PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised, controlled multi-centre trial of 26 weeks subcutaneous liraglutide (a Glucagon-like Peptide-1 receptor agonist), with or without continuous positive airway pressure (CPAP), in patients with Type 2 Diabetes Mellitus (T2D) and Obstructive Sleep Apnoea (OSA) (ROMANCE): Study protocol assessing the effects of weight loss on the apnea-hypnoea index (AHI)
AUTHORS	Sprung, Victoria; Kemp, Graham; Wilding, John; Adams, Valerie; Murphy, Kieran; Burgess, Malcolm; Emegbo, Stephen; Thomas, Matthew; Needham, Alexander; Weimken, Andrew; Schwab, Richard; Manuel, Ari; Craig, Sonya; Cuthbertson, Daniel

VERSION 1 – REVIEW

REVIEWER	Abd Tahrani Institute of Metabolism and Systems Research, University of Birmingham, UK
REVIEW RETURNED	09-Nov-2019

GENERAL COMMENTS	I congratulate the study team on conducting this interesting study. I have the following minor comments: 1. The abstract need to include the study design, I suggest including the randomisation and factorial design are mentioned in the abstract 2. To the limitations, I suggest that the authors add that the dose used is not the 3mg dose considering that they are relying on weight loss as the potential mechanism to improve the AHI and the 3mg dose will produce higher weight loss vs 1.8mg. 3. In the intro, it might be worth mentioning that OSA is associated with increased risk or road traffic accidents, falls, and mortality and impaired quality of life as well as microvascular complications in patients with T2D 4. Throughout the manuscript, please avoid using the terms diabetic and obese patients, please use people or patients with diabetes or with obesity. 5. Why was insulin and SGLT-2i exclusion criteria? 6. Why excessive daytime sleepiness (EDS) was an inclusion criteria? Also, while EDS is an inclusion, EDS >=14 was an exclusion. This means that study population will be compromised of a very highly selected group of patients with narrow window of ESS scores. This is fine but need to be clear from title and abstract as this will not be reflective of the wider T2D or OSA population (unless if I misunderstood the inclusion exclusion criteria)

REVIEWER	Gonzalo Labarca Universidad San Sebastian, chile
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	I would like to congrats Dr. Sprung et al for this protocol. This protocol evaluates the efficacy of liraglutide in T2DM and OSA patients, The design is adequate and both random sequence generation and allocation concealment are clearly reported. Regarding sample size, although previous studies recommended the change in ESS and a minimal clinically relevant difference of 2.0 points as a measure for sample size calculation. This study proposes the change in AHI according to previous investigation, this hypothesis should be evaluated according to study results. Finally, CPAP adherence is relevant to define the population with better results after CPAP therapy, Adherence > 4 hours should be included in a secondary analysis of these data.
REVIEWER	Sally Kerry Queen Mary Univeristy of London
REVIEW RETURNED	27-Jan-2020

GENERAL COMMENTS	This is a trial protocol. There are no dates given in the manuscript for the trial as required by this journal. On the trial registration website the trial recruitment was from 1 Sept 2015 to 1 Oct 2017. The date on the protocol is July 2017. This is 2.5 years ago. The aims of the trial in the abstract and title are unclear. This is a factorial design with the primary aim to compare liraglutide with no liraglutide with or without CPAP. But the astract says 'Twenty-six weeks of treatment with liraglutide (1.8 mg o.d.) will be given either given alone or in combination with CPAP. It is not clear there is a control group. There is no mention of feasibility in this single centre trial and it doesn't look to me as if this is feasible to recruit but I cannot see any mention of recruitment figures which must be known at this stage. The trial statistician is not an author but simply recognised in the acknowledgements. A good robust trial will require team work with the statistician who shoudl be a co author as a recognition of their contribution. The statistical methods are reasonably well described but as ITT is known to be used in different ways by different people some mre explanation about what study cohort will be used would be usefu particularly rgarding patients who fail to attend followup and so all data may be missing. I suspect the losses to followup will be greater than predicted due to the patient burden and the methods for dealing with missing data are not well described as applicable to this study. for example what additional information will be used to impute values for cases that have failed to be followed up. Without any additional information the power and confidence intervals will remain and the risk of bias will remain as well if there is poor followup

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Abd Tahrani

Institution and Country: Institute of Metabolism and Systems Research, University of Birmingham, UK

I congratulate the study team on conducting this interesting study. I have the following minor comments:
1. The abstract need to include the study design, I suggest including the randomisation and factorial design are mentioned in the abstract.

The abstract has now been amended to include more details of the study design, and specifically its 2 x 2 factorial design and the randomisation procedures (Page 2).

2. To the limitations, I suggest that the authors add that the dose used is not the 3mg dose considering that they are relying on weight loss as the potential mechanism to improve the AHI and the 3mg dose will produce higher weight loss *vs.* 1.8mg.

We have added a brief statement (in the strengths and limitations section, Page 3) to explain the rationale for electing to study the effects of liraglutide 1.8mg dosage rather than the higher 3.0mg dosage which would likely be associated with a greater magnitude of weight loss

3. In the introduction, it might be worth mentioning that OSA is associated with increased risk or road traffic accidents, falls, and mortality and impaired quality of life as well as microvascular complications in patients with T2D.

We have modified the introduction accordingly and incorporated the appropriate suppporting references (lower part of Page 3)

4. Throughout the manuscript, please avoid using the terms diabetic and obese patients, please use people or patients with diabetes or with obesity.

We have used the terms suggested throughout the manuscript and agree the language used in reference to these patients is of the utmost importance.

5. Why was insulin and SGLT-2i exclusion criteria?

Insulin and SGLT2i were included as an inclusion criteria as we wished to avoid other glucose-lowering drugs that would either promote weight loss (SGLT2 inhibitors) or weight gain (pioglitazone or insulin). DPP-IV inhibitors were contraindicated as they cannot be used in patients who take GLP1-RA. This is mentioned in the text at the bottom of page 6/top of page 7.

6. Why excessive daytime sleepiness (EDS) was an inclusion criteria? Also, while EDS is an inclusion, EDS >=14 was an exclusion. This means that study population will be compromised of a very highly selected group of patients with narrow window of ESS scores. This is fine but need to be clear from title and abstract as this will not be reflective of the wider T2D or OSA population (unless if I misunderstood the inclusion exclusion criteria).
We wished to study patients who were symptomatic for OSA with daytime sleepiness but EDS>14 was not an exclusion criterion. The protocol states....."*If a patient scores >14 on the Epworth Sleepiness Scale, the sleep apnoea specialist will be consulted to assess and confirm inclusion/exclusion criteria is met".* **This was to ensure that patient participation in the study was safe from a driving perspective. In the vast majority of cases the patient was deemed eligible for inclusion so we believe the study is reflective of a wider T2D or OSA population.**

Reviewer: 2
Reviewer Name: Gonzalo Labarca
Institution and Country: Universidad San Sebastian, Chile

I would like to congrats Dr. Sprung et al for this protocol. This protocol evaluates the efficacy of liraglutide in T2DM and OSA patients, the design is adequate and both random sequence generation and allocation concealment are clearly reported.

Thank you for these positive comments.

Regarding sample size, although previous studies recommended the change in ESS and a minimal clinically relevant difference of 2.0 points as a measure for sample size calculation. This study proposes the change in AHI according to previous investigation, this hypothesis should be evaluated according to study results.

We chose change in AHI as the primary outcome measure being more clinically relevant to this population as patients with type 2 diabetes may have a change in daytime symptoms secondary to an improvement in glycaemic control, weight loss or other non-OSA related factors rather than being attributable to an objective improvement in OSA severity.

Finally, CPAP adherence is relevant to define the population with better results after CPAP therapy. Adherence > 4 hours should be included in a secondary analysis of these data.

This has now been included on Page 9.

Reviewer: 3
Reviewer Name: Sally Kerry
Institution and Country: Queen Mary University of London

This is a trial protocol. There are no dates given in the manuscript for the trial as required by this journal. On the trial registration website the trial recruitment was from 1 Sept 2015 to 1 Oct 2017. The date on the protocol is July 2017. This is 2.5 years ago.

The trial has been ongoing since September 2015 and was ongoing at the time of our submission in mid 2019 to BMJ Open. We have now completed recruitment and are addressing data queries in preparation for data analysis.

The aims of the trial in the abstract and title are unclear. This is a factorial design with the primary aim to compare liraglutide with no liraglutide with or without CPAP. But the abstract says 'Twenty-six weeks of treatment with liraglutide (1.8 mg o.d.) will be given either given alone or in combination with CPAP. It is not clear there is a control group.

As above the title and abstract have now been modified to make clear the nature of the study design and the inclusion of the control group.

There is no mention of feasibility in this single centre trial and it doesn't look to me as if this is feasible to recruit but I cannot see any mention of recruitment figures which must be known at this stage.

We were confident of feasibility of recruitment based on the large number of patients that we treat through the various out-patient diabetes and respiratory clinic settings.

The trial statistician is not an author but simply recognised in the acknowledgements. A good robust trial will require teamwork with the statistician who should be a co-author as a recognition of their contribution.

We would entirely agree with this statement, but we refer Reviewer 3 to the original author list that clearly includes the trial statistician (Alex Needham) and his affiliation to the Liverpool Clinical Trials Unit. Their inclusion has also enabled us to robustly address the statistical concerns raised below but also crucially to design, secure funding, execute and analyse the study from its original conception through to the eventual final publications.

The statistical methods are reasonably well described but as ITT is known to be used in different ways by different people some more explanation about what study cohort will be used would be useful particularly regarding patients who fail to attend follow-up and so all data may be missing.

Thank-you for the comments raised. With respect to the patient groups for analysis, ITT is defined in the following way:

Intention to Treat (ITT) principle will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy, b) patients withdrawn from the study after randomisation because of irregularities with the consent process and c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation.

I suspect the losses to follow-up will be greater than predicted due to the patient burden and the methods for dealing with missing data are not well described as applicable to this study. For example, what additional information will be used to impute values for cases that have failed to be followed up. Without any additional information the power and confidence intervals will remain, and the risk of bias will remain as well if there is poor follow-up

Addressing the point of missing data and possible effects of precision/bias due to patient attrition. Firstly, it is worth stressing that we do not expect any excessive losses-to-follow-up to be an issue with this particular study with respect to analysis of the primary outcome. Secondary outcomes (e.g. quality of life) however may be more susceptible to missing data/losses to follow-up. To account for this the following approaches have been proposed

- **The pattern of missingness will be explored across treatment groups and other clinical/demographic factors to evaluate any underlying causal links that may exist**
- **Where appropriate, analyses will be conducted using multiple imputation (using chained equations). Given that there are a number of outcomes and the imputation routine may differ slightly depending on what is being imputed it is difficult to give precise details of the imputation routine for all scenarios. For the purposes of the**

primary endpoint on which the study is powered some further details are provided below:

- **Imputations will be performed for each treatment arm individually (to protect against bias that can be introduced by imputing across all patients).**
- **Covariates used to impute the missing data will be key clinical/demographic data available and the baseline AHI (if it is the follow-up AHI that that is missing)**
- **Imputations based on chained equations will use a suitable burn-in before**
- **At least 50 imputations will be performed with results averaged across using Rubins' rules**

Further aside from this, sensitivity analyses are planned based both on a complete case basis and on a per protocol basis. No methods to analyse the primary outcome which directly account for missingness (e.g. pattern mixture modelling) are at present planned as we do not expect missing data to be a substantial problem. This may change however as the Statistical Analysis Plan will undergo a blind review prior to final analysis.

VERSION 2 – REVIEW

REVIEWER	Sally Kerry Queen Mary University of London, UK
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	The manuscript is much clearers in the descriptions of the design. The date of starting recruitment is given in the manuscript but not the planned end . In the registration this was planned to be 1 Oct 2017. This is 2.5 years ago. The authors should explain whether recruitment was extended. There is no date on the protocol and any refence to previous versions or any amendments from pervious versions . AS recruitment has already started this is important. The statement that lossto follow up would be small and is hence ignored in the sample size should be justified. The statistical methods better but it still does not explain what additional information will be used to impute values for cases that have failed to be followed up. Without any additional information the power and confidence intervals will remain and the risk of bias will remain as well if there is poor followup

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Sally Kerry
Institution and Country
Queen Mary University of London, UK
Please state any competing interests or state 'None declared':
None
- The manuscript is much clearer in the descriptions of the design.

- The date of starting recruitment is given in the manuscript but not the planned end. In the registration this was planned to be 1 Oct 2017. This is 2.5 years ago. The authors should explain whether recruitment was extended.
We have added detail relating to study extension (page 6).

- There is no date on the protocol and any reference to previous versions or any amendments from previous versions. As recruitment has already started this is important.
We have added the version number and date to the protocol (footer and page 5). On page 6 we also acknowledge study amendments which were submitted to maximise patient recruitment opportunity.

- The statement that loss to follow up would be small and is hence ignored in the sample size should be justified.
Given the non-invasive nature of the interventions and the short follow-up, it was not envisaged that patient retention would be an issue. GLP-1 RAs are generally well tolerated, with gastrointestinal and subcutaneous injection-site reactions being the most common drug-related adverse events, and are also associated with a very low intrinsic risk of hypoglycaemia (Lyseng Williamson, 2019). Further, early study withdrawals formed part of the evaluation by the joint DMC/TSC oversight committee so that this assumption could be evaluated during the course of the study. We have included this justification in the text (page 16).

Lyseng-Williamson, K.A. Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes: Their Use and Differential Features (2019). Clin Drug Investig 39, 805–819. https://doi.org/10.1007/s40261-019-00826-0

- The statistical methods are better but it still does not explain what additional information will be used to impute values for cases that have failed to be followed up. Without any additional information the power and confidence intervals will remain, and the risk of bias will remain as well if there is poor follow up.
Imputation is planned only for cases of missing follow-up outcome data, which is anticipated to be small, and therefore the scope for any bias due to the MI routine is limited. Multiple imputation using chained equations will be applied to each treatment arm individually. Imputation methods will include baseline outcome data as well as other key prognostic information (e.g. sex, age) (page 17).