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Forecasting Trial Milestones: A Predictive Analysis for Early Termination of the SOUL Study

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202460061

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2024 and was last updated on 17 June 2024.

INTRODUCTION

Review question / Objective P = Type 2 diabetes patients with high cardiovascular risk. I = Semaglutide. C = Placebo. O = Reduction in composite CV events (MACE) and their individual components. In addition, a prediction analysis will be performed to predict the effective duration and outcome benefits in the ongoing SOUL study, with an aim to suggest a means of reducing cost of studies being designed for the future.

Rationale Randomised controlled trials with Semaglutide have documented trends toward improvement of cardiovascular outcomes. Most RCTs were designed with a background population CV event rates taken from prevalence studies, and had to be prematurely terminated. We speculate the background population rates are under-estimated resulting in premature termination. I situations for example the SOUL CVOT with semaglutide we have 3 RCTs with the same molecule with the placebo arm providing a robust idea about the background population CV risk.

The aim of this meta-analysis and predictive model is to extract the population CV risk from the PIONEER 6, SUSTAIN 6, and FLOW trials, create a predictive model using the pooled hazard ratio from these 3 trials from the semaglutide arm, and accurately predict the duration of time required to achieve the desired number of events, without necessitating premature termination.

Condition being studied Major adverse cardiac events (MACE), non-fatal myocardial infarction (NFMI), non-fatal stroke (NFS), and CV death.

METHODS

Search strategy 1. Cochrane Library database will be the search engine. 2. No filters as far as date is concerned. 3. English language will be a filter for search. 4. Trials will also be included in the filter.A comprehensive literature search is planned using the Cochrane Library database to identify relevant RCTs with semaglutide with cardiovascular outcomes as the primary end point. The key search terms to be included are “Type 2 diabetes” [MeSH], “Semaglutide”, and “Cardiovascular outcomes trial.”

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Participant or population Type 2 diabetic patients with high cardiovascular risk profile.

Intervention Semaglutide.

Comparator Placebo.

Study designs to be included Randomised controlled trials.

Eligibility criteria Pre-determined inclusion criteria included:
• Age >18 years.
• Patients with T2D.
• Intervention arm including semaglutide.
• Placebo as the comparator arm.
• MACE as the primary end point.
• A minimum duration of follow up for 12 months.

Exclusion criteria:
Diabetes other than Type 2.
Acute hyperglycemic conditions.
pediatric population.
Non randomised trials.
Active control in the comparator arm.

Information sources A comprehensive literature search will be conducted using the Cochrane Library database to identify relevant RCTs with semaglutide with cardiovascular outcomes as the primary end point. The key search terms to be included are "Type 2 diabetes" [MeSH], "Semaglutide", and "Cardiovascular outcomes trial." There will be no limit as far as date is concerned. However, articles published in English will be used as a filter used. Additionally manual searches for relevant citations will be conducted using the Google Scholar search engine. The search strategy will follow the PRISMA guidelines.

Main outcome(s)
1. Major adverse cardiac events (MACE).
2. Subgroup analysis: Non-fatal myocardial infarction (NFMI), non-fatal stroke (NFS), and cardiovascular death (CV death).
3. Predictive analysis by pooling the articles selected for meta-analysis using the mean placebo event rate as the historical baseline comparator and the pooled HR from the meta-analysis as treatment effect taking the calculated event rate & number based on a 90% power calculation, and duration pre-specified in the protocol of the SOUL trial as the baseline.

Additional outcome(s) Predictive analysis based on the findings from the meta-analysis and the baseline characteristics provided in the SOUL study protocol.

Data management A comprehensive literature search will be conducted using the Cochrane Library database to identify relevant RCTs with semaglutide with cardiovascular outcomes as the primary end point. The key search terms to be included are "Type 2 diabetes" [MeSH], "Semaglutide", and "Cardiovascular outcomes trial." There will be no limit as far as date is concerned. However, articles published in English will be used as a filter used. Additionally manual searches for relevant citations will be conducted using the Google Scholar search engine. The search strategy will follow the PRISMA guidelines.

Quality assessment / Risk of bias analysis Cochrane Risk of Bias Algorithm.

Strategy of data synthesis
1. A random effects model will be used for the mean effect size analysis.
2. Hazard ratio with 95% CI will be the measure of the effect size.
3. The "prediction interval" will be used to assess heterogeneity of the effect size distribution.
4. The Comrehensive Meta-analysis (CMA) software will be used for the analysis.

Subgroup analysis Subgroup analysis: The individual components of MACE (NFMI, NFS, and CV death) will be assessed as part of subgroup analysis.

Sensitivity analysis Sensitivity analysis to assess the robustness of the predictive model will also be conducted.

Language restriction English language.

Country(ies) involved India.

Keywords Meta-analysis, semaglutide, MACE, predictive modelling, premature termination.

Contributions of each author
Author 1 - SAMIT GHOSAL - Author 1 conducted the literature search and performed the meta-analysis and predictive modelling. He also contributed to the manuscript writing.
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Author 2 - Binayak Sinha - Author 2 conceptualised the idea of predictive modelling, helped in literature search and wrote the main body & abstract of the manuscript.
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