

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Ottridge, Ryan; Mollan, Susan; Botfield, Hannah; Frew, Emma; Ives, Natalie; Matthews, Tim; Mitchell, James; Rick, Caroline; Singhal, Rishi; Woolley, Rebecca; Sinclair, AJ

VERSION 1 - REVIEW

REVIEWER	Arani Nitkunan St George's University Hospital and Croydon University Hospital, London United Kingdom
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	<p>This is a much needed randomised controlled trial in the field of idiopathic intracranial hypertension. The authors have conducted a pragmatic study with clear outcome measures which are clinically relevant. I have a few minor comments:</p> <ol style="list-style-type: none">1. Venous stenting is considered one of the possible treatment options (despite the lack of randomised controlled studies) and this has not been mentioned at all in this paper. I would suggest that for completeness it is included especially as a trial is due to start in USA shortly I understand.2. Under "Format of assessments", "legs extended 90degrees at the hip" should be "legs flexed 90degrees at the hip".3. Attrition rate - I note that there is minimal natural history prospective data on this group of patients. However as majority of the patients get better, it would be useful to know what systems the authors have put in place to keep the attrition rate to the minimum.
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REVIEWER	Mr Rory Piper Department of Neurosurgery University of Cambridge Addenbrooke's Hospital, Cambridge, UK
REVIEW RETURNED	29-May-2017

GENERAL COMMENTS	I have read with interest this trial protocol - a multi-centre, open-label, randomised controlled trial of bariatric surgery versus weight watchers.
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	<p>This is an interesting and worthwhile trial that has the potential to give high quality guidance on the best management of obese IIH patients.</p> <p>I have some minor comments:</p> <ul style="list-style-type: none"> - I do not like the use of the word 'almost exclusive' in the intro and abstract - 90% is certainly not exclusive. 1/10 is a quite a big number if you work in a busy neurological centre. - how is the trial going to deal with and report those patients taking also topirimate or acetazolamide? - for those of us who are not general surgeons, please explain why patients will receive difference bariatric surgeries - how might this impact the results? - how is the trial going to measure adherence to the weight watchers programme? - are the authors going to follow up and report surgical mortality and complications? - 'sample of blood' - please elaborate <p>Our hands are tied and not able to make protocol changes since the trial has already started, but this manuscript would be a useful contribution for IIH researchers prior to the full trial results.</p>
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<p>REVIEWER</p>	<p>G D Tan Oxford Centre for Diabetes, Endocrinology & Metabolism Oxford NIHR Biomedical Research Centre Churchill Hospital Oxford OX3 7LE</p> <p>Not sure if this counts as a competing interest. I did email and ask; I was told to add it to the competing interests section.</p> <p>1. approached to act as recruitment centre for this study. Did not participate.</p> <p>2. GDT receives funding from the NIHR Biomedical Research Centre, Oxford (and the views herein do not reflect the views of the NIHR or the NHS).</p>
<p>REVIEW RETURNED</p>	<p>Ottridge et al have described a randomised controlled study to assess whether bariatric surgery is better than a community weight loss programme (Weight Watchers) in the treatment of idiopathic intracranial hypertension (IIH).</p> <p>The study attempts to answer an important and clinically relevant question, especially given the limited therapeutic options for this condition. It is well designed and timely.</p> <p>Page 3: Although the primary outcome measure is intracranial pressure at 12 months, the study is to be applauded for its long term follow up plan (5 years). The authors describe the community intervention's impact on weight loss, describing the 12 month and 5 year results (page 3). It would be helpful to quote similar figures for average weight loss associated with bariatric surgery at 12 months and at 5 years.</p> <p>Page 4: Is there any reason that reference 29 has not been included as a</p>

	<p>reference source in the mortality rate? Reference 29 highlights the variability in mortality rates depending on the complexity of the patient pre-operatively (such as sleep apnoea, functional status etc), describing how mortality can rise as high as 2%.</p> <p>However, in the next paragraph, the Ottridge et al write “..IIH patients do not often have alternative co-morbidities”. Of course, one of the consequences of this is that the mortality risk is likely to be low given that patients with co-morbidities have a higher mortality rate.</p> <p>Page 6: On page 6, the protocol acknowledges the different bariatric surgery operations available. I presume that the reason for not limiting the study to a specific operation is that there is an expectation that any benefit to IIH would be driven solely by weight loss. However, different operations do have different metabolic effects – for example, the pace of diabetes resolution is very different between LAGB and RYBG surgery. The authors may consider explaining the rationale for (and potential limitations of) “lumping” the outcomes of different surgical options together under the title “bariatric surgery”. Of course, the study would not be designed (or powered) to differentiate between the efficacy of different surgical procedures and their effect on ICP. However, can the authors confirm that there will be a check for any heterogeneity in outcome between different operations?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Arani Nitkunan

Institution and Country: St George's University Hospital and Croydon University Hospital, London, United Kingdom

1. Venous stenting is considered one of the possible treatment options (despite the lack of randomised controlled studies) and this has not been mentioned at all in this paper. I would suggest that for completeness it is included especially as a trial is due to start in USA shortly I understand.
 - a. Detail added, p3
2. Under "Format of assessments", "legs extended 90degrees at the hip" should be "legs flexed 90degrees at the hip".
 - a. Amended, p7
3. Attrition rate - I note that there is minimal natural history prospective data on this group of patients. However as majority of the patients get better, it would be useful to know what systems the authors have put in place to keep the attrition rate to the minimum.
 - a. Details added, p9

Reviewer: 2

Reviewer Name: Mr Rory Piper

Institution and Country: Department of Neurosurgery, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

I have some minor comments:

1. I do not like the use of the word 'almost exclusive' in the intro and abstract - 90% is certainly not

exclusive. 1/10 is a quite a big number if you work in a busy neurological centre.

a. Amended to “primarily”, p2 and p3

1. How is the trial going to deal with and report those patients taking also topiramate or acetazolamide?

a. Arms will be stratified according to acetazolamide use; medication use will be reported for topiramate and acetazolamide (and others). Due to the low number of patients, stratification could not be done for both drugs. Patient treatment using these drugs is at the discretion of local doctors and recorded at follow up visits at 0,3,6,12,24 and 60 months.

I have added details to p5, p6, p7, p8

2. For those of us who are not general surgeons, please explain why patients will receive difference bariatric surgeries - how might this impact the results?

a. 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/health/co-morbidities. This has been chosen so that results will be as generalizable as possible to patients in the NHS. 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. 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. We will check for heterogeneity in outcomes between the 3 bariatric procedures included in the trial

Detail as above added, p4.

3. How is the trial going to measure adherence to the weight watchers programme?

a. This will be patient reported and given as sessions attended. Amended, p10

4. Are the authors going to follow up and report surgical mortality and complications?

a. Yes. I have amended to make this explicit on p10

5. 'sample of blood' - please elaborate

a. Details given on p7

Reviewer: 3

Reviewer Name: G D Tan

Institution and Country: Oxford Centre for Diabetes, Endocrinology & Metabolism, Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE

1. Page 3:

Although the primary outcome measure is intracranial pressure at 12 months, the study is to be applauded for its long term follow up plan (5 years). The authors describe the community intervention's impact on weight loss, describing the 12 month and 5 year results (page 3). It would be helpful to quote similar figures for average weight loss associated with bariatric surgery at 12 months and at 5 years.

a. I have added the best details I can find on p4 – not exact comparison, but gives an idea of superior maintenance of weight loss at 12/24/60m. Long term follow up data for bariatric surgery is not as good as 12/24 months.

2. Page 4:

Is there any reason that reference 29 has not been included as a reference source in the mortality rate? Reference 29 [NB: Arterburn, now reference 30] highlights the variability in mortality rates depending on the complexity of the patient pre-operatively (such as sleep apnoea, functional status etc), describing how mortality can rise as high as 2%.

However, in the next paragraph, the Ottridge et al write “..IIH patients do not often have alternative co-morbidities”. Of course, one of the consequences of this is that the mortality risk is likely to be low given that patients with co-morbidities have a higher mortality rate.

a. I believe the mortality references were based on discussion with our lead surgeon and taking into account our typical trial patients. I have amended with extra detail on p4.

3. Page 6:

On page 6, the protocol acknowledges the different bariatric surgery operations available. I presume that the reason for not limiting the study to a specific operation is that there is an expectation that any benefit to IIH would be driven solely by weight loss. However, different operations do have different metabolic effects – for example, the pace of diabetes resolution is very different between LAGB and RYBG surgery. The authors may consider explaining the rationale for (and potential limitations of) “lumping” the outcomes of different surgical options together under the title “bariatric surgery”.

a. I have responded to this in Mr Piper’s comment 2 above and added further detail on p4.

4. Of course, the study would not be designed (or powered) to differentiate between the efficacy of different surgical procedures and their effect on ICP. However, can the authors confirm that there will be a check for any heterogeneity in outcome between different operations?

a. Yes, this will be in the statistical analysis plan and I have amended to include this detail on p4.

VERSION 2 – REVIEW

REVIEWER	Arani Nitkunan St George's University Hospital and Croydon University Hospital, London. UK
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	The authors have adequately responded to my queries.
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REVIEWER	Mr. Rory J. Piper Department of Neurosurgery Addenbrooke's Hospital Cambridge, UK
REVIEW RETURNED	20-Jul-2017

GENERAL COMMENTS	Thank you for addressing my comments.
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REVIEWER	Garry Tan Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM) Oxford NIHR-BRC Oxford University Hospitals NHS Trust Churchill Hospital Oxford OX3 7LE The service was approached to recruit for this study. However, we did not participate due to reasons of timing.
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This is now suitable for publication.
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