. All electronic CRFs must be completed on the EDC and thereby submitted to the Trial Office by the Trial Researchers (as delegated on the Trial Delegation Log) within the timeframes above.

In all cases, it remains the responsibility of the CI to ensure that the electronic CRFs have been completed correctly and that the data are accurate. This will be evidenced by the signature of the CI or delegate. The Trial Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the electronic CRFs should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by validating and dating the electronic CRF.

Where the CRF is not the source data, data reported on each electronic CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to IIH-Advance working instructions.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. Example: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. Example: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

13.3. Participant reported questionnaires

Participant reported outcome measures will be completed by the Trial Researcher entering the participant reported data directly into the EDC during the remote interview.

13.4. Actigraphy data

Actigraphy data from a wearable device, provided for the trial, will be collected and the device sent to the Trial Office. A member of the Trial Office will download the data and store it securely on a UoB server.

13.5. OCT Scans

OCT scans are performed by Specsavers. Copies of the OCT scans will be stored by Specsavers as per usual Specsavers processes. Participants will be made aware of this in the PIS and asked to acknowledge it on the ICF.

13.6. Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry, data queries and self-evident corrections on trial data.

Data entry will be completed by the trial researchers via a bespoke BCTU EDC. This system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the researchers within 30 days of receipt. Overdue data entry and data queries will be requested monthly.

13.7. Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The trial EDC incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

13.8. Archiving

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. BCTU has standard processes for both hard copy and digital archiving. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

14. Quality Control and Quality Assurance

14.1. Site set-up and initiation

IIH-Advance will be a centralised trial. University of Birmingham will be the sole site. The IIH-Advance team will be split into the Trial Office, responsible for trial management and coordination, and the Trial Researchers, responsible for participant contact, follow up, and safety. Trial Doctors will be a medically qualified subset of Trial Researcher.

All Trial Researchers are required to sign the Trial Delegation Log, which details which participant-facing and trial delivery tasks have been delegated to them by the CI. The Trial Delegation Log should be kept up to date by the CI. It is the CI's responsibility to inform the Trial Office of any changes in the Trial Researcher team.

Prior to commencing recruitment, the Trial Researcher team will undergo a process of site initiation, either a meeting or a video call, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. All Trial Researchers will be trained by the CI and Trial Office in trial procedures before any participant contact.

Compliance standards with regards to data transfer and participant contact will be described in the UoB-Specsavers contract.

14.2. Monitoring

The central monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

14.2.1. Central monitoring

The Trial Office will check entered ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Trial researchers will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies as per the Data Management Plan. Any such monitoring activities will be reported to the TMG and any issues noted will be followed up to resolution.

14.3. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Trial Researchers must therefore notify the Trial Office of any suspected trial-related serious breach of Good Clinical Practice (GCP) and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether a serious breach has occurred, Trial Researchers must co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

15. End of Trial Definition

The end of trial will be the date of the last data capture including sample analysis and DCF resolution. This will allow time for the completion of protocol procedures, data collection, data input and data cleaning.

The Trial Office will notify the REC and Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

16. Statistical Considerations

16.1. Sample size

Examination of various IIH datasets held (including the IIH:WT trial[25], the IIH:Life cohort, and our previously published clinical trials in IIH[26]) suggest it is anticipated that in the population of patients who receive standard of care only 5% will have resolution of papilloedema (100% reduction in the excess elevation of the optic nerve swelling). Further analysis of these datasets revealed that in those who achieved at least a 12% reduction in body weight, between 30 and 50% had a complete resolution of papilloedema. For the purposes of the sample size calculation, we have taken a conservative estimate of 37% (the median estimate).

With a type I error of 0.05, a type II error of 0.1 (corresponding to a power of 90%), a responder rate in the control arm of 5% and responder rate of 37% in the Tirzepatide arm, a sample size of 32 participants per arm is required. Inflating this to account for 25% attrition (for missing data and withdrawal) would require 43 patients per arm (86 overall).

After 50% of the planned sample size has been recruited and treated (i.e. at the end of the first randomisation R1), an assessment of the missing data is planned to ensure the levels observed fall below that assumed during this calculation, with the option to increase the sample size based on this if needed.

This trial has been powered to answer the primary question for R1 only. The subsequent questions remain unpowered. This remains a limitation, however powering for these questions would result in a trial sample size that was infeasible. The purpose of these questions is to provide some high-quality evidence.

16.2. Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

Unless reported otherwise, the threshold for determining statistical significance from hypothesis testing will be represented by a p-value of <0.05. Where parametric tests have been specified dependent on the normality of data distribution, this will be assessed using appropriate graphics (for example histograms and q-q plots) prior to application of the test. Where randomisation is minimised by stratification variables, the main estimators will be adjusted for such variables for the primary outcome at stage R1.

Data pertaining to outcome measures will be transformed as per user manuals and standard practice to derive clinically meaningful indices where relevant.

16.2.1. Primary outcome

Resolution of papilloedema at the 6 month assessment. Where patients are missing the primary outcome (for example due to non-attendance at 6-month visit), they shall be treated as a failure and included in the denominator only (unless there is data from an unscheduled visits which could be utilised).

Resolution of papilloedema will be reported as n/N where n is the number of participants with resolution of papilloedema and N the total number of participants in the corresponding trial arm, and percentages as appropriate. Logistic regression model will be used to analyse the primary outcome. Risk ratio, risk difference and the associated 95% confidence intervals will then be derived using marginal standardisation method.

16.2.2. Secondary outcomes

Binary outcomes will be compared using an analogous method to that described under the primary outcome.

Non-ophthalmologic continuous, or pseudo-continuous outcomes collected only once post-baseline will be displayed as change from baseline and will be analysed using a linear regression model adjusted for baseline where appropriate. Results will be presented as adjusted mean differences with 95% confidence intervals. Statistical significance of a difference between treatment arms will be assessed based on the model.

Non-ophthalmologic continuous, or pseudo-continuous outcomes where the outcome is collected at multiple timepoints post-baseline (including patient reported outcome measures) will be assessed for differences between arms using mixed effect repeated measures models using linear patient trajectories through time (alternative analytical functions of time may be considered as necessary). In the initial model, a treatment by time interaction effect will be included in the model. If this is not significant, it will be considered that the treatment effect is constant over time, and models without the treatment by time interaction term will be fitted. Results will be presented as adjusted mean differences and 95% confidence intervals.

Ophthalmologic continuous, or pseudo-continuous outcomes (OCT outcomes) may have data collected in more than one eye. To best use this and increase statistical efficiency while accounting for the non-independence and high correlation between eyes within individuals, we will use hierarchical models to nest observations within patients. These models will have adjustments for treatment allocation and group-level effects for the effect of eye within participant. The presence of a linear predictor and slope-varying terms will be dependent on the number of post-baseline observations. The presence of a treatment effects will also be tested by a likelihood ratio test against a nested model with no treatment variable and otherwise identical model specification.

Ordinal outcomes will be analysed akin to the continuous outcomes however will be compared between treatment arms using ordered logistic regression models.

Data pertaining to exploratory outcomes will be summarised descriptively and/or graphically using methods appropriate to the data type. Exploratory outcomes will be presented separately for each of the (randomisation) questions (R2a, R2b, R2c, SA3a, SA3b).

16.2.3. Planned subgroup analyses

No sub-group analyses are planned.

16.2.4. Missing data and sensitivity analyses

For the primary outcome, where patients are missing the primary outcome (for example due to non-attendance at 6-month visit), they shall be treated as a failure and included in the denominator only and thus no imputation of missing data is planned.

An analogous strategy for binary secondary outcomes will be used.

For continuous, or pseudo-continuous secondary outcomes with only one post baseline time-point of collection, no imputation will be performed and the number of participants missing the relevant outcome data reported.

For continuous, or pseudo-continuous secondary outcomes with more than one post-baseline time-point of collection, the above-described modelling approach will implicitly impute observations using patient-within-arm imputations methods suitable for longitudinal data imputation.

Full details will be included in the Statistical Analysis Plan.

16.3. Planned final analyses

Final analyses will take place once the last randomised participant has reached the primary 18 month endpoint and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

17. Exploratory research sample sub-study

Full details of blood, saliva, urine, and stool sample processing are described in the trial laboratory manual.

17.1. Sample collection

Before baseline, 3 month, and 6 month appointments, a sample kit will be posted to participants. This will consist of separate kits for:

- Blood – a capillary blood sampling kit will be provided for the collection of approximately 0.5ml of blood for processing into plasma, and another for approximately 0.5ml of blood for processing into serum. Participants will be requested to fast from midnight (water only) on the day of sample collection.
- Saliva – a swab and prepared tube will be provided for the collection of approximately 1 swab of saliva and 2ml of saliva drool. Participants will be requested to fast from midnight (water only) on the day of sample collection. Participants will also be requested to provide a saliva sample on a day they self-rate as a severe headache day, and another on a good headache day.
- Urine – a kit will be provided for a 24-hour urine collection, of which approximately 20ml of urine will then be sampled and collected for trial use.
- Stool – a kit will be provided for the collection of approximately 1g of stool.

Kits will include secure postage containers to send the samples to the UoB Biomedical Sciences Laboratory.

17.2. Sample labelling

The sample kit sent to participants will be sent with a partially pre-completed set of sample labels coded with trial number, sample type, and timepoint, with the date to be completed by the participant prior to attaching to the sample container.

17.3. Sample handling and storage

Once received in the laboratory, samples will be processed as below before storage:

- Bloods - the microtainers will be centrifuged and the resulting supernatant designated plasma or serum. Following centrifugation, plasma/serum will be divided into aliquots, labelled and stored in the laboratory's -80 freezer.
- Saliva – the saliva will be divided into aliquots, labelled and stored in the laboratory's -80 freezer.
- Urine – the urine will be divided into aliquots, labelled and stored in a -20 freezer.
- Stool - the stool sample will be homogenized and the resulting homogenate centrifuged, and the supernatant stored in the laboratory's -80 freezer.

After all trial analysis is complete, the samples will be destroyed.

17.4. Provisional sample processing

The provisional downstream processing planned may include:

- Real time Polymerase Chain Reaction – serum and saliva swabs for changes in miRNA biomarkers related to IIH and weight change.

- Mass spectrometry – urine and serum for steroid metabolomics related to IIH and weight change.
- ELISA/O-link – plasma and saliva drool analysed for protein biomarkers, inflammatory markers related to IIH and weight change, and calcitonin gene-related peptide.
- 16s rRNA sequencing – to analyse gut microbiome changes with relation to weight change and with correlation to clinical outcomes.

17.5. Future sample use

After the processing described above, it is expected that the samples will be transferred to the University of Birmingham (UoB) Human Biomaterials Resource Centre (HBRC) biobank for storage or any excess sample destroyed. Those samples stored may be used in other related and ethically approved research in the future.

18. Qualitative sub-study

18.1. Justification

An essential component of IIH treatment is weight management. The advent of novel therapeutic options including GLP-1R agonists will necessitate the development of IIH specific weight management services in the future. Research suggests that individuals living with IIH have poor experiences when engaging in weight management discussions with healthcare professionals[81]. IIH-Advance provides a unique opportunity to conduct focus group discussions with individuals living with IIH, to explore their perceived acceptability of weight management strategies, their experiences of weight management discussions with healthcare professionals to date, and gain their insights into what an optimal IIH weight management service should look like.

18.2. Objectives

The qualitative sub-study will answer the following research questions:

- What is the experience of weight management strategies and services for people living with IIH?
- What should an optimal IIH weight management service look like?

18.3. Contact and consent

Optional consent to be contacted about possible participation in the qualitative sub-study will be requested at the point of consenting to trial participation.

The qualitative researcher will contact those participants who consent to this. It will be attempted to contact participants during their first randomisation stage (R1). The qualitative researcher will provide the participant with a qualitative sub-study specific PIS. The qualitative researcher will talk the participant through what participation in the focus group discussions would involve. Consent into the sub-study will be taken by the qualitative researcher prior to the focus group, audio-recorded since the contact and the focus groups will both take place remotely.

18.4. Design

Two focus group discussions with each including 8-10 participants will be conducted on a securely hosted UoB MS Teams channel. Focus group discussions will be recorded for transcription purposes. Transcriptions will be anonymised before analysis for research. Transcripts will be uploaded into NVivo software and a line-by-line coding approach used to develop a coding frame to undertake thematic analysis.

18.5. Study procedures

18.5.1. Qualitative interviews

These will be conducted by a researcher based at UoB. The qualitative sub-study will conduct semi-structured interviews with participants randomised to both Tirzepatide plus standard care and standard of care alone. Topic areas for the interviews are included in **section 18.7** below.

18.6. Data management

All study interviews will be video or audio-recorded and stored on a secure UoB Teams channel.

Personal data of study participants will be kept separately from interview/transcript data. Interview data will be pseudonymised, and personal details included therein may be modified if there are concerns regarding participant identification. Care will be taken to ensure that no identifying data are included in the presentation of any qualitative data.

18.7. Questions

The questions within each theme below are indicative of the general framework that will guide the semi-structured focus group discussions.

Theme 1: Weight management strategies

- What do you think are the challenges of weight management specific to IIH?
- What aspects of weight management would you like support with?
- Can you tell us about your thoughts on the use of weight loss drugs in IIH weight management?
- Can you tell us about your thoughts on the use of bariatric surgery in IIH weight management?

Theme 2: Experience of weight management discussions

- What has been your experience of accessing weight management services?
- What is your perception of access to weight management services?
- Can you tell us about your experience of weight management discussions with healthcare professionals?
- Was there a particular interaction/discussion that you liked, and why?
- Was there a particular interaction/discussion that you disliked, and why?
- What advice did you find the most or least helpful?

Theme 3: IIH weight management service

- Imagine an IIH specific weight management service, what would you like this service to look like?
- How would you like to access this service?
- Which healthcare professionals should be part of this service?
- Given your experience of weight management discussions, what do you think healthcare professionals working in these services should be aware of?
- What are your expectations from a healthcare professional working in a IIH weight management service?

19. Trial Organisational Structure

19.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

19.2. Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

19.3. Trial Management Group

The Trial Management Group (TMG) will take responsibility for the day-to-day management of the trial and will include (but is not limited to) the CI, Trial Statistician, Trial Management Team Leader, Trial Manager, and senior BCTU oversight staff. The TMG are listed at the front of the protocol. Their role is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will also be responsible for drafting the final report and submission for publication. TMG meetings will be scheduled sufficiently frequently to discuss trial progress, management, publications and any issues arising during the trial. Minutes of the meetings and any action points arising at the meetings will be recorded and circulated to the TMG.

19.4. Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the IIH-Advance trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

19.5. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on SAEs and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g. recruitment is faster than anticipated or a safety issue is identified.

19.6. Finance

The research costs of the trial are funded by a Sir Jules Thorn Charitable Trust grant awarded to Professor Alex Sinclair at UoB.

Participant travel costs will be reimbursed for visits to Specsavers UK, up to £20 per visit.

20. Ethical Considerations

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament (and relevant subsequent amendments), which include the Data Protection Act 2018 and Human Tissue Act 2004. The protocol will be approved by the REC prior to the start of the trial. This does not affect the individual Trial Doctors' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

21. Data Protection and Confidentiality

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments).

Participants will only be identified by their unique trial identification number on any correspondence with the Trial Office. For all participants, full name, full date of birth, gender, and NHS/CHI number will be

collected on the Randomisation Form. The participant's full name will also be collected on the participant consent forms in addition to their email address and/or mobile phone number. Participants will give their explicit consent for the storage of their consent form, on the EDC at BCTU. This will facilitate in-house monitoring of the consent process. Participants will also give their explicit consent for transfer of data between BCTU and Specsavers and/or the qualitative researcher to facilitate OCT scans and qualitative interviews respectively.

BCTU will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party (other than Specsavers and the trial pharmacy as required for the needs of the trial).

In the case of specific issues or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

OCT reports from Specsavers UK will contain trial number and RNFL measurements and will be sent to the Trial Office. Upon receipt, these reports will be stored securely on UoB servers.

Participants attending OCT scans will not be listed by Specsavers for active commercial recall after the trial. Participants who are not existing Specsavers customers will have marketing preferences automatically set to "no". Participants who are existing Specsavers customers will retain their existing marketing preferences. If any participant requests an eye test during their involvement on the trial, this will be done outside of the setting of the research visit and the visit will be booked separately as an independent customer.

22. Financial and other Competing Interests

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to declare potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

23. Insurance and Indemnity

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

24. Post-Trial Care

There is no provision for participants to receive Tirzepatide after trial participation ends.

25. Access to Final Dataset

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI

and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent TSC. Data transfer will use a secure and encrypted method and be subject to appropriate data sharing agreements.

26. Publication Plan

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review. In all publications, authors should acknowledge that the trial was performed with the support of University of Birmingham and BCTU.

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