

BMJ Open 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

Ryan Ottridge,¹ Susan P Mollan,² Hannah Botfield,³ Emma Frew,⁴ Natalie J Ives,¹ Tim Matthews,² James Mitchell,^{3,5} Caroline Rick,¹ Rishi Singhal,⁶ Rebecca Woolley,¹ Alexandra J Sinclair^{3,5}

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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 primarily in obese women. Weight loss and lowering body mass index (BMI) have been shown to lower ICP and improve symptoms in IIH; however, weight loss is typically not maintained, meaning IIH symptoms return. The Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) will assess whether bariatric surgery is an effective long-term treatment for patients with IIH with a BMI over 35 kg/m². The National Institute for Health and Care Excellence recommends bariatric surgery in people with a BMI over 35 kg/m² and a qualifying comorbidity; currently IIH does not qualify as a comorbidity.

Methods and analysis IIH:WT is a multicentre, open-label, randomised controlled clinical trial of 64 participants with active IIH and a BMI over 35 kg/m². 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, and IIH symptoms, visual function, papilloedema, headache, quality of life and cost-effectiveness at 12, 24 and 60 months.

Trial registration number IIH:WT is registered as ISRCTN40152829 and on ClinicalTrials.gov as NCT02124486 and is in the pre-results stage.

INTRODUCTION

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH), also known as benign intracranial hypertension or pseudotumour cerebri, is a condition of unknown aetiology characterised by raised intracranial pressure (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

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 were 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 Care Excellence guidelines for bariatric surgery; however, the benefits of weight loss may be relevant to those with a lower BMI.

range from medical therapies to surgical procedures that offer symptomatic relief and prevent blindness.³ The overall age-adjusted 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 IIH³; hence, there is no clear guidance regarding standardised management.



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For numbered affiliations see end of article.

Correspondence to

Dr Alexandra J Sinclair;
a.b.sinclair@bham.ac.uk

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 are 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 2.89 kg)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*²¹ give a mean reduction in body mass index (BMI) of 7.05–15.34 m/kg² at 12 months using the three procedures in use in this trial.
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 with 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

The National Institute for Health and Care Excellence recommends bariatric surgery for people with a BMI over 40 kg/m² or in people with a BMI of over 35 kg/m² and a significant comorbidity (e.g. type 2 diabetes) that may be improved with weight loss.³⁴ IIH is not one of the listed comorbidities, and patients with IIH do not often have alternative comorbidities 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 are 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 to 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 that will broadly reflect current practice in the National Health Service (NHS) and will be chosen by participant and surgeon to best suit their preferences and any comorbidities. This range of procedures has been chosen so that results will be as generalisable as possible to patients in the NHS rather than dependent on one procedure type. Different procedures result in different mean weight loss, but all three 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 three 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 with an alternative weight loss regimen (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 with 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 4.4 kg 3 months after joining the programme.³⁶

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

METHODS

Design

IIH:WT is a multicentre, randomised controlled, parallel-arm, clinical trial of 64 participants with active IIH and a BMI over 35 kg/m². 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.

Inclusion criteria and exclusion criteria

The following are the inclusion criteria:

1. female patients with IIH aged between 18 and 55 years, diagnosed according to the Friedman Jacobson criteria,³⁷ who have active disease (papilloedema (Frisén grade ≥ 1 in at least one eye), significantly raised ICP >25 cmCSF) of over 2 months' duration and no evidence of venous sinus thrombosis (MRI or CT and venography as noted at diagnosis)³⁸
2. BMI >35 kg/m²
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.

The following are the exclusion criteria:

1. age less than 18 or older than 55 years
2. pregnant

3. significant comorbidity, Cushing's syndrome, Addison's disease or the use of oral or injected steroid therapy
4. undergone ONSF
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 the last 12 months)
7. previous bariatric surgery
8. inability to give informed consent, for example, 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 topiramate 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, Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. This will take approximately 4 months from randomisation to surgery. The choice of surgery will be made between the surgeon and the participant based on 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 (HVF) 24-2, Mars charts to assess contrast sensitivity, Ishihara colour vision)
- papilloedema (measured by spectral optical coherence tomography and fundus photography)

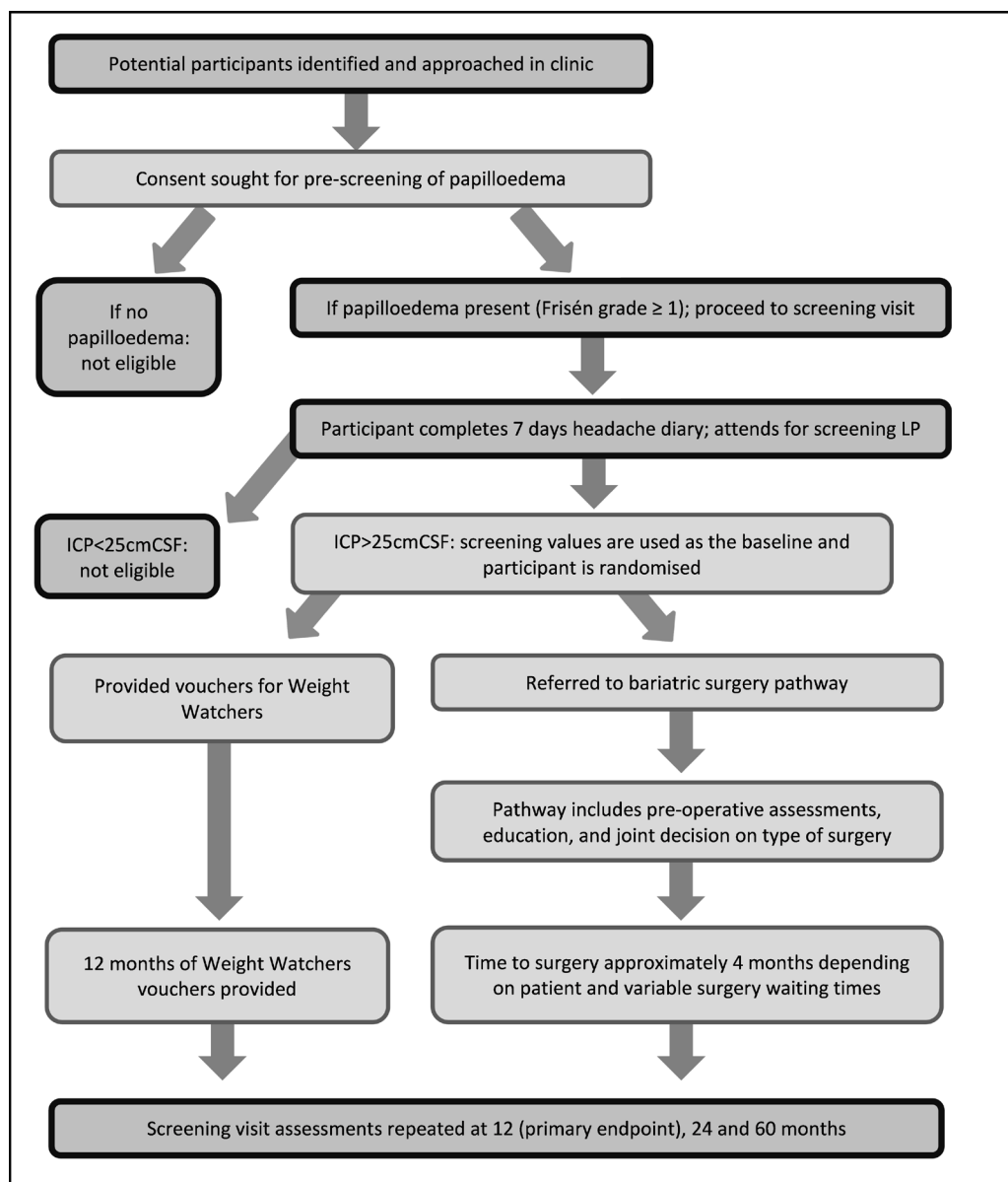


Figure 1 Participant pathway from approach to primary endpoint. ICP, intracranial pressure; LP, lumbar puncture.

- ▶ 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 well-being (EuroQol 5 Dimensions (EQ-5D-5L) questionnaire, ICEpop CAPability measure for Adults (ICECAP-A), RAND 36-Item Short Form Survey (SF-36), Hospital Anxiety and Depression score)
- ▶ difference in number of referrals to CSF shunting and ONSF procedures between treatment arms
- ▶ change in quality-adjusted life years and/or capability well-being; 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 (36 mL) and

CSF (10 mL) 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 substudies looking at the aetiology of IIH and the relationship between IIH and other obesity comorbidities, from which they may suffer. The substudies include a sleep apnoea observational substudy, a cognitive function substudy, an MRI substudy and a metabolic syndrome substudy. Patients will be assessed at baseline (to evaluate the presence of comorbidities 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 substudies will not be carried out at all sites and are not discussed in further detail in this paper. The control participants will undergo the

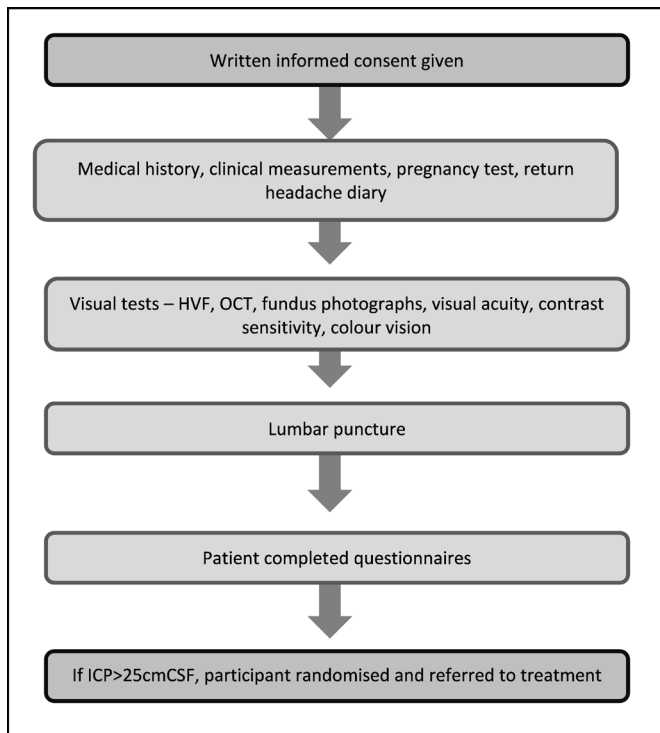


Figure 2 The format of the baseline visit is shown. HVF, Humphrey visual field; ICP, intracranial pressure; OCT, optical coherence tomography.

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 prescreening assessment. This will consist of having their papilloedema assessed and graded according to the modified Frisén criteria. If papilloedema is 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 the following:

- ▶ 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 an HVF analyser using the SITA (Swedish Interactive Thresholding Algorithm) 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 optical coherence tomography (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° 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 (eg, topiramate) 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, SF-36 Version 1 and ICECAP-A, and the Hospital Anxiety and Depression score.

If participants have ICP > 25 cmCSF, they will be randomised, and the data collected at the prescreening 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 postsurgery for an LP assessment of ICP.

Analysis

Sample size

The sample size is 64 with 32 participants in each arm (bariatric surgery vs dietary weight loss programme).

For this trial we hypothesise that the greater weight loss anticipated in the bariatric surgery arm compared with 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 patients with IIH 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 8 cmCSF and a change of 3 cmCSF in the dietary arm (to reflect changes

Table 1 Outcome measures and assessments

Outcome	Measure	Baseline	3 months	6 months	Postoperative	12 months (primary endpoint)	24 months	60 months
ICP	Lumbar puncture	x			x	x	x	x
Clinical measures	BMI, blood pressure, 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

BMI, body mass index; EQ-5D-5L, EuroQol 5 Dimensions questionnaire; HADS, Hospital Anxiety and Depression Scale; HIT-6, Headache Impact Test-6; ICECAP-A, ICEpop CAPability measure for Adults; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension; SF-36 v1, RAND 36-Item Short Form Survey Version 1.

slightly greater than the baseline fluctuations seen in our previous study), we wish to detect a mean difference of 5 cmCSF between the groups. To detect this difference of 5 cmCSF with 90% power and $\alpha=0.05$ using a two-sided t-test (assuming an SD of 5.1)¹⁵ requires 46 patients (23 per arm). Allowing for a 28% dropout 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 month¹⁵; 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 are not known; we have allowed a 28% rate of dropout. 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, that is, 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 (eg, mean differences, relative risks) will be reported, with 95% CIs 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 (eg, quality of life) will be analysed as per the primary outcome measure. Categorical outcomes (eg, 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 well-being 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

A Trial Steering Committee 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

A Data Monitoring Committee 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 trial³⁶ and we expect a lower attendance rate over 12 months).

Ethics and dissemination

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

The trial will be conducted according to the standards of the International Conference on Harmonisation-Good Clinical Practice 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 online publications.

Author affiliations

¹Birmingham Clinical Trials Unit, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

²Birmingham Neuro-Ophthalmology Unit, University Hospitals Birmingham, Queen Elizabeth Hospital, Birmingham, UK

³Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

⁴Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

⁵Department of Neurology, University Hospitals Birmingham, Queen Elizabeth Hospital, Birmingham, UK

⁶Upper GI and Minimally Invasive Unit, Heartlands Hospital, Birmingham, UK

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Contributors AJS, EF, NJI, RO, CR and RW conceptualised and designed the trial, helped with statistics for the trial, and helped in writing the manuscript. AJS, JM, SPM, TM and RS are recruiting participants to the trial. HB, JM, SPM, TM and RS provided critical input into trial design and helped in writing the manuscript. All authors inputted to the writing of the paper.

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Competing interests None declared.

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