PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and cost of integrating a pragmatic pathway for prescribing liraglutide 3.0 mg in obesity services (STRIVE study): Study protocol of an open-label, real-world, randomised, controlled trial.
AUTHORS	Papamargaritis, Dimitris; Al-Najim, Werd; Lim, Jonathan; Crane, James; Lean, Mike; Le Roux, Carel; McGowan, Barbara; O'Shea, Donal; Webb, David; Wilding, John; Davies, Melanie

VERSION 1 – REVIEW

REVIEWER	Joan Khoo Department of Endocrinology, Changi General Hospital
REVIEW RETURNED	26-Sep-2019

GENERAL COMMENTS	This is a very well-designed and timely study of the real-world cost-effectiveness of liraglutide in management of obese patients in the community. Just to clarify: Page 4 line 40: are the workflow and accessibility of services and interventions in the 5 SWMS sites broadly similar? Page 9 line 4: were these stopping rules based on previous protocols or trials? Page 11 line 9: will data on diet and exercise be obtained from dieticians/physiotherapists?

REVIEWER	Lars Erik KRsitensen Bispebjerg and Frederiksberg Hospital, The Parker Institute
REVIEW RETURNED	10-Oct-2019

GENERAL COMMENTS	Well written and transparent protocol Please add more key limitations - ie. open label design - internal validity issues etc. Please explain Novos role of funding more explicit in funding statement

REVIEWER	Henrik Gudbergsen The Parker Institute, Department of Rheumatology
REVIEW RETURNED	27-Oct-2019

GENERAL COMMENTS	- I suggest to align details outlined in the manuscript and on clinicaltrials.gov (i.e. no. of patients) - Specify time frames in the section outlining secondary objectives - Page 14, line 3-4, ”more likely…” – compared to who? Controls or those who did not achieve a 15% weight loss within 52 weeks?

	- How do you account for the usage of including data from patients not achieving the 52 week target and subsequently being treated with a effective intervention enabling a significant weight loss in a comparison up against patients achieving the 52 week target? (15% weight loss) [lines 31-35, page 8] - Are patients/HCPs required to escalate doses of liraglutide to a minimum, e.g. 1.8 mg? - Suggest to update clinicaltrials.gov to reflect a 2 year recruitment period (FPFV & LPFV) & the 2 year study duration (FPLV & LPLV) - Would it be possible for patients to shift from one SWMS to another? - Can I kindly ask the authors to supplement their description of 'data sharing' in relation to this trial?

REVIEWER	Tim Holt Oxford University, Department of Primary Care Health Sciences
REVIEW RETURNED	01-Nov-2019

GENERAL COMMENTS	This is a well designed study and I look forward eventually to seeing the trial results, which may well impact on practice and policy in this area. Strict rules are applied and this is a strength of the trial, even though in the real world beyond it it may be difficult to withhold treatment to someone who has achieved less than but close to the rule threshold. The protocol has received the necessary approvals so this review is largely about clarity of presentation. In this regard I thought the first half of paragraph 2 on page 6 (before 'as well as') could be more clearly written - on first reading I did not understand the use of the word 'stratify'. However my main issue was the description of the health economic analysis. The authors make the important point earlier that NICE are guided by cost-effectiveness as much as by clinical benefits in determining policy. For this reason, the health economic analysis methods, which are not adequately described in the main text and rely on a simple list of secondary outcomes in the Appendix, needs expanding.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name

Joan Khoo

Institution and Country

Changi General Hospital

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
1) This is a very well-designed and timely study of the real-world cost-effectiveness of liraglutide in management of obese patients in the community.

We thank the reviewer for the positive comments.

Just to clarify:
2) Page 4 line 40: are the workflow and accessibility of services and interventions in the 5 SWMS sites broadly similar?

We thank the reviewer for his comment.

One of the main strengths of this study is that it is multicentre and that the five participating sites are culturally and racially diverse and in different geographical areas, reflecting typical specialist weight management services (SWMS) settings across UK and Ireland.

The workflow of the five SWMS participating in this study is broadly similar as participants in SWMS are offered regular appointments with both dieticians and physicians for intensive lifestyle intervention, assessment of obesity related comorbidities and prescription of anti-obesity medication. Other members of the multidisciplinary team for weight management may include a physiotherapist/exercise physiologist, a psychologist and/or a specialist nurse in weight management (depending on what is available on each SWMS). The majority of the SWMS in this study are based on secondary care, however there is one site where the SWMS is based on primary care. Participants in SWMS usually remain routinely in SWMS for at least 12 months, in accordance with the national recommendations.

Despite that each SWMS may have its own criteria of accepting patients (depending on local Clinical Commissioning Group funding), the accessibility of the service for the participants recruited in this study (patients with severe and complex obesity, BMI at least of 35 kg/m^2) is broadly similar among all 5 recruiting sites. All patients with severe and complex obesity can either access the SWMS by GP referral or in some cases by direct referral from specialist services (for example diabetes service, orthopaedics or sleep apnoea clinic). The waiting time for the first appointment at the SWMS may vary between different SWMS services.

The interventions for weight loss management offered at the 5 participating SWMS may indeed differ significantly between them as mentioned in the manuscript [paragraph Study Design, Control (Standard Care), “The nature of the standard care will vary between the different SWMS at each site” and at the same paragraph “Participants in the control group will follow the best medical care provided by the SWMS at the relevant site. This typically involves…”.

Some of the SWMS may offer total diet replacement or formula-diet meal replacement, other may offer 600-kcal daily deficit diet supported by behavioural change techniques and other SWMS may offer in addition to dietetic intervention, physical activity programs. In terms of medical therapies, the only currently available option in NHS is orlistat and this is offered in all the SWMS participating in this study.

A sentence now has been added to the manuscript to explain that the workflow and accessibility to the 5 SWMS is broadly similar.

Page 8, Paragraph Study Design, Control (Standard Care)

"Across the UK and Ireland, each region has a SWMS. This service typically… physical activity physiologist. The accessibility and the workflow of the SWMS are broadly similar for all the five participating sites in this study."

Page 9 line 4: were these stopping rules based on previous protocols or trials?

The stopping rule of 5% at 16 weeks is based on European Medicines Agency stopping rule, as described at the manuscript (Introduction, Page 5, "EMA has approved the LIRA 3mg with a single stopping rule.."). This 5% stopping rule has been created based on the responders sub analysis of the SCALE Obesity/Prediabetes and SCALE Diabetes study (ref 27 in the manuscript, Fujioka K et al., PMID 27804269) which demonstrates that patients who achieve ≥4% weight loss at the first 16 weeks after initiation of treatment with LIRA 3mg (responders) were more likely to achieve ≥10% and ≥15% weight loss at 52 weeks compared to those who did not manage ≥4% weight loss at first 16 weeks (non-responders).

The 15% weight loss stopping rule at 52 weeks, which is the stopping rule for the long –term use of LIRA 3mg, is based on the fact that 15% weight loss is the average long-term weight loss achieved by gastric band, one of the bariatric operations (SOS study, PMID 15616203). The maintenance of this amount of weight loss long-term has been associated with mortality benefit in patients after bariatric surgery (SOS Study, PMID 17715408 and PMID 15616203). So, if patients are able to maintain ≥15% weight loss with the targeted prescribing pathway, it is very likely that they will achieve major health benefits (PMID: 26421334) and potentially the use of LIRA 3mg in this population will be cost-effective long-term without having to undergo a bariatric operation. We have explained this at the manuscript (Introduction, page 4, Paragraph 2 "Maximal benefits for the treatment of obesity…"). Moreover, from SCALE Obesity and Prediabetes trial, we know that 15% weight loss is feasible for 14.4% of patients on the LIRA 3mg group.

The 10% weight loss stopping rule at 32 weeks is not based on previous protocols or trials. However, we took into account that the rate of weight loss in SCALE Obesity/Prediabetes and SCALE Diabetes trials seems to reduce/plateau after the first 28-32 weeks, suggesting that patients who have not achieved 10% weight loss until then, it is less likely to further lose

significant amount of weight. Moreover, we felt that allowing all the patients who will achieve 5% weight loss at 16 weeks ("early responders") after initiation of LIRA 3mg (estimated 62%-77% of patients initiated on treatment) to continue for another 36 weeks on LIRA 3mg (until the end of the first year) before the next stopping rule, it may compromise the cost-effective use of the medication for this population.

Page 11 line 9: will data on diet and exercise be obtained from dieticians/physiotherapists?

Thank you for your comment. There is no plan for data to be obtained from dieticians and physiotherapists on diet and exercise for the participants in the study. However, an IPAQ-Long questionnaire on physical activity will be completed by the participants at baseline, 52 weeks and 104 weeks as described in Appendix 3.

Reviewer: 2

Reviewer Name

Lars Erik KRsitensen

Institution and Country

Parker Institute, CPH, DK

Please state any competing interests or state 'None declared':
n/a

Please leave your comments for the authors below
1) Well written and transparent protocol

We thank the reviewer for his positive comment.

2) Please add more key limitations - ie. open label design - internal validity issues etc.
We thank the reviewer for the comment. We intentionally design the study as open-label in order to reflect real-world circumstances, as this is a phase 4 trial investigating the effectiveness and cost-effectiveness of the suggested targeting prescribing pathway for LIRA 3mg in obesity services, rather than an efficacy and safety study (efficacy and safety for LIRA 3mg have been proven in the phase 3 SCALE studies). Effect sizes may be affected by the strict protocols of placebo-controlled randomised controlled trials (RCTs) and these data may not be optimal for health economic analyses as real-world applicability and generalisability of

these RCTs are limited. So we believe that for the intention of this study, the open-label, real-world design is strength of the study, rather than a weakness. However, while we deliberately design the study as open-label, one potential limitation could be the reduced motivation for adherence in the SWMS program and attendance to data collection study visits for some participants randomized to control group. In each case, the adherence to the SWMS is one of the secondary outcomes of the study.

We have now added at Page 3, Strengths and Limitations of the study, the following:

- **The study has been deliberately designed as open-label, however randomization to control (standard care) group, without the opportunity to receive LIRA 3mg, may be a disincentive to adherence to the SWMS program and attendance to study visits for some participants.**

3) Please explain Novos role of funding more explicit in funding statement.

We thank the reviewers for their comment. Please see also our answer to editors' comment number 4.

Page 18, Paragraph Funding: This study is investigator-initiated and the investigators received a grant from Novo Nordisk to enable them to conduct the study. Novo Nordisk provided also the medication for the study. The funder (Novo Nordisk) did not contribute to study design and will not contribute to data collection, analyses and interpretation of the results. Moreover, the funder will not contribute to the writing of the report and the decision to submit the report for publication.

Reviewer: 3

Reviewer Name

Henrik Gudbergsen

Institution and Country

The Parker Institute
Denmark

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

1) I suggest to align details outlined in the manuscript and on clinicaltrials.gov (i.e. no. of patients)

We thank the reviewer for the comment. The clinicaltrials.gov has now been updated and the number of patients in the study, as well as the secondary outcomes, they have been modified in accordance with the submitted manuscript and the latest version of the protocol of the study.

2) Specify time frames in the section outlining secondary objectives

We thank the reviewer for the comment. We have now specified the time frames in the section outlining the secondary objectives of the study.

We have now modified the manuscript as follows:

Pages 6 and 7, Paragraph "Aims and Objectives" :

"The secondary objectives (see also Supplementary Material, Appendix 1) are to compare the targeted prescribing pathway plus SWMS standard care vs SWMS standard care alone in terms of:

1. **improving obesity-related complications (prediabetes, diabetes, hypertension, obstructive sleep apnoea, dyslipidaemia, depression) at 52 and 104 weeks**
2. **referral rates to other obesity interventions at 52 and 104 weeks**
3. **long-term weight maintenance (defined as the proportion of participants maintaining weight loss of ≥15% at 104 weeks among those who achieved ≥15% weight loss at 52 weeks)**
4. **budget impact on a SWMS at 52 weeks and 104 weeks**
5. **estimated cost-effectiveness of treatment over 104 weeks**
6. **direct healthcare costs in terms of admissions, frequency, and cost of appointments at 52 and 104 weeks**
7. **safety-related outcomes at 52 and 104 weeks**
8. **adherence to treatment at 16, 32, 52 and 104 weeks**
9. **patient satisfaction and quality of life at 52 and 104 weeks"**

Just to clarify here that for the long-term weight maintenance (secondary objective 3), the time frame of the outcome is included in the definition (104 weeks)

3) Page 14, line 3-4, "more likely…" – compared to who? Controls or those who did not achieve a 15% weight loss within 52 weeks?

We thank the reviewer for the comment. We believe that he refers at the phrase "The second 52 weeks of the study will assess whether patients who lose ≥15% of their baseline weight by the first 52 weeks are more likely to maintain ≥15% weight loss for another 52 weeks in the targeted prescribing pathway plus standard care compared with standard care alone." at page 8 (clean version) of the manuscript, paragraph Study design.

We actually mean here that we will assess whether patients who lose ≥15% of their baseline weight by the first 52 weeks with the targeted prescribing pathway plus standard care are more likely to maintain ≥15% weight loss for another 52 weeks compared with patients in the control group (standard care alone) who were also able to achieve ≥15% weight loss by the first 52 weeks of the study.

In order to make it clear at the manuscript, we have now modified this sentence as following:

"The second 52 weeks of the study will assess whether patients who lose ≥15% of their baseline weight by the first 52 weeks with the targeted prescribing pathway plus standard care are more likely to maintain ≥15% weight loss for another 52 weeks compared with patients in the control group (standard care alone) who were also able to achieve ≥15% weight loss by the first 52 weeks."

4) How do you account for the usage of including data from patients not achieving the 52 week target and subsequently being treated with a effective intervention enabling a significant weight loss in a comparison up against patients achieving the 52 week target? (15% weight loss) [lines 31-35, page 8]

We thank the reviewer for the comment. The main intervention in the targeted prescribing pathway plus standard care group which could lead to significant weight loss and help people to achieve ≥15% weight loss at 52 weeks despite that they have not reached the weight loss targets to continue with LIRA 3mg is bariatric surgery. We would like to highlight here, that NICE (national) guidelines recommend that the majority of patients with severe and/or complex obesity aiming for bariatric surgery should receive support from SWMS at least for 52 weeks before they will be referred for bariatric surgery. In reality, only a small proportion of people attending the SWMS are referred for bariatric surgery and in the majority of the recruitment centers the waiting time for bariatric surgery is more than 52 weeks. So, we expect that only a small number of patients will undergo bariatric surgery during the first 52 weeks of the study which is the time point for the primary outcome (and we also expect that the number of participants who will undergo bariatric surgery during the 2-year period of the study will also be small for the reasons explained above). However, patients who will have "fast-track" bariatric surgery during the first 52 weeks after randomisation will be excluded from the complete cases population - which will be used for the primary analysis of the primary outcome – as well as from the per protocol analysis, because these participants are likely to have substantial weight loss.

This has now been highlighted at pages 13-14, section Statistics – Statistical methods and analysis which has been modified as following: "Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the complete cases population analysis (the primary analysis) and the per protocol analysis for the primary outcome (but they will be included at the ITT analysis)".
Referral rates to bariatric surgery services (Tier 4 weight management services) are also one of the secondary outcomes of this study.
Regarding the secondary outcomes measured at 52 and 104 weeks, these will be analysed based only on the complete cases population in order to reduce the number of models (as described at the manuscript). Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the secondary outcomes analyses at 52 weeks. Participants who have undergone bariatric surgery during the study period (104 weeks) will also be excluded from the secondary outcomes analysis at 104 weeks.

This has now been highlighted at page 14, section Statistics- Statistical methods and analysis where the following sentences have been added: "Participants who have undergone bariatric surgery during the first 52 weeks of the study will be excluded from the analyses for secondary outcomes at 52 weeks. Moreover, participants who have undergone bariatric surgery during the study period will be excluded from the analyses for secondary outcomes at 104 weeks."

Otherwise, as explained at the statistical analysis section for the primary outcome, all the patients randomized to the targeted prescribing pathway who are able to achieve weight loss ≥15% at 52 weeks from baseline visit with non-surgical methods (independent of whether they achieved or not to pass the 3 stopping rules for use of LIRA 3mg) will be compared to patients who are able to achieve weight loss ≥15% at 52 weeks in the control group (with non-surgical methods). Nevertheless, we will report at the results of the study how many participants in the targeted prescribing pathway plus standard care have achieved the ≥15% weight loss at 52 weeks by successfully passing all the 3 stopping rules for use of LIRA 3mg and how many have achieved the target weight loss of ≥15% with other non-surgical interventions, despite a stopping rule for use of LIRA 3mg has been applied before.

However, we believe that if a stopping rule for use of LIRA 3mg has been applied for a participant at the intervention group (stopped LIRA 3mg at 16 or 32 weeks), it is very unlikely that other non-surgical interventions offered in SWMS will result to weight loss ≥15% for this participant at 1 year after initiation of the study. In the majority of the cases, intensive lifestyle interventions (which are based on patient's preference) take place from the very beginning of the SWMS program and their intensity decreases over time. So, if a participant at the study is not able to reach the weight loss targets for continuing using LIRA 3mg with the combination of pharmacotherapy and intensive lifestyle intervention, it is unlikely that he/she will reach the ≥15% weight loss target at 52 weeks with a lifestyle intervention alone, after stopping the LIRA

3mg (especially as the intensity of the lifestyle intervention is usually gradually reduced). This is also supported from the fact that only 1% of the "early non-responders" in the placebo group of SCALE Obesity and Prediabetes study (defined as those not achieving ≥4% weight loss with lifestyle intervention and placebo during the first 16 weeks of treatment) and 0% of "early non-responders" in the placebo group in SCALE Diabetes study achieved weight loss more than 15% at 52 weeks (Fujioka et al, PMID 27804269). These sub analyses highlight that similar to what is happening with LIRA 3mg, the chances to achieve ≥15% weight loss at 52 weeks with a lifestyle intervention alone are limited if you are not an "early responder" over the first few weeks of treatment.

5) Are patients/HCPs required to escalate doses of liraglutide to a minimum, e.g. 1.8 mg?

We thank the reviewer for this comment. Liraglutide doses will be self-administered daily by the participants. Liraglutide will be initiated for participants randomised to the intervention group at a dose of 0.6mg daily for the first week and then increased to 1.2mg in Week 2, 1.8mg in Week 3, 2.4mg in Week 4, and 3.0mg in Week 5 as per the Summary of Product Characteristics (SpC). The dose will be maintained at 3.0mg. Participants in the targeted prescribing pathway will also undergo titration reviews during titration weeks 1, 3 and 5. During these visits, there will be the option for calls between weeks 1-3 and weeks 3-5 available to research team and for participants to counsel them on titration requirements. Titration protocol will also be explained to the participants during the baseline visit. Participants who have withdrawn from LIRA 3mg due to intolerance, adverse effects or inability to titrate up to a maximum dose of LIRA 3mg, will continue to be offered the standard care provided by the relevant SWMS. The conditions for participants' withdrawal from the study as well as for temporary and/or permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules) are described in detail at Supplementary Material, Appendix 2. Participants who cannot tolerate the maximum dose of LIRA 3mg will not be able to remain into the study on lower doses of Liraglutide (for example 2.4 mg), as the licensed dose for treatment of obesity is LIRA 3mg.

The above are described at the following areas at the manuscript and supplementary material

- **Appendix 2 [Withdrawal of participants from the study, temporary and permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules)]**
- **Page 12, Treatment of Trial Participants, Study Medication, "Participants will be given specific instruction to adhere to the titration policy of LIRA 3mg in accordance with the SpC." and**
- **Page 8, Methods and Analysis, Intervention (Targeted Prescribing Pathway plus Standard Care) "Dose escalation of liraglutide will occur in accordance with the Summary of Product Characteristics (SPC) from 0.6 mg to a maximum of 3.0 mg.**

Participants will be withdrawn from receiving LIRA 3mg if the doses are not tolerated during or following the titration period.

- **Page 9, Methods and Analysis, Intervention (Targeted Prescribing Pathway plus Standard Care) "Participants who fail to reach the thresholds to continue LIRA 3mg treatment, or who have withdrawn from LIRA 3mg due to intolerance, adverse effects or inability to titrate up to a maximum dose of LIRA 3mg, will continue to be offered the standard care provided by the relevant SWMS. The conditions for participants' withdrawal from the study as well as for temporary and/or permanent treatment discontinuation for LIRA 3mg (outside prespecified stopping rules) are described in Supplementary Material, Appendix 2."**
- **Appendix 3. Table 1. Outcome measures and planned visits during the enrolment and control visits (Titration/Review Visit (dose$)/or telephone call)$$**

6) Suggest to update clinicaltrials.gov to reflect a 2 year recruitment period (FPFV & LPFV) & the 2 year study duration (FPLV & LPLV)

We thank the reviewer for the comment. We have now updated the clinicaltrials.gov information in order to reflect the 2 year recruitment period (FPFV & LPFV) and the 2 year duration of study (FPLV and LPLV). First patient first visit was in November 2017 (already on clinicaltrials.gov) and subsequently first patient last visit was in November 2019 (not required as information at clinicaltrials.gov). LPLV is estimated on December 2021 (estimated Study Completion Date, updated in clinictrials.gov). The recruitment will be completed on December 2019 (not required as information from clinicaltrials.gov). Estimated Primary Completion Date (Estimated Date to collect final data for the primary outcome of the study) has been updated in clinicaltrials.gov to December 2020.

7) Would it be possible for patients to shift from one SWMS to another?

We thank the reviewer for the comment. Each local area has usually only one Specialist Weight Management Service funded by the local Clinical Commissioning Group and in order a patient to be accepted in the SWMS, a referral by GP or a specialist service needs to be done. For this study, it is extremely unlikely that a patient will shift from one SWMS to another, as patient needs to be relocated to a different area (the study takes place in 5 different geographical areas, which are culturally and racially diverse) and to be referred to the new SWMS.

8) Can I kindly ask the authors to supplement their description of 'data sharing' in relation to this trial?

We thank the reviewer for his comment. We have consulted before submission of the protocol the Editorial Office of BMJ Open regarding whether a "data availability" statement should be included in this manuscript. Their response was that this manuscript is the protocol of the

study, so a "data availability" statement was not required.
However, in view of this comment, we have now added a "data availability" statement at the end of the manuscript, page 18:

"Data availability statement: De-identified participant data will be made available after publication of the main paper of the study by application to the chief investigator of the study and after assenting to a data access agreement."

Reviewer: 4

Reviewer Name

Tim Holt

Institution and Country

Oxford University, UK

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
1) This is a well designed study and I look forward eventually to seeing the trial results, which may well impact on practice and policy in this area. Strict rules are applied and this is a strength of the trial, even though in the real world beyond it may be difficult to withhold treatment to someone who has achieved less than but close to the rule threshold.

We thank the reviewer for his positive comments.

2) The protocol has received the necessary approvals so this review is largely about clarity of presentation. In this regard I thought the first half of paragraph 2 on page 6 (before 'as well as') could be more clearly written - on first reading I did not understand the use of the word 'stratify'.

We thank the reviewer for his comment. The paragraph has now been reviewed and modified as following:

"In this paper, we describe the rationale and methodology of a study investigating the effectiveness and cost of a targeted prescribing pathway (with multiple pre-specified stopping rules) for the use of LIRA 3mg in SWMS settings for the treatment of severe and complex obesity. The targeted prescribing pathway aims to optimise the use of LIRA 3mg in "early responders" (in accordance with the EMA stopping rule) to the combination of lifestyle

intervention plus LIRA 3mg as well as identifying patients who are most likely to benefit more from continued long-term prescription of LIRA 3mg (i.e. those who are able to achieve ≥15% weight loss at 1 year). This approach aims to direct the use of this medication…"

3) However my main issue was the description of the health economic analysis. The authors make the important point earlier that NICE are guided by cost-effectiveness as much as by clinical benefits in determining policy. For this reason, the health economic analysis methods, which are not adequately described in the main text and rely on a simple list of secondary outcomes in the Appendix, needs expanding.

We thank the reviewer for his comment. We have now expanded the section of cost-effectiveness analysis and we have added the following information to the manuscript:

Pages 14-15 (clean version of manuscript), Paragraph Health Economic Input:

"The model projects development of T2D, myocardial infarction, stroke, asthma cancer or mortality in the long term (up to lifetime horizon) based on short term effects of interventions in surrogate outcomes – BMI, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol and (for patients with T2D) glycated haemoglobin (HbA1c). Effects on surrogate outcomes are translated into lifetime risks through risk-prediction models.

Treatment effects are applied incrementally to the efficacy of the targeted prescribing pathway group. Effect on weight, in terms of BMI % reduction, is applied at every subsequent cycle starting from 3 months after treatment start for as long as the cohort remains on treatment and over the predefined catch-up time post-treatment. Note that a natural increase in weight is applied each year to all interventions considered, including no treatment.

Treatment can be discontinued at 16 weeks, 32 weeks or at 52 weeks (based on the pre-specified stopping rule). Discontinuation causes the cohort to receive the same standard care providing via the SWMS as at the control group. Thus, if the discontinuation is allowed at 16 weeks, "non-responders" will have the same effect of the cohort in the control group, and "responders" will have the effect of the targeted prescribing pathway in the clinical trial.

Discontinuation of treatment beyond 52 weeks causes BMI, and other cardio-metabolic risk factors, to revert to the levels projected under the no treatment option. Reversal takes place over a given number of cycles (years). Costs and quality of life outcomes are applied to the health state in which the cohort resides at each particular moment in time or once-off to events. Costs and health benefits (life years, quality-adjusted life-years, years T2D free, years cancer free etc.) are summed-up for the time horizon of the model and results reported as

incremental cost-effectiveness ratios. The risk of acquiring obesity-related co-morbidities has been taken from published epidemiological studies."

VERSION 2 – REVIEW

REVIEWER	Henrik Gudbergsen The Parker Institute, Department of Rheumatology
REVIEW RETURNED	12-Jan-2020

GENERAL COMMENTS	This is a well designed study and I look very much forward to seeing the trial results which I expect to impact practice as well as policies within this area

REVIEWER	Tim Holt Oxford University, Department of Primary Care Health Sciences
REVIEW RETURNED	31-Dec-2019

GENERAL COMMENTS	I am happy with the changes made in response to my original review, and recommend publication.