

Principal Investigator

First Name: David
Last Name: McAllister
Degree: MD, MPH, MBChB
Primary Affiliation: University of Glasgow
E-mail: r.mcchrystal.1@research.gla.ac.uk
State or Province: Lanarkshire
Country: United Kingdom

General Information

Key Personnel (other than PI):

First Name: Jennifer
Last name: Lees
Degree: MD; MBChB; MA
Primary Affiliation: University of Glasgow
SCOPUS ID: 56678309200
Requires Data Access? Unknown

First Name: Peter
Last name: Hanlon
Degree: PhD; MSc; MBChB
Primary Affiliation: University of Glasgow
SCOPUS ID: 55983211700
Requires Data Access? Unknown

First Name: Ryan
Last name: McChrystal
Degree: MSci Biological Sciences with Professional Studies; (In-progress) PhD Public Health
Primary Affiliation: University of Glasgow
SCOPUS ID:
Requires Data Access? Unknown

First Name: Kirsty
Last name: Crowe
Degree: MBChB / MBBS, BMedSci
Primary Affiliation: University of Glasgow
SCOPUS ID:
Requires Data Access? Yes

First Name: Andrew
Last name: Rutenberg
Degree: PhD
Primary Affiliation: Dalhousie University
SCOPUS ID:
Requires Data Access? Yes

First Name: Aziza
Last name: Satkhozhina
Degree: MA/MS/MSc
Primary Affiliation: Dalhousie University
SCOPUS ID:
Requires Data Access? Yes

First Name: Thomas
Last name: Downes
Degree: MBChB / MBBS, MPhil
Primary Affiliation: University of Glasgow
SCOPUS ID:
Requires Data Access? Yes

First Name: Avery
Last name: Tidgwell
Degree: 2 years towards BSc
Primary Affiliation: Dalhousie University
SCOPUS ID:
Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2016/05/davidmcallister_coiform.pdf
https://yoda.yale.edu/wp-content/uploads/2021/09/jenniferlees_coiform.pdf
https://yoda.yale.edu/wp-content/uploads/2017/05/peterhanlon_coiform.pdf
https://yoda.yale.edu/wp-content/uploads/2019/10/ryanmcchrystal_coiform.pdf
<https://yoda.yale.edu/wp-content/uploads/2022/12/coi-form-KC.pdf>
<https://yoda.yale.edu/wp-content/uploads/2022/12/coi-form-AR.pdf>
<https://yoda.yale.edu/wp-content/uploads/2022/12/coi-form-AS.pdf>
<https://yoda.yale.edu/wp-content/uploads/2022/12/coi-form-TD.pdf>
<https://yoda.yale.edu/wp-content/uploads/2022/12/coi-form-AT.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. [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 Pioglitazone Therapy](#)
2. [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](#)
3. [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](#)
4. [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](#)
5. [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](#)
 6. [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 Sulphonylurea Therapy](#)
 7. [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](#)
 8. [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](#)
 9. [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](#)
 10. [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](#)
 11. [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](#)
 12. [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](#)
 13. [NCT02065791 - 28431754DNE3001 - A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Understanding frailty, multimorbidity and renal failure in clinical trials: Attrition, retention and heterogeneity of treatment effects in trials

Narrative Summary:

Clinical trials can be unrepresentative with respect to clinical characteristics (e.g. multimorbidity, kidney function). We have previously made observations about the relationships between multimorbidity, frailty and serious adverse events, changes in treatment effects and trial calibration to real-world populations to improve representativeness. We wish to develop these findings by better understanding the relationships between frailty, multimorbidity and renal failure; and attrition, representativeness and heterogeneity of treatment effects.

Scientific Abstract:

Background: Clinical trials are the key method for determining treatment effects, but are known to be unrepresentative with respect to a range of important clinical characteristics such as age, kidney function, race/ethnicity, multimorbidity and frailty. Declining kidney function is associated both with increasing age and multimorbidity and has important additional implications for drug selection and dosing which are not adequately considered in the clinical trial setting. We have previously made a number of important observations regarding trials and representativeness. First, multimorbidity and frailty are present (albeit underrepresented) in clinical trials and both predict serious adverse event rates. Secondly, morbidity count (a metric of multimorbidity) is not associated with heterogeneity in treatment effects, but is associated with increased rates of trial attrition. Finally, clinical trials can be calibrated to real-world populations in order to improve the representativeness of trial findings. However, while these findings are novel, they are difficult to operationalise.

Objectives: 1. Better understand the relationship between frailty and kidney function and trial outcomes and characteristics; 2. Determine whether it is practical to increase trial representativeness by recruiting more individuals with frailty, multimorbidity and impaired kidney function, or whether this would simply lead to greater trial attrition; 3. Determine whether calibrating trials to target populations modifies treatment effects, and whether the magnitude of this differs depending on the level of frailty, multimorbidity and kidney function within each trial.

Study Design: We will include descriptive elements concerning frailty, multimorbidity and kidney function in trials as well as an examination of heterogeneity of treatment effects according to these characteristics, and on aspects of trial conduct - trial attrition and screening. We will also develop risk prediction models for trial attrition and screening respectively, including but not limited to these characteristics.

Participants: Participants from trials of novel antidiabetics for type 2 diabetes

Primary and Secondary Outcome Measures: Screen failure (Collapsed into Wholly objective/Partially subjective/Wholly subjective); Causes of attrition; Adverse events; Target events

(Primary/Secondary/Other trial outcomes); Kidney events (incidence and grade of renal events)

Statistical Analysis: Models will be fit to individual trials and outputs (coefficients and variance-covariance matrices) alongside obtained summary statistics for study variables. Cox models (or parametric survival models) will be fit to time-to-event data. Linear, logistic and poisson models will be fit to continuous, binary and count data. Model outputs will be treated as outcomes in meta-analyses, with predictor variables being trial-level characteristics (e.g. index condition, treatment comparisons, phase). Meta-analysis level models will have normal likelihoods (or when multiple coefficients are being simultaneously modelled, multivariate normal likelihoods). For all models, we will explore non-linearity for continuous variables using fractional polynomials and estimate treatment/covariance interactions using terms between treatment effect and transformed variables.

Brief Project Background and Statement of Project Significance:

Clinical trials are the key method for determining treatment effects, but are known to be unrepresentative with respect to a range of important clinical characteristics such as age, kidney function, race/ethnicity, multimorbidity and frailty. Declining kidney function is associated both with increasing age and multimorbidity and has important additional implications for drug selection and dosing which are not adequately considered in the clinical trial setting.

We have previously made a number of important observations regarding trials and representativeness. First, multimorbidity and frailty are present (albeit underrepresented) in clinical trials and both predict serious adverse event rates (Hanlon 2019, Hanlon 2021 and Hanlon 2022). Secondly, morbidity count (a metric of multimorbidity) is not associated with heterogeneity in treatment effects (File attachments), but is associated with increased rates of trial attrition (Lees 2022). Finally, clinical trials can be calibrated to real-world populations in order to improve the representativeness of trial findings (Butterly 2022).

However, while these findings are novel, they are difficult to operationalise. We intend to take these findings in three directions. First, we wish to better understand the relationship between frailty and kidney function and trial outcomes and characteristics. Secondly, we wish to determine whether it is practical to increase trial representativeness by recruiting more individuals with frailty, multimorbidity and impaired kidney function, or whether this would simply lead to greater trial attrition. Thirdly, we wish to determine whether calibrating trials to target populations modifies

treatment effects, and whether the magnitude of this differs depending on the level of frailty, multimorbidity and kidney function within each trial.

We propose addressing these questions using two specific exemplars: 1. Novel antidiabetics for type 2 diabetes (see this protocol document for a description of the trials). Where feasible (e.g. for the attrition risk prediction scores) we will also validate the findings against the heterogeneous set of trials (21 index conditions across general medicine) which we have already extensively studied and for which we have considerable R code within the Vivli repository.

Specific Aims of the Project:

To determine:-

1. The distribution of multimorbidity, frailty and kidney function (measured via eGFR) within trials
2. Whether the rates of target and adverse outcomes differ by multimorbidity, frailty and kidney function
3. Whether treatment effects on target and adverse outcomes differ by multimorbidity, frailty and kidney function
4. Whether a) multimorbidity, frailty and kidney function affect the risk of failing trial screening, and b) whether these characteristics feature in/improve a prediction model estimating the risk of screen failure, which we will develop
5. Whether a) multimorbidity, frailty and kidney function affect the risk of trial attrition, and whether b) whether these characteristics feature in/improve a prediction model estimating the risk of trial attrition, which we will develop
6. Whether calibrating trials to routine data populations richer in people with multimorbidity, frailty and kidney impairment, modifies trial findings.

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

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

Data Source: As we are completing this data request per the requirements of a Vivli data request, we will pool these studies with studies received from Vivli. Studies request are from trials for diabetes, cancer and a heterogeneous set of index conditions. We will also pool the YODA and Vivli trials together with study-level data from the AACT platform which we will provide ourselves. IPD analysis will take place within the Vivli secure platform.

Inclusion/Exclusion Criteria: We will include all randomised participants.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Screen failure defined using variables typically found in the "Inclusion/Exclusion Criterion Not Met" SDTM Table. Will collapse criteria into: Wholly objective (e.g. laboratory result); Partially subjective (e.g. Severe co-existing cardiovascular disease); Wholly subjective (e.g. Opinion of the investigator). Causes of attrition (outlined by ClinicalTrials.gov reporting definitions as Adverse event; Death; Lack of efficacy; Lost to Follow-Up; Physician Decision; Pregnancy; Protocol Violation; Withdrawal by Subject; Other collapsed into a 5-level categorical variable: Adverse event; Loss to Follow-up; Clinician/Sponsor decision; Participant decision; Other.

Adverse events categorised as serious and other, further categorised according to whether: They pertain to a target index condition; Are known adverse events of the investigational product under study; Pertain to a comorbid condition.

Target events as trial outcomes (Primary, secondary or other).

Kidney events defined as the incidence and grade of renal events using creatinine and eGFR levels, urinalysis results and adverse event recording.

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

Kidney function as estimated glomerular filtration rate (eGFR) calculated from serum creatinine using various formulae and compared to other kidney function measures (e.g. creatinine clearance) Frailty as an index value between 0 and 1 calculated by identifying 40 health-related deficits, calculating total deficits present and dividing by total number of possible deficits. Deficits will be identified using: Medical history data for comorbidities, identified from a pre-specified list using lower-level MedDRA coded terms, and supplemented by concomitant medication data.; Symptoms and functional limitations identified from symptom questionnaires and quality of life scores, such as generic questionnaires (e.g. EQ5D or SF-36) or disease-specific measures (e.g. impact of weight on quality of life scale); Laboratory values (e.g. cholesterol); and Physical measurements (e.g. body mass index).

Multimorbidity measured as a count of conditions derived from medical history and concomitant medication data, as well as a binary variable for the presence or absence of the six commonest comorbidities for each index condition.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Participant-level data.

For objectives 2, 3, 4a and 5a the following predictors are relevant as potential confounders. For objectives 5a and 5b, they are potential useful predictors. For Objective 6, they will be included as potential treatment effect modifiers.

Age ideally as 5 year age bands or finer-grained; Sex; Race/ethnicity - White, Black, Asian, other (in order of prevalence) will be the categories into which we will collapse the existing categories; Smoking status; Markers of severity of index condition (e.g. baseline symptom scores); Disease duration; Medical history data (lower-level MedDRA terms); Concomitant medications ideally as 5 character ATC code (eg A10AB) or as preferred terms alongside route data (eg nasal, inhaled, topical etc); Laboratory measures ideally all as a minimum albumin, creatinine, estimated glomerular filtration rate, platelets, AST, ALT, and haemoglobin; Physical measurements (e.g. height, weight, BMI, forced expiratory volume in one second, blood pressure).

Trial-level data (e.g. total number and duration of visits) in studying screen failure and attrition, extracted from public documentation and held/examined within trial repositories.

Statistical Analysis Plan:

All analyses will be performed in two stages. In stage one, models will be fit to individual trials. The model outputs (coefficients and variance-covariance matrices) alongside summary statistics for study variables, will then be obtained. In stage two these model outputs will be treated as outcomes in meta-analyses, with predictor variables being trial-level characteristics such as index condition, treatment comparisons and phase. We have previously used a similar approach in a number of publications (Hanlon et al., 2020; Hanlon et al., 2021; Hanlon et al., 2022; Lees et al., 2022). Meta-analysis level models will have normal likelihoods (or when multiple coefficients are being continuously modelled multivariate normal likelihoods). For the intercepts trial will be treated as a random effect. For other predictors (condition, index condition, etc) we will explore fixed and random effects. We will fit the meta-analysis models using the Bayesian modelling software Stan. For the trial-level models, the choice of model depends on the outcome and so is described separately for each outcome below. For all models, we will explore non-linearity for continuous variables using fractional polynomials. Having decided on appropriate polynomials for continuous variables, we will include interaction terms between treatment effect and these transformed variables to estimate treatment/covariate interactions (Royston et al., 2002) Generalised linear models will be fit in R using the GLM function and survival models will be fit in R using the flexsurv package. Due to the complexities of these analyses we will either be using simple single imputation (as in the case of the frailty index) or complete case analysis to handle missing data. We will state the limitations of using this approach in any publications.

Objective-specific analysis details (Listed in Specific Aims of the Project):

#1: We will summarise the distribution of each variable by selecting a parametric distribution which fits the data well. For example we previously found that frailty was well described using the generalised gamma distribution (Hanlon et al., 2020).

#2: We will fit Poisson regression models of adverse events on these characteristics, with and without adjustment for potential confounders, using the log of the person-time to follow-up as an offset variable.

#3: For continuous outcomes which are approximately normally distributed we will fit linear regression models. For continuous outcomes which are not approximately normally distributed we will perform an appropriate transformation. For binary, count and time to event variables we will perform logistic, Poisson and Cox regression modelling respectively.

#4 (a, b): For both a and b we will model screen failure using logistic regression models. These will be two-stage analyses as per 3.

#5 (a, b): For both a and b we will model screen failure using time to event models. We hope to use parametric survival models (e.g. Weibull, Generalised Gamma) provided these fit the data adequately.

#6: The outputs from 3 will be meta-analysed then subsequently used to ?predict? treatment effects in a target population. The methodology is described in detail in the active application Vivli ID 00006115 and in a protocol paper pertaining to that project (Butterly et al., 2022). Essentially it is a weighted summation of treatment main effects and covariate-treatment interactions over the distribution of patients in a real-world setting.

Project Timeline:

Project start date: 03/01/2023

Analysis completion date: 04/20/2025

Dissemination Plan:

We will present these findings at scientific conferences and submit them for publication to peer-reviewed journals. We will also disseminate these findings to patients and other interested stakeholders through patient groups and social media with advice from Patient and Public Involvement and Engagement groups (including the west of Scotland kidney PPIE research group).

Bibliography:

Butterly, E., Wei, L., Adler, A. I., Almazam, S. A. M., Alsallumi, K., Blackbourn, L. A. K., Dias, S., Hanlon, P., Hughes, K., Lewsey, J., Lindsay, R., McGurnaghan, S., Petrie, J., Phillippo, D., Sattar, N., Tomlinson, L. A., Welton, N., Wild, S., & McAllister, D. (2022). Calibrating a network meta-analysis of diabetes trials of sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor analogues and dipeptidyl peptidase-4 inhibitors to a representative routine population: a systematic review protocol. *BMJ Open*, 12(10), e066491.

<https://doi.org/10.1136/bmjopen-2022-066491>

ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies. (n.d.). Retrieved 11 December 2022, from

https://prsinfo.clinicaltrials.gov/results_definitions.html

Hanlon, P., Hannigan, L., Rodriguez-Perez, J., Fischbacher, C., Welton, N. J., Dias, S., Mair, F. S., Guthrie, B., Wild, S., & McAllister, D. A. (2019). Representation of people with comorbidity and multimorbidity in clinical trials of novel drug therapies: An individual-level participant data analysis. *BMC Medicine*, 17(1), 201. <https://doi.org/10.1186/s12916-019-1427-1>

Hanlon, P., Butterly, E., Lewsey, J., Siebert, S., Mair, F. S., & McAllister, D. A. (2020). Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. *BMC Medicine*, 18(1), 309.

<https://doi.org/10.1186/s12916-020-01752-1>

Hanlon, P., Corcoran, N., Rughani, G., Shah, A. S. V., Mair, F. S., Guthrie, B., Renton, J. P., & McAllister, D. A. (2021). Observed and expected serious adverse event rates in randomised clinical trials for hypertension: an observational study comparing trials that do and do not focus on older people. *The Lancet Healthy Longevity*, 2(7), e398?e406.

[https://doi.org/10.1016/S2666-7568\(21\)00092-1](https://doi.org/10.1016/S2666-7568(21)00092-1)

Hanlon, P., Butterly, E., Shah, A. S. V., Hannigan, L. J., Wild, S. H., Guthrie, B., Mair, F. S., Dias, S., Welton, N. J., & McAllister, D. A. (2022). Assessing trial representativeness using serious adverse events: an observational analysis using aggregate and individual-level data from clinical trials and routine healthcare data. *BMC Medicine*, 20(1), 410.

<https://doi.org/10.1186/s12916-022-02594-9>

Lees, J. S., Hanlon, P., Butterly, E. W., Wild, S. H., Mair, F. S., Taylor, R. S., Guthrie, B., Gillies, K., Dias, S., Welton, N. J., & McAllister, D. A. (2022). Effect of age, sex, and morbidity count on trial attrition: meta-analysis of individual participant level data from phase 3/4 industry funded clinical trials. *BMJ Medicine*, 1(1). <https://doi.org/10.1136/bmjmed-2022-000217>

Royston, Patrick & Sauerbrei, W.. (2002). The use of fractional polynomials to model interactions between treatment and continuous covariates in clinical trials. Stata Users Group, United Kingdom Stata Users' Group Meetings 2002.

Symbicort Single Inhaler Therapy vs Conventional Best Practice for the Treatment of Persistent Asthma in Adults – Study Results – ClinicalTrials.gov. (n.d.). Retrieved 19 December 2022, from <https://clinicaltrials.gov/ct2/show/results/NCT00385593>