Principal Investigator

First Name: Frank
Last Name: Moriarty
Degree: BSc (Pharm), MPharm, PhD, MPSI
Primary Affiliation: Royal College of Surgeons in Ireland
E-mail: dbyrne21@tcd.ie
Phone number: 0035314028575
Address: Mercer Building, Royal College of Surgeons in Ireland
St Stephen's Green
City: Dublin 2
State or Province: Dublin 2
Zip or Postal Code: D02 YH72
Country: Ireland

General Information

Key Personnel (in addition to PI):
First Name: Dr David
Last name: Byrne
Degree: MB BCh BAO
Primary Affiliation: Royal College of Surgeons in Ireland
SCOPUS ID: 1984121

First Name: Prof Tom
Last name: Fahey
Degree: MSc MD DCH DObs Med Cert MFPH
Primary Affiliation: Royal College of Surgeons in Ireland

First Name: Dr Frank
Last name: Moriarty
Degree: BSc (Pharm), MPharm, PhD, MPSI
Primary Affiliation: Royal College of Surgeons in Ireland

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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_forms_0.pdf
https://yoda.yale.edu/system/files/yoda_project_certificate_of_disposition_2019-4071_signed.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

Reporting of harms in SGLT2 clinical study reports compared to trial registries and publications: a methodological review

Narrative Summary:

Focusing on the SGLT2 inhibitor medications, the aim of this project is to assess the consistency in reporting of harms in clinical trials and timeliness of access to safety data between clinical study reports and the usual sources, namely publications, clinical trial registries.
Requests for trial data related to the SGLT2 inhibitors have been requested directly from the EMA, from Yale Open Data Access (YODA) and have been obtained directly from the EMA's public Clinical Data platform. Matched publications for each trial have been obtained using PubMed, and matched clinical trial registry entries on ClinicalTrials.gov have also been identified.

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. The Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel group of medications which are recommended as a second-line option after metformin in type 2 diabetes, and more recently have been cited as having benefits in those with heart failure. Some safety concerns have been raised in relation to these medications, so it is important that all evidence for these safety signals are reported in a timely and consistent manner.
Objective: Focusing on the SGLT2 inhibitors, the objectives of this project are to document procedures for identifying, accessing, extracting data from, and analysing CSRs for research purposes. To evaluate the differences between published sources and clinical study reports in terms of reporting of safety outcomes. To assess the completeness of reporting of harms, discrepancies in reported safety data and timeliness of access to such data across three main sources of trial data, namely publications, clinical trial registries and clinical study reports.
Study Design: A methodological review of reporting of harms for SGLT2 medications across three main sources of trial data
Participants: Clinical trials involving SGLT2 inhibitors
Outcomes: Total adverse events, serious adverse events (SAEs), SAEs leading to death and leading to discontinuation. Renal impairment, DKA, UTI, amputation, fracture, hypovolaemia/osmotic diuresis and any other clinically relevant outcome. Timeliness of reporting of safety outcomes across sources.
Statistical Analysis: Completeness / consistency of reporting
Descriptive statistics will be reported for the relevant trials. Completeness of reporting of the pre-specified outcomes will be reported for each of the three sources, including proportions of trials with discrepancies between sources. Where relevant, narrative descriptions of the discrepancies in reporting between each source will included.
Timeliness
Delays in the availability of safety results for all three sources will be reported as median time (in days) from study completion to the availability of results, and the relevant interquartile range. Kaplan-Maier analysis will be performed to assess the delay from trial completion to the availability of results for each source.

Brief Project Background and Statement of Project Significance:

The Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel group of medications used in diabetes, of which four are currently licenced for use in the EU; Dapagliflozin, Canagliflozin, Empagliflozin and Ertugliflozin. SGLT2 inhibitors have been recommended for use as a second-line option, after metformin, in patients with type 2 diabetes, including by the National Institute for Health and Clinical Excellence (NICE). Recently SGLT2 inhibitors have been discussed as potential options in the management of heart failure, even in the absence of diabetes. Specific safety concerns have been raised in relation to these medications, with acute kidney injury (AKI), euglycaemic DKA, urinary tract infections (UTI), fractures and lower limb amputations being highlighted, with calls for further research to refine the evidence for these outcomes. The EMA has updated the summary of product

characteristics (SmPC) for all SGLT2 inhibitors in relation to Diabetic Ketoacidosis (DKA) risk perioperatively. Safety updates have been circulated by the Medicines and Healthcare products Regulatory Authority (MHRA) in relation to the potential risk of Fournier's gangrene and by the FDA in relation to the risk of severe UTI.
In addition, several studies have highlighted the delays and associated risks in the reporting of safety concerns by regulators for medications. To the author's knowledge, to date no study has used clinical study reports in assessing the consistency and timeliness of reporting of safety outcomes for SGLT2 inhibitors.

Specific Aims of the Project:

The aim of this project is to assess the completeness of reporting of harms, discrepancies in reported safety data and timeliness of access to such data across three main sources of trial data, namely publications, clinical trial registries and clinical study reports.
Focusing on the SGLT2 inhibitors, the objectives of this project are to document procedures for identifying, accessing, extracting data from, and analysing CSRs for research purposes. To evaluate the differences between published sources and clinical study reports in terms of reporting of safety outcomes. To assess the completeness of reporting of harms, discrepancies in reported safety data and timeliness of access to such data across three main sources of trial data, namely publications, clinical trial registries and clinical study reports.
The specific hypothesis to be evaluated is that clinical study reports provide an earlier opportunity to access safety data for clinical trials and that this earlier access will allow for safety issues to be highlighted and quantified earlier and more comprehensively compared to traditional sources.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety
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 available documents of randomised control trials involving Canagliflozin / SGLT2s will be analysed. Clinical Study Reports of the main trials involved in the regulatory approval of SGLT2 inhibitors have been requested directly from the EMA, from Yale Open Data Access (YODA) and have been obtained directly from the EMA's public Clinical Data platform. Matched publications for each trial have been obtained using PubMed, and matched clinical trial registry entries on ClinicalTrials.gov have also been identified.

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

Main safety outcomes of interest include those highlighted already as potential safety issues with these medications. They include total adverse events, serious adverse events (SAEs), SAEs leading to death and leading to discontinuation. Renal impairment, DKA, UTI, amputation, fracture, hypovolaemia/osmotic diuresis, timeliness of reporting of safety outcomes across sources and any other clinically relevant safety outcome.

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

The above outcomes will be analysed with particular focus on completeness of reporting and discrepancies in their reporting.

Statistical Analysis Plan:

Descriptive statistics will be reported for the outcomes analysed in the relevant trials. Completeness of reporting of the pre-specified outcomes will be reported for each of the three sources, including proportions of trials with discrepancies between sources. Where relevant, narrative descriptions of the discrepancies in reporting between each source will included.
Delays in the availability of safety results for all three sources will be reported as median time (in days) from study completion to the availability of results, and the relevant interquartile range. Kaplan-Maier analysis will be performed to assess the delay from trial completion to the availability of results for each source. Data extraction will be analysed separately for clinical study reports and published trial reports.

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Software Used:
STATA
Project Timeline:

It is anticipated that analysis will be completed within a year of this date (September 2022) 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:

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 results will include the completeness and timeliness of reporting of safety outcomes. Specific target journals of interest include the British Medical Journal, BMJ Evidence Based Medicine, BMJ Open, BMC Series and Plos 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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Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_project_certificate_of_disposition_2019-4071_signed.pdf