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ABSTRACT

Introduction

Effective treatments are lacking for idiopathic intracranial hypertension (IIH), a condition characterised by raised intracranial pressure (ICP) and papilloedema, and found almost exclusively in obese women. Weight loss and lowering body mass index (BMI) has been shown to lower ICP and improve symptoms in IIH; however, weight loss is typically not maintained meaning IIH symptoms return. The IIH:WT trial will assess whether bariatric surgery is an effective long term treatment for IIH patients with a BMI over 35 kg/m^2. The National Institute for Health and Care Excellence (NICE) recommends bariatric surgery in people with a BMI over 35 kg/m^2 and a qualifying co-morbidity; currently IIH does not qualify as a co-morbidity.

Methods and analysis

IIH:WT is a multi-centre open-label randomised controlled clinical trial of 64 participants with active IIH and a BMI over 35 kg/m^2. Participants will be randomised in a 1:1 ratio to bariatric surgery or a dietary weight loss programme and followed up for 5 years. The primary outcome measure is ICP at 12 months. Secondary outcome measures include: ICP at 24 and 60 months; IIH symptoms; visual function; papilloedema; headache; quality of life; and cost-effectiveness, at 12, 24 and 60 months.

Ethics and dissemination

National Research Ethics Committee West Midlands – The Black Country approved IIH:WT on 28th February 2014 (14/WM/0011). Results will be disseminated through relevant conferences, peer-reviewed scientific journals and on-line publications.

Registration details

IIH:WT is registered as ISRCTN40152829 and on clinicaltrials.gov as NCT02124486.

Keywords

Idiopathic intracranial hypertension, bariatric surgery, weight loss, diet.

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Strengths and limitations of this study

- This is the first randomised controlled trial to evaluate the efficacy of long term weight loss strategies to modify underlying disease in Idiopathic Intracranial Hypertension (IIH).
- This trial will drive changes in clinical practice and impact on IIH treatment guidance.
- Cost-effectiveness will be assessed with relevance to future policy decisions.
- A potential limitation could be that there was limited data available to inform the sample size calculation, as so few trials have been performed in this area.
- The body mass index (BMI) eligibility in this trial is in line with current UK National Institute for Health and Clinical excellence (NICE) guidelines for bariatric surgery; however the benefits of weight loss may be relevant to those with a lower BMI.

INTRODUCTION

Idiopathic Intracranial Hypertension

IIH, also known as benign intracranial hypertension or pseudotumour cerebri, is a condition of unknown aetiology characterised by raised ICP and papilloedema. IIH is found almost exclusively in obese women (90%), causing daily headaches and visual loss, which can be severe and permanent [1, 2]. Effective treatments are lacking and range from medical therapies to surgical procedures which offer symptomatic relief and prevent blindness [3]. The overall age- and gender-adjusted annual incidence is reported as 1.8 per 100,000, with an increase from 1.0 per 100,000 (1990-2001) to 2.4 per 100,000 (2002-2014; P = 0.007) [4]; in line with the global obesity epidemic, the incidence of IIH is expected to rise [1]. The increasing economic burden of IIH has been highlighted by a number of groups [5, 6].

Current therapy for IIH

The 2015 Cochrane review concluded there was insufficient evidence to determine which treatments are potentially beneficial in IIH [3]; hence there is no clear guidance regarding standardised management.

Medical therapy can be used with the aim of lowering ICP. The Idiopathic Intracranial Hypertension Treatment Trial demonstrated acetazolamide has beneficial effects in patients with mild visual loss [7]. However, a pilot trial in the UK suggested many patients do not tolerate the drug well [8]. Topiramate has also been evaluated in IIH, but in the absence of a placebo arm it is difficult to interpret the results of this study [9].

In cases of deteriorating vision, surgical techniques such as cerebrospinal fluid (CSF) diversion (shunting) or optic nerve sheath fenestration (ONSF) can be used to prevent blindness [10]. Shunting is generally not a satisfactory treatment, with a high revision rate [11]. There is significant morbidity from CSF shunting [11, 12]. The evidence for ONSF is mainly case based [13], with reports of ongoing visual decline in a third of patients at 1 year and in nearly half at 3 years [14]. Patients waiting for a shunt and suffering disabling headaches with very high pressures may be offered repeated lumbar punctures (LP) to lower ICP, offering symptomatic relief.

Weight loss

We published a prospective study showing that a very low calorie diet leading to significant weight loss (15.3% ± 7.0% of body weight) significantly lowered ICP (8.0 ± 4.2 cmCSF, $p<0.001$) and significantly improved papilloedema, vision, and headache [15]. However, patients in our study later regained weight and their symptoms and signs of IIH returned, a documented phenomenon in the condition [16].

Despite the recurrence of IIH following weight regain, our study demonstrates the efficacy of therapeutic weight loss. However, maintaining long term weight loss is difficult to achieve, with patients on average regaining one third to one half of lost weight at 12 months, and returning to original weight in 5 years [17, 18]. Sustainable approaches to weight loss are therefore likely to offer patients an effective treatment. Obesity pharmacological therapies such as orlistat are unlikely to achieve sufficient weight loss (typical reduction of 2.89kg [19]) to significantly modify IIH.

Bariatric surgery for IIH

Bariatric surgery has many advantages as a potential treatment for IIH:

1) Weight loss is greater than other weight reducing approaches [20]. Hutter et al. give a mean reduction in BMI of 7.05-15.34 m/kg^2 at 12 months using the 3 procedures in use in this trial [21];
2) Weight loss is sustained [22-24];
3) Bariatric surgery is cost-effective compared to non-surgical interventions to manage obesity [25];
4) Bariatric surgery is safe: Mortality rates are typically 0.05-0.14%, similar to cholecystectomy or hysterectomy [21, 26, 27]. Major complications rates are 2–6% [21, 26-32], similar to other common elective operations [26].

NICE recommends bariatric surgery for people with a BMI over 40 kg/m^2 or in people with a BMI of over 35 kg/m^2 and a significant co-morbidity (e.g. type 2 diabetes) that may be improved with weight loss [33]. IIH is not one of the listed co-morbidities and IIH patients do not often have alternative co-morbidities that would qualify them for surgery.

There are no published systematic reviews or meta-analyses of weight modification or bariatric surgery in IIH, although an increasing number of case series and reports have been published describing its beneficial effects [34]. There is no long term data about sustained weight loss in IIH.

Rationale

The aim of this trial is to assess if sustained weight loss results in sustained reduction of ICP, visual symptoms and headaches, and which method, bariatric surgery or a dietary weight loss programme, is a viable method of achieving this. Bariatric surgery is an approach to sustainable significant weight loss, and so may offer long-term treatment of IIH. As it is not established how much weight loss is necessary to treat IIH, conservative weight management with dietary interventions may also offer long-term treatment.

Bariatric surgery is an invasive approach to weight reduction and a significant change from the current accepted treatment for IIH. To impact current clinical practice, we will compare bariatric surgery to an alternative weight loss regime (rather than current practice). The comparator arm will be a dietary weight loss programme using the internationally recognised Weight Watchers diet programme.

Weight Watchers is a widely available commercial weight loss programme, achieving superior weight loss and attendance compared to other commercially available (such as Slimming World or Rosemary Conley) or primary care led weight loss programmes [35]. Participants in Weight Watchers receive group support, access to online tools, and resources and advice on healthy eating. In one study, participants in Weight Watchers lost on average 4.4kg 3 months after joining the programme [35].

Participants in the IIH:WT trial will be randomised between referral to bariatric surgery or to a dietary weight loss programme (Weight Watchers) for 12 months.

METHODS

Design

IIH:WT trial is a multi-centre randomised controlled parallel arm clinical trial of 64 participants with active IIH and a BMI over 35 kg/m^2. Participants will be randomised in a 1:1 ratio to either bariatric surgery or a dietary weight loss programme and followed up for 5 years.

Blinding

The trial will necessarily be open label due to the nature of the intervention; assessors of visual outcomes will be masked to randomised treatment allocation. The primary outcome, ICP, is an objective measure.

Recruitment

Patients will be identified at Neurology and Ophthalmology clinics in UK NHS Trusts between July 2014 and October 2017.

The participant pathway through the trial is shown in Figure 1.

Figure 1: Participant pathway from approach to primary endpoint

Inclusion criteria and exclusion criteria

Inclusion criteria are:

1. Female IIH patients aged between 18 and 55 years, diagnosed according to the Freidman Jacobsen criteria [36] who have active disease (papilloedema [Frisén grade ≥ 1 in at least one eye], significantly raised ICP > 25cmCSF) of over 2 months' duration and no evidence of venous sinus thrombosis (magnetic resonance or CT imaging and venography as noted at diagnosis) [37].
2. BMI >35kg/m^2.
3. Tried other appropriate non-surgical treatments to lose weight but have not been able to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months.
4. Able to give informed consent.

Exclusion criteria are:

1. Age less than 18 or older than 55 years.
2. Pregnant.
3. Significant co-morbidity, Cushing's syndrome, Addison's disease or the use of oral or injected steroid therapy.
4. Undergone optic nerve sheath fenestration.
5. Definite indication for or contraindication against surgery or dieting.
6. Have a specific medical or psychiatric contraindication for surgery, including drug misuse, eating disorder or major depression (suicidal ideation, drug overdose or psychological admission in last 12 months).
7. Previous bariatric surgery.
8. Inability to give informed consent e.g. due to cognitive impairment.

Apart from the trial treatments allocated at randomisation, other aspects of patient management are at the discretion of the local doctors.

Randomisation

Participants are randomised into the trial by telephone call to the Birmingham Clinical Trials Unit. A computer-generated randomisation list with allocation of treatment stratified by acetazolamide use will be used.

Treatment arms

Intervention arm

- Participants randomised to surgery will be referred to bariatric surgery. If judged suitable according to the local screening processes, the participant will undergo Laparoscopic Adjustable Gastric Banding (LAGB), Roux-en-Y Gastric Bypass (RYGBP), or Laparoscopic Sleeve Gastrectomy (LSG). This will take approximately 4 months from randomisation to surgery. The choice of surgery will be made between surgeon and participant based upon the participant's health and preference, and standard NHS follow-up will be included.

Active control arm

- Participants randomised to the dietary weight loss programme will be given vouchers allowing access to weekly meetings at their local Weight Watchers group and Weight Watchers online and mobile tools for 12 months.

FOLLOW-UP AND OUTCOME MEASURES

Primary Outcome Measure

- ICP at 12 months.

Secondary Outcome Measures

- ICP at 24 and 60 months.
- Reported IIH symptoms (pulsatile tinnitus, visual loss, diplopia, visual obscurations).
- Visual function (LogMAR chart to assess visual acuity, Humphrey Visual Fields 24-2, MARS charts to assess contrast sensitivity, Ishihara colour vision).
- Papilloedema (measured by spectral optical coherence tomography and fundus photography).
- Headache associated disability (headache diary, Headache Impact Test-6 score (HIT-6)).
- Anthropometric measures (BMI, waist/hip ratio, fat mass, blood pressure).
- Quality of life and wellbeing (EQ-5D-5L, ICECAP-A, SF-36, Hospital Anxiety and Depression score).
- Difference in number of referrals to CSF shunting and optic nerve sheath fenestration procedures between treatment arms.
- Change in Quality-Adjusted Life Years and/or Capability Wellbeing; offset against cost of treatment.

All outcomes will be measured at 12, 24 and 60 months.

Exploratory objectives

Participants with IIH and 20 matched obese control participants will give samples of blood and CSF. Some participants, including the 20 matched obese controls, will participate in sub-studies looking at the aetiology of IIH and the relationship between IIH and other obesity co-morbidities, from which they may suffer. These sub-studies will not be carried out at all sites and are not discussed in this paper. The control participants will undergo the same baseline assessment as randomised participants and then exit the study.

Format of assessment visits

When initially approached, participants will be asked to consent to a pre-screening assessment. This will consist of having their papilloedema assessed and graded according to the modified Frisén criteria. If papilloedema are present the participant will be asked to return for a screening visit. In the 7 days before the screening visit, the participant will complete a headache diary recording severity and frequency of headache, as well as analgesic use.

Participants will then have a screening assessment (0 months) which will be carried out according to Figure 2 and is described below.

Informed consent will first be taken and a urine pregnancy test carried out. Then the participant will undergo a series of visual assessments. If any of these assessments have been carried out in the 30 days prior to the screening visit as part of routine care then they will not be repeated, but the results taken from patient notes provided they have been performed as per trial protocol.

The visual assessments will be recorded in both eyes and these include:

- Best corrected visual acuity will be measured using LogMAR (log of the minimum angle of resolution) charts;
- Best corrected contrast sensitivity will be measured using MARs charts;
- Colour vision will be assessed using the Ishihara pseudo-isochromatic plates;
- Automated perimetry with a Humphrey Visual Field (HVF) Analyzer using the SITA Standard 24-2 program. Where there is a high false positive rate the HVF will be repeated prior to LP;
- Optical Coherence Tomography (Heidelberg Spectralis Spectral Domain OCT) will be acquired to record measurements including retinal nerve fibre layer. OCT scans will be sent for masked review by designated specialist readers;
- Digital colour fundus photographs will be taken, centred on the optic disc with focus on the anterior surface of the swollen nerve head. These will be graded by masked reviewers.

After visual assessments are complete an LP will be performed. LP will be performed with the participant breathing steadily in the lateral position; legs extended greater than 90^{o} at the hip, with adequate time taken to ensure a stable reading. ICP will be recorded in cmCSF. Where required, LP will be performed with image guidance.

The LP will be carried out after all visual assessments as the LP temporarily lowers ICP and so potentially alters visual measurements. In all cases the LP will be done on the day of randomisation as ICP is the primary outcome.

Further assessment of headache will use the HIT-6 [38], an assessment of the impact of headache over the previous month. Headache preventative use and use of acetazolamide/diuretics will be recorded.

The participant will complete quality of life questionnaires (QoL) following the LP. These include the generic health-related QoL questionnaires EQ-5D-5L (EuroQol five dimensions questionnaire), SF-36 Version 1 (RAND 36-Item Short Form Survey) and ICECAP-A (ICEpop CAPability measure for Adults), and the Hospital Anxiety and Depression score.

If the participant has ICP >25cmCSF, they will be randomised and the data collected at the pre-screening and screening visits will be used for baseline data.

Participants will then be evaluated at 3, 6, 12, 24 and 60 months as shown in Table 1. Participants randomised to surgery will also be evaluated at approximately 2 weeks post-surgery for an LP assessment of ICP.

Figure 2: format of baseline assessment visits

Figure 2 legend:
The format of the baseline visit is shown. HVF indicates Humphrey Visual Field; OCT is Optical Coherence Tomography; and ICP is Intracranial Pressure.

Table 1: Outcome measures and assessments

Outcome	Measure	Baseline	3 months	6 months	Post-op	(Primary endpoint) 12 months	24 months	60 months
ICP	Lumbar puncture	x			x	x	x	x
Anthropometric measures	BMI, BP, waist/hip, fat mass	x	x	x	x	x	x	x
IIH symptoms	Pulsatile tinnitus, visual loss, diplopia, visual obscurations	x				x	x	x
Visual function	Visual acuity, contrast sensitivity, colour assessment	x				x	x	x
	Humphrey visual field (24-2)	x				x	x	x
Papilloedema	Optical coherence tomography	x				x	x	x
	Retinal photographs	x				x	x	x
Headache	HIT-6, headache diary	x				x	x	x
Quality of Life	EQ-5D-5L, ICECAP-A, SF-36 v1, HADS	x				x	x	x
Health Economics	Resource use questionnaire	x				x	x	x

ANALYSIS

Sample size

Total n=64. 32 participants in each arm (bariatric surgery versus dietary weight loss programme).

For this trial we hypothesise that the greater weight loss anticipated in the bariatric surgery arm compared to the dietary arm will consequently reduce the ICP further in the bariatric arm than in the dietary arm. A weight loss of 15.3% ± 7.0% of body weight over 3 months was achieved by patients following a low calorie diet [15]. Data from this study showed that ICP was significantly reduced by 20% (ICP at baseline in 20 IIH patients was 39.8 ± 5.1 cmCSF and ICP was reduced by 8 ± 4.2 cmCSF, $p<0.001$).

Assuming a conservative change of ICP in the bariatric surgery arm to that previously observed of 8cmCSF and a change of 3cmCSF in the dietary arm (to reflect changes slightly greater than the baseline fluctuations seen in our previous study), then we wish to detect a mean difference of 5cmCSF between the groups. To detect this difference of 5cmCSF with 90% power and alpha=0.05 using a 2-sided t-test (assuming a standard deviation of 5.1 [15]) requires 46 patients (23 per arm). Allowing for a 25-28% drop out rate will require 32 patients per arm.

We believe that the SD of 5.1 is a true reflection of the variability of the data as this is taken from the baseline measurements from our previous study, in a similar population [15]. This assumption for the sample size calculation will be monitored during the trial.

Projected accrual and attrition rates

Recruitment for our previous study with very similar inclusion criteria was at a rate of 1.5 participants per month [15]; we consequently feel that the recruitment target of 1.8 participants per month (64 participants over 3 years) is realistic and achievable. Attrition rates for this treatment and patient group is not known; we have allowed a 28% rate of drop out.

Statistical Analysis

The primary comparison groups will be composed of those randomised to the bariatric surgery arm and those randomised to the dietetic intervention arm. Analyses will be based on the intention to treat principle, i.e. all patients will be analysed in the treatment group to which they were randomised irrespective of compliance with the randomised allocated treatment or other protocol violation. Summary statistics and differences between groups (e.g. mean differences, relative risks) will be reported, with 95% confidence intervals and p-values from two-sided tests given. Outcomes will be adjusted for the stratification variable (acetazolamide use at entry). For all analyses, a p-value <0.05 will be considered statistically significant and there will be no adjustment for multiple testing.

Primary Outcome Analysis

The primary outcome will assess the ICP at 12 months. The ICP at 12 months for the two study arms will be compared using a linear regression model with baseline ICP and acetazolamide use at entry (stratification variable) included as covariates in the model.

Secondary Outcome Analyses

Secondary outcome measures include a mixture of continuous and categorical data items. Continuous outcomes (e.g. quality of life) will be analysed as per the primary outcome measure. Categorical outcomes (e.g. presence or absence of symptoms, number of CSF shunting referrals) will be expressed as the number and percentage of patients experiencing these outcomes in the two groups. Log-binomial models will be used to compare the data between the two study arms, with baseline data (where available, i.e. baseline symptom data) and acetazolamide use at entry (stratification variable) included in the model as covariates.

Health economic outcomes

The following analyses will assess the cost-effectiveness of bariatric surgery versus diet for IIH:

1. Cost-effectiveness analysis - ICP measured at baseline and 12 months will be evaluated in terms of cost to reduce ICP by 12.5%.
2. Cost-utility analysis – quality of life and wellbeing information from the EQ-5D-5L and ICECAP-A questionnaires at baseline and 12 months; cost-effectiveness will be expressed as 'cost per QALY gained' and 'cost per sufficient and full capability achieved'.
3. Cost-benefit analysis – monetary outcomes will be elicited using the 'Willingness to Pay' method asked at baseline and at 12 months. Results will be expressed as a cost-benefit ratio and net-present value.

MONITORING

Safety reporting

There are no novel medical devices or Investigational Medicinal Products used as part of this trial. Any Serious Adverse Events (SAEs) will be reported on a trial-specific SAE form, evaluated by the Chief Investigator, and where required reported to sponsor and ethics committee.

Independent Trial Steering Committee (TSC)
A TSC will provide oversight of the study. The independent members are a consultant neurologist and neuro-ophthalmologist as chair, a consultant bariatric surgeon as independent expert, an independent statistician, and a patient representative.

Data Monitoring Committee (DMC)
A DMC will independently monitor the efficacy and safety data at least annually. The members are a consultant ophthalmologist as chair, a consultant bariatric surgeon as independent expert, and an independent statistician.

Compliance monitoring
Data on compliance in the bariatric surgery arm will be collected from local surgery teams. Compliance will be considered as undergoing bariatric surgery. Reasons for non-compliance will be recorded.

Data on attendance to Weight Watchers for participants in the dietary arm will be self-reported. It is not expected that participants will attend every session (30% of participants attended less than 50% of sessions over 12 weeks in one trial [35] and we expect a lower attendance rate over 12 months).

ETHICS AND DISSEMINATION

National Research Ethics Committee West Midlands – The Black Country approved IIH:WT on 28th February 2014 (14/WM/0011). The current protocol is version 3.0, 6th February 2017, available at www.birmingham.ac.uk/iihwtdocuments and last accessed on 24th April 2017.

The trial will be conducted according to the standards of the International Conference on Harmonisation-Good Clinical Practice (GCP) and the Research Governance Framework for Health and Social Care. Written informed consent will be provided by all patients prior to any trial-related procedures. Participants will be free to withdraw from the trial at any time without any effect on their standard of care.

Results will be disseminated through internal reports, relevant conferences, peer-reviewed scientific journals and on-line publications.

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AUTHORS' CONTRIBUTIONS

AS, EF, NI, RO, CR and RW conceptualised and designed the trial, helped with statistics for the trial, and helped writing the manuscript.
AS, JM, SM, TM and RS are recruiting participants to the trial.
HB, JM, SM, TM and RS provided critical input into trial design and helped writing the manuscript.

All authors inputted to the writing of the paper.

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CONFLICT OF INTEREST STATEMENT
None declared.

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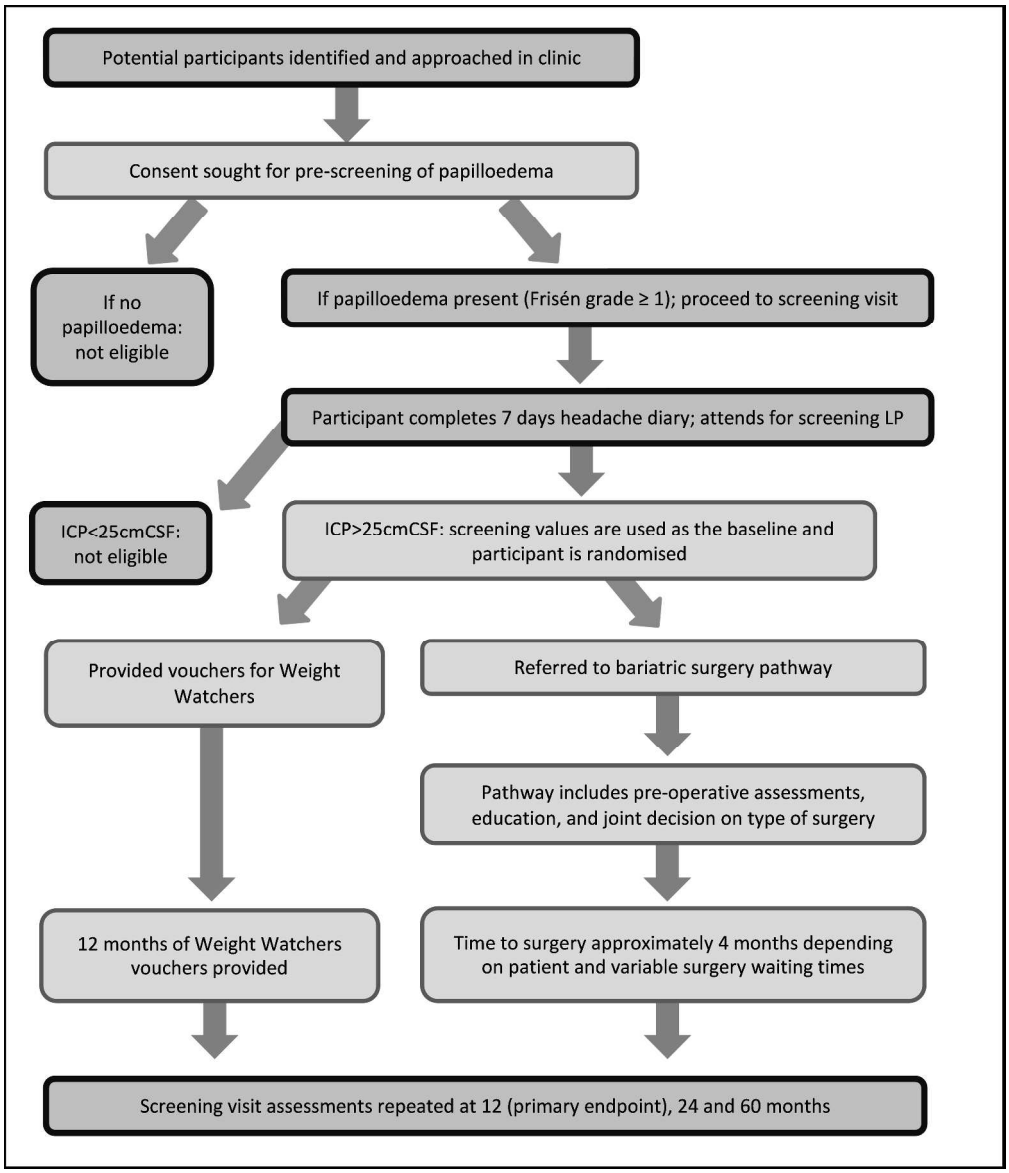

Figure 1: Participant pathway from approach to primary endpoint

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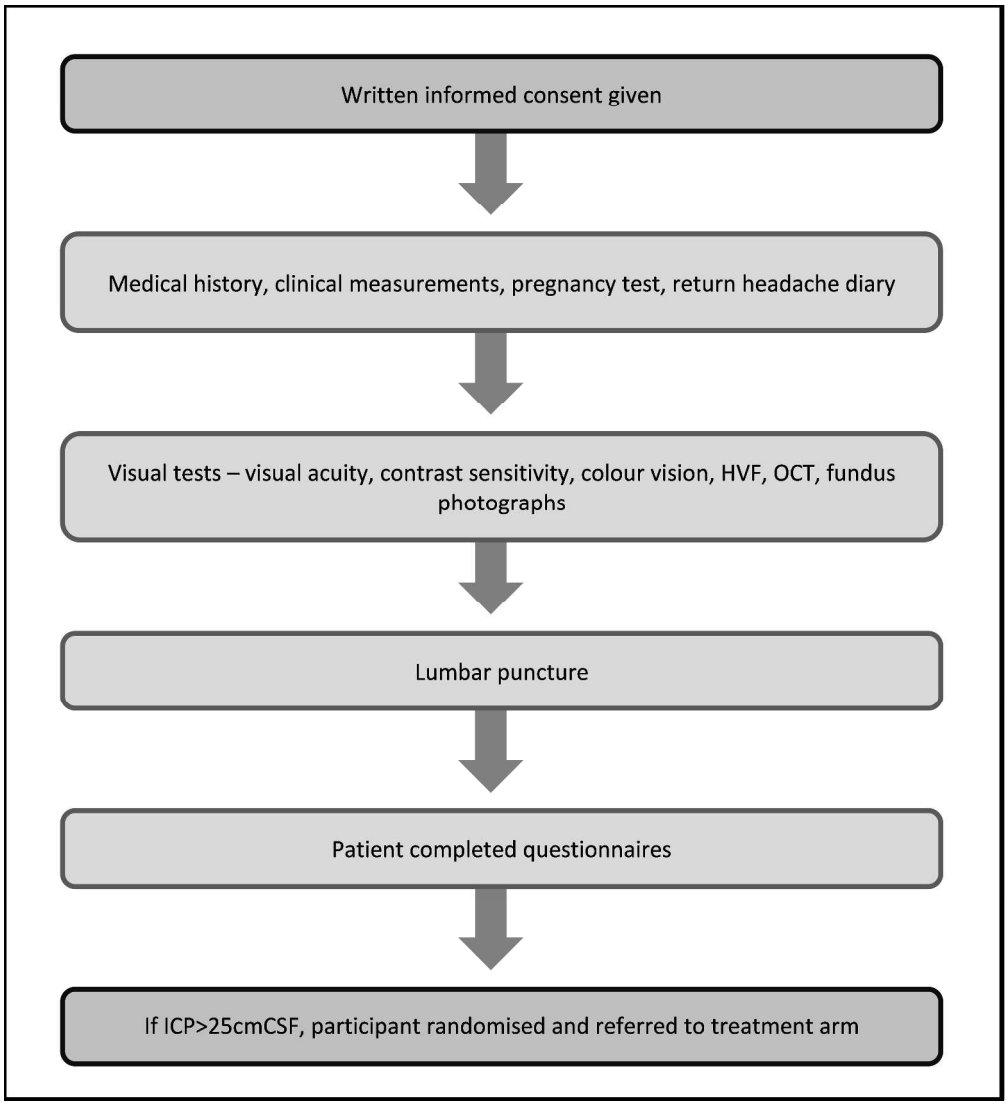

Figure 2: format of baseline assessment visits

892x977mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – page 2
	2b	All items from the World Health Organization Trial Registration Data Set – trial is registered, see 2a
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support – page 11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – page 1
	5b	Name and contact information for the trial sponsor – page 10
	5c	Role of study sponsor – page 10 and funders – page 11, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre , steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – page 10
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – page 3-4
	6b	Explanation for choice of comparators – page 4
Objectives	7	Specific objectives or hypotheses – page 4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – page 4
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – page 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – page 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request – page 10, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – page 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – page 6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – page 6-7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – page 9
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – page 5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – page 5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – page 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – n/a
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – page 5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – see protocol; link in paper
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – page 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – page 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – page 9

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – page 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – see protocol; link in paper
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – this information is held in the monitoring plan, an in-house BCTU document

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – page 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – see protocol; link in paper
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – see protocol; link in paper
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – see protocol; link in paper
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – see protocol (link in paper) and in-house BCTU data management plan
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – page 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – this is covered in the clinical trial site agreements between sites and sponsor

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – see protocol; link in paper
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – page 10
	31b	Authorship eligibility guidelines and any intended use of professional writers – no professional writers intended
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – protocol is publicly available on BCTU trial website
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – n/a?
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – see protocol; link in paper

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of Idiopathic Intracranial Hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol.

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Ophthalmology, Nutrition and metabolism
Keywords:	Idiopathic intracranial hypertension, bariatric surgery, weight loss, diet

A randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of Idiopathic Intracranial Hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol.

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Word count excluding abstract, figures, tables, acknowledgements and references: 3924.

ABSTRACT

Introduction

Effective treatments are lacking for idiopathic intracranial hypertension (IIH), a condition characterised by raised intracranial pressure (ICP) and papilloedema, and found primarily in obese women. Weight loss and lowering body mass index (BMI) has been shown to lower ICP and improve symptoms in IIH; however, weight loss is typically not maintained meaning IIH symptoms return. The IIH:WT trial will assess whether bariatric surgery is an effective long term treatment for IIH patients with a BMI over 35 kg/m^2. The National Institute for Health and Care Excellence (NICE) recommends bariatric surgery in people with a BMI over 35 kg/m^2 and a qualifying co-morbidity; currently IIH does not qualify as a co-morbidity.

Methods and analysis

IIH:WT is a multi-centre open-label randomised controlled clinical trial of 64 participants with active IIH and a BMI over 35 kg/m^2. Participants will be randomised in a 1:1 ratio to bariatric surgery or a dietary weight loss programme and followed up for 5 years. The primary outcome measure is ICP at 12 months. Secondary outcome measures include: ICP at 24 and 60 months; IIH symptoms; visual function; papilloedema; headache; quality of life; and cost-effectiveness, at 12, 24 and 60 months.

Ethics and dissemination

National Research Ethics Committee West Midlands – The Black Country approved IIH:WT on 28th February 2014 (14/WM/0011). Results will be disseminated through relevant conferences, peer-reviewed scientific journals and on-line publications.

Registration details

IIH:WT is registered as ISRCTN40152829 and on clinicaltrials.gov as NCT02124486.

Keywords

Idiopathic intracranial hypertension, bariatric surgery, weight loss, diet.

Abstract word count: 248

Strengths and limitations of this study

- This is the first randomised controlled trial to evaluate the efficacy of long term weight loss strategies to modify underlying disease in Idiopathic Intracranial Hypertension (IIH).
- This trial will drive changes in clinical practice and impact on IIH treatment guidance.
- Cost-effectiveness will be assessed with relevance to future policy decisions.
- A potential limitation could be that there was limited data available to inform the sample size calculation, as so few trials have been performed in this area.
- The body mass index (BMI) eligibility in this trial is in line with current UK National Institute for Health and Clinical Excellence (NICE) guidelines for bariatric surgery; however the benefits of weight loss may be relevant to those with a lower BMI.

INTRODUCTION

Idiopathic Intracranial Hypertension

IIH, also known as benign intracranial hypertension or pseudotumour cerebri, is a condition of unknown aetiology characterised by raised ICP and papilloedema. IIH is found primarily in obese women (90%), causing daily headaches and visual loss, which can be severe and permanent.[1, 2] Effective treatments are lacking and range from medical therapies to surgical procedures which offer symptomatic relief and prevent blindness.[3] The overall age- and gender-adjusted annual incidence is reported as 1.8 per 100,000, with an increase from 1.0 per 100,000 (1990-2001) to 2.4 per 100,000 (2002-2014; P = 0.007);[4] in line with the global obesity epidemic, the incidence of IIH is expected to rise.[1] The increasing economic burden of IIH has been highlighted by a number of groups.[5, 6]

Current therapy for IIH

The 2015 Cochrane review concluded there was insufficient evidence to determine which treatments are potentially beneficial in IIH;[3] hence there is no clear guidance regarding standardised management.

Medical therapy can be used with the aim of lowering ICP. The Idiopathic Intracranial Hypertension Treatment Trial demonstrated acetazolamide has beneficial effects in patients with mild visual loss.[7] However, a pilot trial in the UK suggested many patients do not tolerate the drug well.[8] Topiramate has also been evaluated in IIH, but in the absence of a placebo arm it is difficult to interpret the results of this study.[9]

In cases of deteriorating vision, surgical techniques such as cerebrospinal fluid (CSF) diversion (shunting), optic nerve sheath fenestration (ONSF) or venous sinus stenting can be used to prevent blindness.[10] Shunting is generally not a satisfactory treatment, with a high revision rate.[11] There is significant morbidity from CSF shunting.[11, 12] The evidence for ONSF is mainly case based,[13] with reports of ongoing visual decline in a third of patients at 1 year and in nearly half at 3 years.[14] The evidence for venous sinus stenting is based on case series and retrospective studies, and long-term data is limited.[1, 2] Patients waiting for surgical intervention and suffering disabling headaches with very high pressures may be offered repeated lumbar punctures (LP) to lower ICP, offering symptomatic relief.

Weight loss

We published a prospective study showing that a very low calorie diet leading to significant weight loss (15.3% ± 7.0% of body weight) significantly lowered ICP (8.0 ± 4.2 cmCSF, p<0.001) and significantly improved papilloedema, vision, and headache.[15] However, patients in our study later regained weight and their symptoms and signs of IIH returned, a documented phenomenon in the condition.[16]

Despite the recurrence of IIH following weight regain, our study demonstrates the efficacy of therapeutic weight loss. However, maintaining long term weight loss is difficult to achieve, with patients on average regaining one third to one half of lost weight at 12 months, and returning to original weight in 5 years.[17, 18] Sustainable approaches to weight loss are therefore likely to offer patients an effective treatment. Obesity pharmacological therapies such as orlistat are unlikely to achieve sufficient weight loss (typical reduction of 2.89kg)[19] to significantly modify IIH.

Bariatric surgery for IIH

Bariatric surgery has many advantages as a potential treatment for IIH:

1) Weight loss is greater than other weight reducing approaches.[20] Hutter et al. give a mean reduction in BMI of 7.05-15.34 m/kg^2 at 12 months using the 3 procedures in use in this trial;[21]
2) Weight loss is sustained.[22-25] Although the most recent Cochrane review notes that follow-up in bariatric surgery trials is often only 12-24 months and so long-term effects are unclear,[20] one prospective observational study showed a mean weight loss of 17% at 10 years.[25] Weight loss peaks at 12-24 months;[24, 25]
3) Bariatric surgery is cost-effective compared to non-surgical interventions to manage obesity;[26]
4) Bariatric surgery is safe: Mortality rates are typically 0.05-0.14%, similar to cholecystectomy or hysterectomy.[21, 27, 28] Depending on patient complexity this can rise as high as 2%,[29] but our patient population is typically younger and healthier than the average bariatric surgery patient. Major complications rates are 2–6%,[21, 27-33] similar to other common elective operations.[27]

NICE recommends bariatric surgery for people with a BMI over 40 kg/m^2 or in people with a BMI of over 35 kg/m^2 and a significant co-morbidity (e.g. type 2 diabetes) that may be improved with weight loss.[34] IIH is not one of the listed co-morbidities and IIH patients do not often have alternative co-morbidities that would qualify them for surgery.

There are no published systematic reviews or meta-analyses of weight modification or bariatric surgery in IIH, although an increasing number of case series and reports have been published describing its beneficial effects.[35] There is no long term data about sustained weight loss in IIH.

Rationale

The aim of this trial is to assess if sustained weight loss results in sustained reduction of ICP, visual symptoms and headaches, and which method, bariatric surgery or a dietary weight loss programme, is a viable method of achieving this.

Bariatric surgery is an approach to sustainable significant weight loss, and so may offer long-term treatment of IIH. Participants will receive a range of bariatric surgeries which will broadly reflect current practice in the NHS and will be chosen by participant and surgeon to best suit their preferences and any co-morbidities. This range of procedures has been chosen so that results will be as generalizable as possible to patients in the NHS rather than dependent on one procedure type. Different procedures result in different mean weight loss, but all 3 procedures in use in this trial should result in sufficient weight loss to be disease modifying according to our weight loss study.[15] Different metabolic effects from different procedures may additionally result in disease modification; this will be detected through the analysis of biomarkers from both blood and CSF samples and we will check for heterogeneity in outcomes between the 3 bariatric procedures included in the trial.

Bariatric surgery is an invasive approach to weight reduction and a significant change from the current accepted treatment for IIH. As it is not established how much weight loss is necessary to treat IIH, conservative weight management with dietary interventions may also offer long-term treatment. To impact current clinical practice, we will compare bariatric surgery to an alternative

weight loss regime (rather than current practice). The comparator arm will be a dietary weight loss programme using the internationally recognised Weight Watchers diet programme.

Weight Watchers is a widely available commercial weight loss programme, achieving superior weight loss and attendance compared to other commercially available (such as Slimming World or Rosemary Conley) or primary care-led weight loss programmes.[36] Participants in Weight Watchers receive group support, access to online tools, and resources and advice on healthy eating. In one study, participants in Weight Watchers lost on average 4.4kg 3 months after joining the programme.[36]

Participants in the IIH:WT trial will be randomised between referral to bariatric surgery or to a dietary weight loss programme (Weight Watchers) for 12 months.

METHODS

Design

IIH:WT trial is a multi-centre randomised controlled parallel arm clinical trial of 64 participants with active IIH and a BMI over 35 kg/m^2. Participants will be randomised in a 1:1 ratio to either bariatric surgery or a dietary weight loss programme and followed up for 5 years.

Blinding

The trial will necessarily be open label due to the nature of the intervention; assessors of visual outcomes will be masked to randomised treatment allocation. The primary outcome, ICP, is an objective measure.

Recruitment

Patients will be identified at Neurology and Ophthalmology clinics in UK NHS Trusts between March 2014 and October 2017.

The participant pathway through the trial is shown in Figure 1.

Figure 1: Participant pathway from approach to primary endpoint

Inclusion criteria and exclusion criteria

Inclusion criteria are:

1. Female IIH patients aged between 18 and 55 years, diagnosed according to the Freidman Jacobsen criteria [37] who have active disease (papilloedema [Frisén grade ≥ 1 in at least one eye], significantly raised ICP > 25cmCSF) of over 2 months' duration and no evidence of venous sinus thrombosis (magnetic resonance or CT imaging and venography as noted at diagnosis).[38]
2. BMI >35kg/m^2.
3. Tried other appropriate non-surgical treatments to lose weight but have not been able to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months.
4. Able to give informed consent.

Exclusion criteria are:

1. Age less than 18 or older than 55 years.
2. Pregnant.

3. Significant co-morbidity, Cushing's syndrome, Addison's disease or the use of oral or injected steroid therapy.
4. Undergone optic nerve sheath fenestration.
5. Definite indication for or contraindication against surgery or dieting.
6. Have a specific medical or psychiatric contraindication for surgery, including drug misuse, eating disorder or major depression (suicidal ideation, drug overdose or psychological admission in last 12 months).
7. Previous bariatric surgery.
8. Inability to give informed consent e.g. due to cognitive impairment.

Apart from the trial treatments allocated at randomisation, other aspects of patient management (e.g. use of acetazolamide or topiramate) are at the discretion of the local doctors.

Randomisation

Participants are randomised into the trial by telephone call to the Birmingham Clinical Trials Unit. A computer-generated randomisation list with allocation of treatment stratified by acetazolamide use will be used. Stratification will not be according to topirimate as well as acetazolamide use due to the low number of participants.

Treatment arms

Intervention arm

- Participants randomised to surgery will be referred to bariatric surgery. If judged suitable according to the local screening processes, the participant will undergo Laparoscopic Adjustable Gastric Banding (LAGB), Roux-en-Y Gastric Bypass (RYGBP), or Laparoscopic Sleeve Gastrectomy (LSG). This will take approximately 4 months from randomisation to surgery. The choice of surgery will be made between surgeon and participant based upon the participant's health and preference, and standard NHS follow-up will be included.

Active control arm

- Participants randomised to the dietary weight loss programme will be given vouchers allowing access to weekly meetings at their local Weight Watchers group and Weight Watchers online and mobile tools for 12 months.

FOLLOW-UP AND OUTCOME MEASURES

Primary Outcome Measure

- ICP at 12 months.

Secondary Outcome Measures

- ICP at 24 and 60 months.
- Reported IIH symptoms (pulsatile tinnitus, visual loss, diplopia, visual obscurations).
- Visual function (LogMAR chart to assess visual acuity, Humphrey Visual Fields 24-2, MARS charts to assess contrast sensitivity, Ishihara colour vision).
- Papilloedema (measured by spectral optical coherence tomography and fundus photography).
- Headache associated disability (headache diary, Headache Impact Test-6 score (HIT-6)).
- Anthropometric measures (BMI, waist/hip ratio, fat mass, blood pressure).
- Quality of life and wellbeing (EQ-5D-5L, ICECAP-A, SF-36, Hospital Anxiety and Depression score).

- Difference in number of referrals to CSF shunting and optic nerve sheath fenestration procedures between treatment arms.
- Change in Quality-Adjusted Life Years and/or Capability Wellbeing; offset against cost of treatment.

All outcomes will be measured at 12, 24 and 60 months.

Exploratory objectives

Participants with IIH and 20 matched obese control participants will give samples of blood (36mls) and CSF (10mls) at baseline and 12, 24 and 60 months for fasting metabolic evaluation, evaluation of polycystic ovary syndrome status, and exploratory analysis including biomarkers such as fasting insulin.

Some participants, including the 20 matched obese controls, will participate in sub-studies looking at the aetiology of IIH and the relationship between IIH and other obesity co-morbidities, from which they may suffer. The sub-studies include a sleep apnoea observational sub-study, a cognitive function sub-study, a magnetic resonance imaging sub-study, and a metabolic syndrome sub-study. Patients will be assessed at baseline (to evaluate the presence of co-morbidities in our patient population and for comparison to the matched obese control patients) and at 12 months (to evaluate possible changes due to weight loss). These sub-studies will not be carried out at all sites and are not discussed in further detail in this paper. The control participants will undergo the same baseline assessment as randomised participants and then exit the study.

Format of assessment visits

When initially approached, participants will be asked to consent to a pre-screening assessment. This will consist of having their papilloedema assessed and graded according to the modified Frisén criteria. If papilloedema are present the participant will be asked to return for a screening visit. In the 7 days before the screening visit, the participant will complete a headache diary recording severity and frequency of headache, as well as analgesic use.

Participants will then have a screening assessment (0 months) which will be carried out according to Figure 2 and is described below.

Informed consent will first be taken and a urine pregnancy test carried out. Then the participant will undergo a series of visual assessments. If any of these assessments have been carried out in the 30 days prior to the screening visit as part of routine care then they will not be repeated, but the results taken from patient notes provided they have been performed as per trial protocol.

The visual assessments will be recorded in both eyes and these include:

- Best corrected visual acuity will be measured using LogMAR (log of the minimum angle of resolution) charts;
- Best corrected contrast sensitivity will be measured using MARs charts;
- Colour vision will be assessed using the Ishihara pseudo-isochromatic plates;
- Automated perimetry with a Humphrey Visual Field (HVF) Analyzer using the SITA Standard 24-2 program. Where there is a high false positive rate the HVF will be repeated prior to LP;
- Optical Coherence Tomography (Heidelberg Spectralis Spectral Domain OCT) will be acquired to record measurements including retinal nerve fibre layer. OCT scans will be sent for masked review by designated specialist readers;

- Digital colour fundus photographs will be taken, centred on the optic disc with focus on the anterior surface of the swollen nerve head. These will be graded by masked reviewers.

After visual assessments are complete an LP will be performed. LP will be performed with the participant breathing steadily in the lateral position; legs flexed 90^{o} at the hip, with adequate time taken to ensure a stable reading. ICP will be recorded in cmCSF. Where required, LP will be performed with image guidance.

The LP will be carried out after all visual assessments as the LP temporarily lowers ICP and so potentially alters visual measurements. In all cases the LP will be done on the day of randomisation as ICP is the primary outcome.

Further assessment of headache will use the HIT-6,[39] an assessment of the impact of headache over the previous month. Headache preventative use (e.g. topirimate) and use of acetazolamide/diuretics will be recorded.

The participant will complete quality of life questionnaires (QoL) following the LP. These include the generic health-related QoL questionnaires EQ-5D-5L (EuroQol five dimensions questionnaire), SF-36 Version 1 (RAND 36-Item Short Form Survey) and ICECAP-A (ICEpop CAPability measure for Adults), and the Hospital Anxiety and Depression score.

If the participant has ICP >25cmCSF, they will be randomised and the data collected at the pre-screening and screening visits will be used for baseline data.

Participants will then be evaluated at 3, 6, 12, 24 and 60 months as shown in Table 1. Participants randomised to surgery will also be evaluated at approximately 2 weeks post-surgery for an LP assessment of ICP.

Figure 2: format of baseline assessment visits

Figure 2 legend:
The format of the baseline visit is shown. HVF indicates Humphrey Visual Field; OCT is Optical Coherence Tomography; and ICP is Intracranial Pressure.

Table 1: Outcome measures and assessments

Outcome	Measure	Baseline	3 months	6 months	Post-op	(Primary endpoint) 12 months	24 months	60 months
ICP	Lumbar puncture	x			x	x	x	x
Clinical measures	BMI, BP, waist/hip, fat mass, medication use	x	x	x	x	x	x	x
IIH symptoms	Pulsatile tinnitus, visual loss, diplopia, visual obscurations	x				x	x	x
Visual function	Visual acuity, contrast sensitivity, colour assessment	x				x	x	x
	Humphrey visual field (24-2)	x				x	x	x
Papilloedema	Optical coherence tomography	x				x	x	x

	Retinal photographs	x				x	x	x
Headache	HIT-6, headache diary	x				x	x	x
Quality of Life	EQ-5D-5L, ICECAP-A, SF-36 v1, HADS	x				x	x	x
Health Economics	Resource use questionnaire	x				x	x	x

ANALYSIS

Sample size

Total n=64. 32 participants in each arm (bariatric surgery versus dietary weight loss programme).

For this trial we hypothesise that the greater weight loss anticipated in the bariatric surgery arm compared to the dietary arm will consequently reduce the ICP further in the bariatric arm than in the dietary arm. A weight loss of 15.3% ± 7.0% of body weight over 3 months was achieved by patients following a low calorie diet.[15] Data from this study showed that ICP was significantly reduced by 20% (ICP at baseline in 20 IIH patients was 39.8 ± 5.1 cmCSF and ICP was reduced by 8 ± 4.2 cmCSF, p<0.001).

Assuming a conservative change of ICP in the bariatric surgery arm to that previously observed of 8cmCSF and a change of 3cmCSF in the dietary arm (to reflect changes slightly greater than the baseline fluctuations seen in our previous study), then we wish to detect a mean difference of 5cmCSF between the groups. To detect this difference of 5cmCSF with 90% power and alpha=0.05 using a 2-sided t-test (assuming a standard deviation of 5.1)[15] requires 46 patients (23 per arm). Allowing for a 28% drop out rate will require 32 patients per arm.

We believe that the SD of 5.1 is a true reflection of the variability of the data as this is taken from the baseline measurements from our previous study, in a similar population.[15] This assumption for the sample size calculation will be monitored during the trial.

Projected accrual and attrition rates

Recruitment for our previous study with very similar inclusion criteria was at a rate of 1.5 participants per month;[15] we consequently feel that the recruitment target of 1.4 participants per month (64 participants over 45 months) is realistic and achievable. Attrition rates for this treatment and patient group is not known; we have allowed a 28% rate of drop out. Attrition will be monitored by the Trial Management Group and by the oversight committees and we will attempt to improve participant engagement through participant newsletters, participant compensation, patient support days, and engagement with the IIH UK patient charity.

Statistical Analysis

The primary comparison groups will be composed of those randomised to the bariatric surgery arm and those randomised to the dietary weight loss arm. Analyses will be based on the intention to treat principle, i.e. all patients will be analysed in the treatment group to which they were randomised irrespective of compliance with the randomised allocated treatment or other protocol violations. Summary statistics and differences between groups (e.g. mean differences, relative risks) will be reported, with 95% confidence intervals and p-values from two-sided tests given. Outcomes will be adjusted for the stratification variable (acetazolamide use at entry). For all analyses, a p-value <0.05 will be considered statistically significant and there will be no adjustment for multiple testing.

Primary Outcome Analysis

The primary outcome will assess the ICP at 12 months. The ICP at 12 months for the two study arms will be compared using a linear regression model with baseline ICP and acetazolamide use at entry (stratification variable) included as covariates in the model.

Secondary Outcome Analyses

Secondary outcome measures include a mixture of continuous and categorical data items. Continuous outcomes (e.g. quality of life) will be analysed as per the primary outcome measure. Categorical outcomes (e.g. presence or absence of symptoms, number of CSF shunting referrals) will be expressed as the number and percentage of patients experiencing these outcomes in the two groups. Log-binomial models will be used to compare the data between the two study arms, with baseline data (where available, i.e. baseline symptom data) and acetazolamide use at entry (stratification variable) included in the model as covariates.

Health economic outcomes

The following analyses will assess the cost-effectiveness of bariatric surgery versus diet for IIH:

1. Cost-effectiveness analysis - ICP measured at baseline and 12 months will be evaluated in terms of cost to reduce ICP by 12.5%.
2. Cost-utility analysis – quality of life and wellbeing information from the EQ-5D-5L and ICECAP-A questionnaires at baseline and 12 months; cost-effectiveness will be expressed as 'cost per QALY gained' and 'cost per sufficient and full capability achieved'.
3. Cost-benefit analysis – monetary outcomes will be elicited using the 'Willingness to Pay' method asked at baseline and at 12 months. Results will be expressed as a cost-benefit ratio and net-present value.

MONITORING

Safety reporting

There are no novel medical devices or Investigational Medicinal Products used as part of this trial. Any Serious Adverse Events (SAEs) including surgical mortality and complications will be reported on a trial-specific SAE form, evaluated by the Chief Investigator, and where required reported to sponsor and ethics committee.

Independent Trial Steering Committee (TSC)

A TSC will provide oversight of the study. The independent members are a consultant neurologist and neuro-ophthalmologist as chair, a consultant bariatric surgeon as independent expert, an independent statistician, and a patient representative.

Data Monitoring Committee (DMC)

A DMC will independently monitor the efficacy and safety data at least annually. The members are a consultant ophthalmologist as chair, a consultant bariatric surgeon as independent expert, and an independent statistician.

Compliance monitoring

Data on compliance in the bariatric surgery arm will be collected from local surgery teams. Compliance will be considered as undergoing bariatric surgery. Reasons for non-compliance will be recorded.

Data on attendance to Weight Watchers for participants in the dietary arm will be self-reported and given in terms of percentage of sessions attended. It is not expected that participants will

attend every session (30% of participants attended less than 50% of sessions over 12 weeks in one trial [36] and we expect a lower attendance rate over 12 months).

ETHICS AND DISSEMINATION

National Research Ethics Committee West Midlands – The Black Country approved IIH:WT on 28th February 2014 (14/WM/0011).

The trial will be conducted according to the standards of the International Conference on Harmonisation-Good Clinical Practice (GCP) and the Research Governance Framework for Health and Social Care. Written informed consent will be provided by all patients prior to any trial-related procedures. Participants will be free to withdraw from the trial at any time without any effect on their standard of care.

Results will be disseminated through internal reports, relevant conferences, peer-reviewed scientific journals and on-line publications.

ACKNOWLEDGEMENTS

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We gratefully acknowledge the Birmingham Clinical Trials Unit for trial coordination, data management, and analysis, and the Research Governance team at the University of Birmingham for research governance and Sponsor duties. We acknowledge the support of the National Institute of Health Research Clinical Research Network (NIHR CRN), and the National Institute of Health Research / Wellcome Trust Clinical Research Facility.

AUTHORS' CONTRIBUTIONS

AS, EF, NI, RO, CR and RW conceptualised and designed the trial, helped with statistics for the trial, and helped writing the manuscript.
AS, JM, SM, TM and RS are recruiting participants to the trial.
HB, JM, SM, TM and RS provided critical input into trial design and helped writing the manuscript.

All authors inputted to the writing of the paper.

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The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

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CONFLICT OF INTEREST STATEMENT

None declared.

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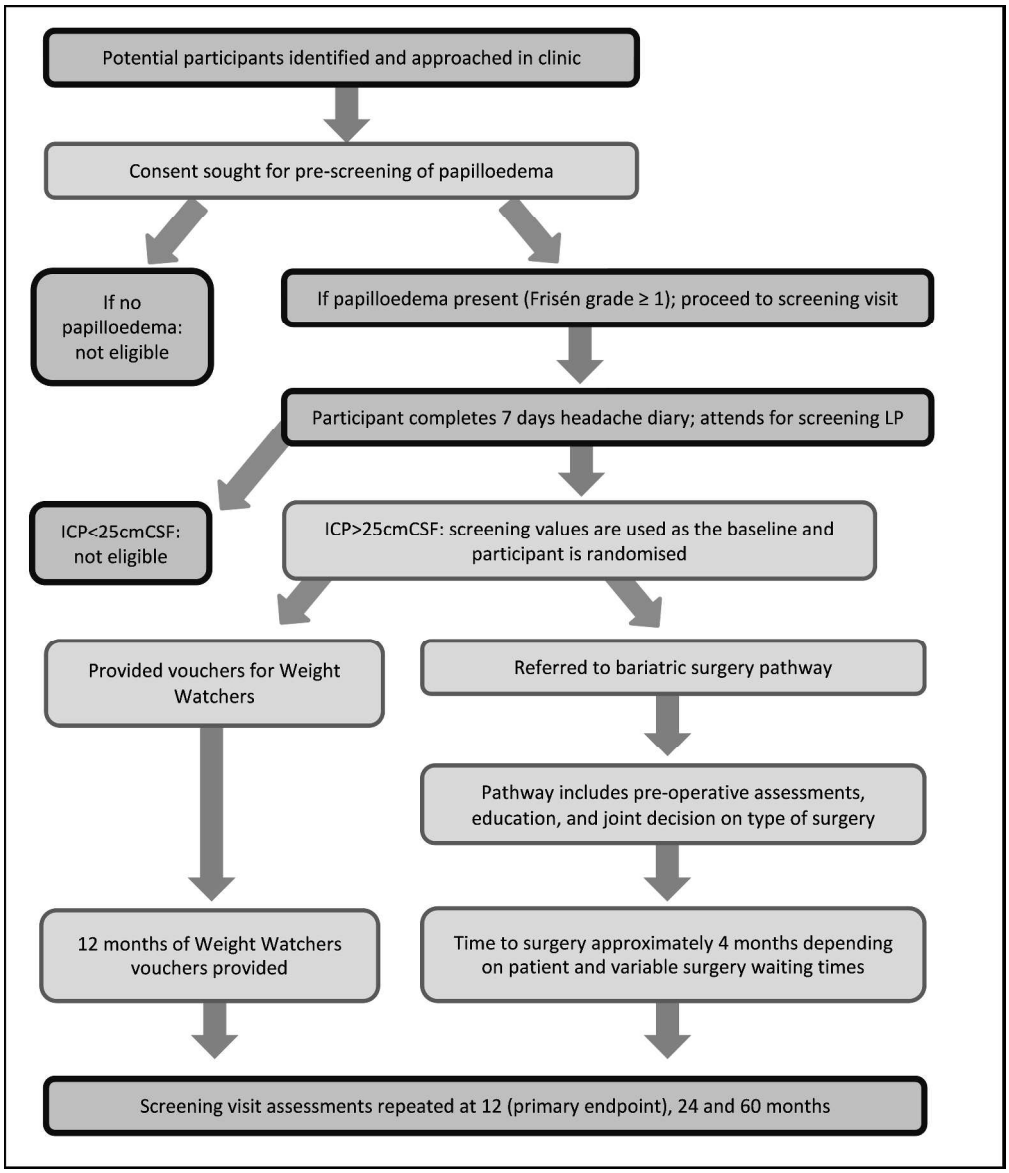

Figure 1: Participant pathway from approach to primary endpoint

339x394mm (300 x 300 DPI)

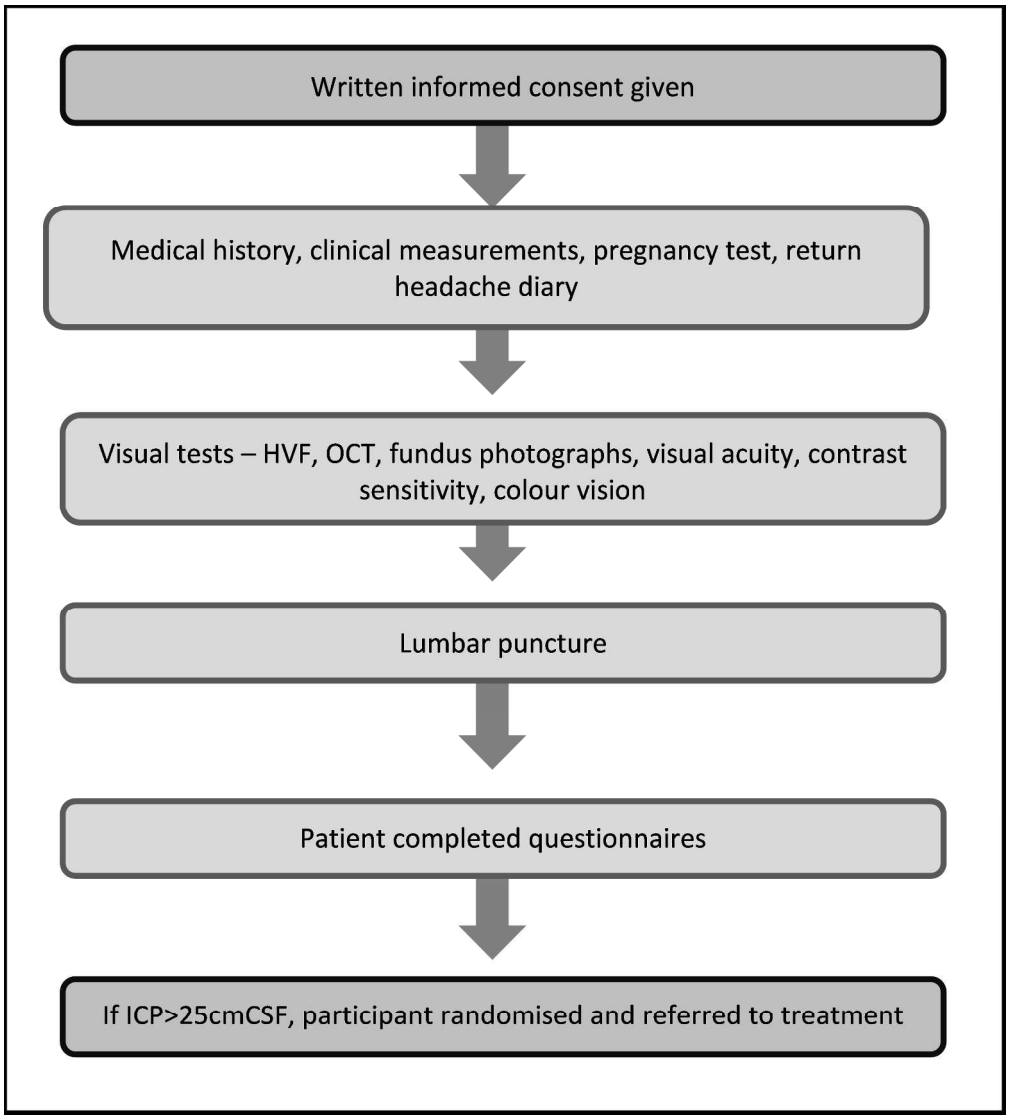

Figure 2: Format of baseline assessment visits

238x264mm (300 x 300 DPI)

TO BE PRINTED ON LOCAL TRUST HEADED PAPER

IIH:WT Trial No.:

☐☐☐☐☐

CONSENT FORM – Part 2. Full trial consent.

The IIH Weight Trial

		Please initial box to confirm consent
1.	I have read and understood the information sheet for the IIH Weight trial (version 2.0 dated 2nd February 2016). I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	
2.	I understand that my participation in this trial is voluntary and if I take part I am free to withdraw at any time without giving a reason, and without my medical care or legal rights being affected.	
3.	I understand that information about my progress will be supplied in confidence to the trial coordinators outside of this NHS trust at the Birmingham Clinical Trials Unit (BCTU) by my own doctors for use in the IIH Weight trial.	
4.	I understand that relevant sections of any of my medical notes may be looked at in confidence by responsible individuals from BCTU, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research and to check that the trial is being carried out correctly. I give permission for these individuals to have access to my records.	
5.	I give permission for my initials, date of birth and hospital number to be given to BCTU when I am randomised to the trial.	
6.	I agree to take part in the IIH Weight trial.	
7.	I agree to my samples and tissues, along with associated clinical data, being taken, stored and used for analysis of biomarkers and in polymorphism (genetic) studies to look for potential risk factors for Idiopathic Intracranial Hypertension both as part of this trial and in future related studies. Future studies on these samples outside of this trial would require Research Ethics Committee approval. I agree to these samples being moved outside of this NHS trust and stored at the University of Birmingham.	
8.	I agree that a copy of this consent form will be sent to the BCTU.	
Additional consent:		
9.	I agree to my GP being informed of my participation in the IIH Weight trial.	
10.	I agree that any unused samples and tissues obtained from this trial can be donated to an Idiopathic Intracranial Hypertension Biobank for future research.	

Name of Participant	Date (dd/mmm/yyyy)	Signature

Name of Researcher	Date (dd/mmm/yyyy)	Signature

One copy to be kept in the IIH:WT trial site file, one for the patient, one kept with patient's notes, one to BCTU.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – page 2
	2b	All items from the World Health Organization Trial Registration Data Set – trial is registered, see 2a
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support – page 11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – page 1
	5b	Name and contact information for the trial sponsor – page 10
	5c	Role of study sponsor – page 10 and funders – page 11, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre , steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – page 10
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – page 3-4
	6b	Explanation for choice of comparators – page 4
Objectives	7	Specific objectives or hypotheses – page 4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – page 4
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – page 5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – page 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – page 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request – page 10, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – page 5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – page 6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – page 6-7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – page 9
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – page 5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – page 5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – page 5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – page 5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – n/a
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – page 5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – page 9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – see protocol; link in paper
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – page 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – page 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – page 9

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed – page 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – see protocol; link in paper
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – this information is held in the monitoring plan, an in-house BCTU document

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – page 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – see protocol; link in paper
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – see protocol; link in paper
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – see protocol; link in paper
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – see protocol (link in paper) and in-house BCTU data management plan
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – page 11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – this is covered in the clinical trial site agreements between sites and sponsor

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – see protocol; link in paper
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – page 10
	31b	Authorship eligibility guidelines and any intended use of professional writers – no professional writers intended
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – protocol is publicly available on BCTU trial website
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – n/a?
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – see protocol; link in paper

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.