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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Health Research Board (HRB) in Ireland has funded this doctoral project
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_forms_0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00642278 - 28431754DIA2001 - A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy,

Parallel Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm

2. NCT01106625 - 28431754DIA3002 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy
3. NCT01064414 - 28431754DIA3004 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment
4. NCT01081834 - 28431754DIA3005 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise
5. NCT01106677 - 28431754DIA3006 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy
6. NCT00968812 - 28431754DIA3009 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled on Metformin Monotherapy
7. NCT01106651 - 28431754DIA3010 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy
8. NCT01106690 - 28431754DIA3012 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Pioglitazone Therapy
9. NCT01137812 - 28431754DIA3015 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sulphonylurea Therapy
10. NCT01809327 - 28431754DIA3011 - A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise
11. NCT01381900 - 28431754DIA3014 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 18-Week Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Alone or in Combination With a Sulphonylurea
12. NCT01340664 - 28431754DIA2003 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin
13. NCT02025907 - 28431754DIA4004 - A Randomized, Double-blind, Placebo Controlled, 2-arm, Parallel-group, 26-week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sitagliptin Therapy
14. NCT01032629 - 28431754DIA3008 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus
15. NCT01989754 - 28431754DIA4003 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes: systematic review incorporating unpublished clinical study reports

Narrative Summary:

In this project, it is planned that CSR data for the SGLT2 inhibitors, which include canagliflozin, will be incorporated into a thorough systematic review of these medications. A thorough review of all benefits and harms on this medication will be compiled from all published sources, as well as from CSRs and trial registries. All data will be analysed and compared. It is planned to study the impact of CSR information on clinical outcomes and also appraise the methodological quality of these documents. The overall aim of this project is to see whether any additional information held in the CSRs could improve our knowledge and improve decision making for these medications.

Scientific Abstract:

Background: The prevalence of symptomatic type 2 diabetes in the Irish population is approximately 5.2%, a figure which has more than doubled over the course of almost 20 years.
Objective: The objectives of this project are outlined here. Objective 1: To synthesise all available randomised control trial evidence on the efficacy and safety of Canagliflozin / SGLT2s and to determine the impact of using clinical study reports on the estimated clinical outcomes. Objective 2: To document procedures for identifying, accessing, extracting data from, and analysing CSRs for research purposes. Objective 3: To evaluate the differences between published sources and clinical study reports in terms of reporting outcomes & bias.
Study Design: Systematic Review and meta-analysis using both published and unpublished sources.
Participants: The population of interest will be adults with type 2 diabetes.
Main outcome measures: Particular outcomes of interest will include change in HbA1 and specific clinical efficacy and safety outcomes relevant to diabetes.
Statistical analysis: A narrative synthesis of included studies will be conducted. Meta-analysis will be undertaken where possible for included efficacy and safety outcomes using appropriate random effects regression models. We would plan to perform a network metanalysis contingent on access to CSR related data for other agents in the same class.

Brief Project Background and Statement of Project Significance:

Background: Type 2 diabetes is a significant public health burden with an associated reduced life expectancy, increased mortality and is associated with greater risk of other diseases including cancer, cognitive impairment and arthritis.
The Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel group of medications used in diabetes. There are four SGLT2s currently licenced for use in the EU; Dapagliflozin, Empagliflozin, Ertugliflozin and Canagliflozin. Obtaining a more complete picture of the evidence base for these medications will involve a thorough systematic review and meta-analysis of all available RCTs, including both published sources and also unpublished sources, namely clinical study reports (CSRs). The importance of including such unpublished evidence in decision making for medications has been illustrated in a number of studies and systematic reviews
Clinical Study Reports (CSRs) are documents submitted by drug companies to organisations such as the European Medicines Agency (EMA) to evaluate new medications. They include information on the data and statistics involved in drug trials for these medications. When compared to information published in the usual medical journals, CSRs provide richer information on these trials and more detailed results. CSRs are becoming much more widely available so it is vital for researchers to be able to analyse these lengthy documents and draw conclusions from the information. This will hopefully provide greater knowledge on medications and improve decision making for medications which will ultimately benefit patients.
In this project, it is planned that CSRs will be analysed for a novel medication group called the SGLT2 inhibitors (SGLT2s) which are licensed for use in type 2 diabetes. Information on the patient benefits and harms will be obtained from the CSRs. A thorough review of all published information on these medications will also be obtained and compared with that in the CSRs. It is planned to study the impact of CSR information on the areas of (i) Patient

benefits and harms (ii) Appraisal of methodological quality.
Following this, it may also be possible to use these estimates of treatment effects to perform an economic evaluation of these medications. This would hopefully highlight the importance of using CSRs for costing of medications by decision makers. The overall aim of this project is to see whether any additional information held in the CSRs could improve our knowledge and improve decision making for medications.

Specific Aims of the Project:

The relevant research question for this doctoral project is as follows: How can clinical study reports, as an unpublished source of evidence, be used to evaluate novel drug treatments used in chronic conditions to inform prescribing and healthcare spending decisions?
The overarching aim of this project is to explore the role of clinical study reports as unpublished sources of randomised control trial reporting in evidence synthesis for Canagliflozin / SGLT2s and its impact on estimates of effectiveness and safety. This project's aims will be achieved by focusing on the selected medication in terms of safety and efficacy and CSR methodology.

What is the purpose of the analysis being proposed? Please select all that apply.
Confirm or validate previously conducted research on treatment effectiveness
Confirm or validate previously conducted research on treatment safety
Research on clinical trial methods

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

All relevant randomised control trials on Canagliflozin / SGLT2s will be considered, mainly phase 3 trials with phase 2b trials being considered if appropriate. In terms of patient characteristics, the population of interest will be adults with type 2 diabetes. The intervention will be the use of medication Canagliflozin / SGLT2s. The control will be usual care with an active comparator, or placebo.

A conventional systematic review of publised RCTs related to the SGLT2 inhibitors Dapagliflozin, Canagliflozin, Ertugliflozin and Empagliflozin will be carried out using traditional medical databases for systematic reviewing. In addition CSRs for trials related to these medications will be requested from YODA Project (Canagliflozin) and from the European Medicines Agency.

Main Outcome Measure and how it will be categorized/defined for your study:

Particular outcomes of interest will include change in HbA1c, all-cause mortality, reduction in micro- and macro-vascular complications, patient-reported symptoms and quality of life and specific adverse outcomes reported for Canagliflozin / SGLT2s including renal impairment, diabetic ketoacidosis, volume depletion, fournier's gangrene and lower limb amputation. The outcomes of note will be both clinically significant and significant from the point of view of patients. Any other relevant outcomes will also be included.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The above outcomes will be analysed with particular focus on patient related outcomes. All relevant clinical efficacy and safety outcomes will be considered. In terms of treatment effect measures, relative risk (RR) will be used for dichotomous data (e.g. cardiovascular mortality) and mean difference or standardised mean difference for continuous data. For event rate data (e.g. numbers of hospitalisations) incidence rate ratio will be used and for time-to-event data (e.g. time to first hospitalisation) hazard ratio will be used.

Statistical Analysis Plan:

A narrative synthesis of included studies will be conducted. Data extraction will be performed separately for clinical study reports and published trial reports. In terms of effect measure of interest, the relative risk for pre-specified clinical outcomes of interest will be analysed. Meta-analysis will be undertaken where possible for included efficacy and safety outcomes using appropriate random effects regression models (treatment effect varying across studies). We would plan to perform a network metanalysis contingent on access to CSR related data for other agents in the

same class.
Meta-analyses will be conducted using all available sources (to include CSR-based sources), as well as just with published sources. In cases of discrepancy between trial registry and publication, sensitivity analysis using publication information will also be conducted. Heterogeneity in outcomes due to study characteristics will be evaluated using meta-regression, if sufficient studies are identified.
With regard to examining the methodology and quality of CSR-based trials compared with published trials as outlined above, outcomes will be summarised across CSRs and published sources and differences will be assessed using appropriate statistical test for paired data (i.e. paired t test, Wilcoxon test, McNemar test).
Software Used:
STATA

Project Timeline:

The project is proposed to begin in earnest in January 2020 with a full systematic review and meta-analysis to be carried out. It is anticipated that analysis will be completed within a year of this date (January 2021) and the results of the study submitted for publication within a further year after this. Results can be reported back to the YODA Project at this time.

Dissemination Plan:

It is planned that the protocol for the relevant systematic review for this medication will be published on PROSPERO. Following completion of this doctoral project it is planned that the results of each relevant part will be published in high impact peer reviewed journals to ensure that the results of the study are appropriately disseminated. It is envisaged that this will include results on the impact of CSR-informed estimates on efficacy and safety, as well as on cost-effectiveness. Specific target journals of interest include the British Medical Journal, BMJ Evidence Based Medicine, BMJ Open, BMC Series and JAMA Internal Medicine as a number of similar relevant papers in relation to clinical study reports have been published through these media previously.

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