The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #:   )

Reviewers:

☐ Nihar Desai

☐ Cary Gross

☐ Harlan Krumholz

☐ Richard Lehman

☐ Joseph Ross

Review Questions: **Decision:**

1. Is the scientific purpose of the research proposal clearly described?

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?

3. Can the proposed research be reasonably addressed using the requested data?

4. Recommendation for this data request:

Comments:

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.

The following pages contain the original YODA Project review and

the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #:   )

Reviewers:

☐ Nihar Desai

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Review Questions: **Decision:**

1. Is the scientific purpose of the research proposal clearly described?

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?

3. Can the proposed research be reasonably addressed using the requested data?

4. Recommendation for this data request:

Comments:

Principal Investigator

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2017-1746

General Information

Key Personnel (in addition to PI):   First Name: Sofia
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SCOPUS ID: 9337815800

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: Wellcome Trust - Intermediate Clinical Fellowship 201492_Z_16_Z
How did you learn about the YODA Project?: Other

coi_form_dm.pdf

coi_nickyw.pdf

yoda_sd.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

Associated Trial(s): NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis

NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis

NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic

NCT00264537 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid Arthritis

NCT00264550 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy

NCT00265083 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis

NCT00299546 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Rheumatoid Arthritis and Previously Treated with Biologic Anti

NCT00361335 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy

NCT00487539 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis

NCT01106625 - 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 Glycemi

NCT01081834 - 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 Co

NCT01106677 - 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 Inadequ

NCT00968812 - 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

NCT01106651 - 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 In

NCT01106690 - 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 Glycemi

NCT01137812 - 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 Con

NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease

NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease

NCT00236028 - A Randomized, Double-blind, Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab) in Combination With Methotrexate Compared With Methotrexate Alone for the Treatment of Patients With Early Rheumatoid Arthritis

NCT00236509 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine

NCT00231595 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine

NCT00236561 - A Randomized, Double-Blind, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and

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

Research Proposal

Project Title

Heterogeneity in relative treatment efficacy by age, sex, socioeconomic status and comorbidity

Narrative Summary:
Randomised clinical trials provide the best evidence about treatment effectiveness. Trial results can be applied to "target" populations, for example; if a diabetes trial shows that a drug reduces blindness by 20%, and other data shows that 8 out of 100 people with diabetes develop blindness, then 2 fewer people are expected to develop blindness per 100 treated.

We would like to use a similar approach for a new target, people with additional (co-morbid) diseases. To make

sure this is valid, we will examine clinical trial data from YODA, and other clinical trial repositories, to see if trial participants with and without different co-morbid diseases experience similar treatment benefits.

Scientific Abstract:

Background
Using evidence synthesis, estimates of efficacy from clinical trials can be applied to standard treatment comparator (natural history) event rates from observational data to estimate effectiveness in target populations.
In order to extend this approach to estimate treatment effectiveness in people with additional secondary diseases (comorbidity), we need to determine whether treatment efficacy is similar in people with and without comorbidity.

Objective
To estimate the variation in efficacy by comorbidity within clinical trials, and summarise this for different drug-classes and wider groupings of related drug classes.

Study design
Meta-analysis

Participants
Trials of drugs to prevent or treat long-term medical conditions (38 trials from the YODA repository, ~200 trials from other repositories)

Main outcome measures
Outcomes common to trials of specific drug-classes, eg HbA1c in diabetes trials.

Statistical analysis
For each outcome, in each trial, we will model main effects and interactions with treatment allocation for age, sex and the 6 commonest comorbidities. We will use generalized linear models, or Cox regression as appropriate to the outcome.

In subsequent analyses, using the coefficients and variance-covariance matrix from these models as the dependent variables, we will estimate the mean (and variance) of each comorbidity-treatment interaction for specific drug-classes, and across drug-classes for wider related drug-groupings.

We will explore the effect of different scales and transformations on the extent of heterogeneity.

Brief Project Background and Statement of Project Significance:
Multimorbid patients are less likely than those with single diseases to receive recommended drugs, even where there are no specific contraindications.[6–11] This difference may represent under treatment or may have arisen from uncertainty among clinicians as to the applicability of clinical guidelines, which rarely provide specific advice on managing multimorbidity.[3,12,13]

Where multimorbidity alters the (baseline) natural history of diseases, the effects of treatment are likely to differ. For example, while there is strong evidence that the benefits of dual antiplatelet therapy (DAPT) following myocardial infarction (versus a single antiplatelet) outweigh the risks,[14,15] this may not be true for patients with comorbid chronic obstructive pulmonary disease (COPD). Cardiovascular mortality is commoner in COPD than the general population, favouring DAPT.[16] However, non-cardiovascular mortality is also higher,[17] favouring single-antiplatelet therapy because of competing risks. Glucose and intensive risk factor control in diabetes[18,19] and anticoagulant use in atrial fibrillation[20] provide similar examples, where the net overall treatment benefits are uncertain for multimorbid patients.

Neither clinical trials nor observational studies fully address this problem.[21] Trialists do not report results stratified by combinations of important comorbidities.[12] Nor is it feasible to conduct trials sufficiently large to allow such comparisons for all indications.[5,21] Administrative healthcare databases are sufficiently large. However, while estimates of treatment effectiveness obtained from observational studies are generally comparable to those from clinical trials,[22] they have in several cases led to inaccurate conclusions.[23–25]

There is therefore a need to find alternative approaches to produce estimates of net overall treatment benefits for patients with multimorbidity.

In a Wellcome Trust funded project, we intend to develop and validate an approach using Bayesian Evidence Synthesis to estimate treatment effectiveness in multimorbidity. As with standard evidence synthesis, we plan to apply estimates of treatment efficacy from clinical trials to observational data representative of the target population. However, in most evidence synthesis it is assumed that estimates of relative treatment efficacy (RTE) from clinical trials can be applied, unmodified, to the target population. It is not known whether this assumption is valid in applying efficacy estimates to patients with multimorbidity.

In a limited number of large individual-patient meta-analyses (such as of aspirin for primary and secondary prevention) RTE was similar regardless of cardiovascular risk factors, age and sex.[27,28] However, for most drugs and conditions empirical evidence is lacking as to whether and how RTE differs between patients with and without comorbidity, especially for comorbidities which are not established causes or complications of the target disease.

Specific Aims of the Project:
Therefore, in this proposal we aim to examine and quantify the variation in relative treatment efficacy by comorbidity. We intend to do so by examining such variation within clinical trials, for a range of drug-classes, within wider groupings of related drug-classes (eg blood glucose lowering drugs).

Objectives
Stage One – Produce trial-level summary estimates
1. Assign drugs to broad drug-classes based on 5-character ATC codes
2. Assign related drug-classes to wider drug-groupings
3. Identify comorbidities within individual clinical trials according to the Clinical Classification Software scheme[29]
4. For each trial estimate interactions between treatment allocation and age, sex, socio-economic status and selected comorbidities
Stage Two – Analyse trial-level aggregated estimates
5. In Bayesian hierarchical generalized linear models, use the estimates from 4 alongside estimates from clinical trials obtained from other repositories to estimate average drug-class-level and drug-grouping level comorbidity-treatment interaction
6. Summarise 5 as a probability distribution for use in subsequent evidence synthesis; either as off-the-shelf informative priors for meta-analyses, or as inputs to probabilistic sensitivity analyses in which treatment effects are modelled

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
The purpose of this project is to produce summaries, for and across drug-classes, of the covariate-treatment interactions for different outcomes within drug-groupings formed of clinically-related drug-classes, for subsequent use by ourselves and others either as informative priors, or in probabilistic sensitivity analyses. The covariates of interest being comorbidities, age, sex and socio-economic status.

Consequently, trials were chosen to include drugs used to treat or prevent long term medical (and, as these are a common issue in the elderly, urological) conditions. Both short and long term indications were included (eg short term post MI therapy). We have excluded trials where the indication was for neoplastic, infectious, affective, psychotic or developmental disorders. Topical eye and primary prevention trials in the general adult population were also excluded. Small trials, and those with highly restrictive inclusion criteria were also excluded.

This led to us identifying 38 relevant trials in the YODA repository. Covariate-treatment interaction estimates from which will be analysed alongside estimates from similar trials obtained from other repositories

Main Outcome Measure and how it will be categorized/defined for your study:
As our aim, is to 'survey' many trials to determine how much variation in treatment effect by comorbidity is plausible within different clinically-meaningful groupings, we intend to obtain measures which are similar across multiple trials. Therefore, within each indication we will select endpoints common to trials for that indication. For

example, the majority of trials for rheumatoid arthritis include the American College of Rheumatology Criteria and Disease Activity Score endpoints.

In order to simplify comparisons, we will scale continuous outcomes and will also use log-transformation in order to examine heterogeneity by comorbidity on the relative scale. After examining trial documentation and datasets, but prior to performing any comparisons by treatment allocation, we will with our steering group agree on the final outcomes, transformations etc.

While we believe that this approach is suitable for our analysis, we recognise that it is not likely to be optimal for estimating the main effect for each trial. For that reason, we will not report the main effects (ie marginal across sub-groups) from individual trials.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
We will examine covariate-treatment interactions for each trial. The covariates included will be age, sex, socio-economic status and comorbid disease.

Age will be modelled as a continuous variable, where there is evidence of non-linearity we will use fractional polynomials. Sex will be defined as per the study documentation. We will define socio-economic status separately using educational attainment and income as proxies, collapsing the reported categories into a three-level variable.

Comorbidities will be categorised using the Agency for Healthcare Research and Quality clinical classifications system (CCS). [30] We will attempt to define in the trial datasets comorbid conditions from 94 of the CCS groups. Trial-specific operational definitions of each comorbidity will be defined using a combination of demographic, past medical history, lifestyle (eg smoking) and drug variables as well as information from trial protocols (ie inclusion and exclusion criteria). We anticipate that it will frequently not be possible to arrive at an operational definition for many of the comorbidities.

Each operational trial definition will be finalised prior to analysing outcome data.

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

Statistical Analysis Plan:
Stage one
For each outcome, we will model main effects and interactions with treatment allocation for age, sex, socio-economic status (in 3-levels) and the 6 commonest comorbidities for that drug-grouping. Where a particular trial does not have a comorbidity variable defined we will record that variable as missing.

We are not aware of any study which has examined the effect of different scales on the extent of heterogeneity in treatment-comorbidity interactions between patients. Therefore, for continuous measures we will model outcomes on both the absolute and relative (log-transformed) scale, and for yes/no event outcome data we will model outcomes on the log-odds ratio, log-rate ratio and log-risk ratio scales. We will estimate hazard ratios using Cox regression, and for all other models will use Generalized Linear Models with appropriate link functions and error distributions.

Analyses will be conducted in R. We will obtain the coefficients and variance covariance matrices from each of these models. For simplicity, missingness will be treated using complete case analysis. We will however record and report, for each operational comorbidity definition, the proportion of participants for whom sufficient data was missing to prevent a participant being defined as having a comorbid disease.

In summary, therefore, the following results, all of which are trial-level aggregates/summaries, will be obtained from the above analyses, conducted on the YODA server:-
1. The proportion of participants with each combination of comorbidities
2. The proportion of participants with missing data included in the definition of each comorbidity
3. The coefficients and variance-covariance matrix of the regression models described above.

Stage Two
All subsequent modelling will be conducted on trial summary-level data within our institution.

In the second part of a two-step approach we will model the comorbidity-treatment interactions across multiple trials using the parameters described above as the dependent variables in Bayesian hierarchical generalized linear models (eg with a multivariate Gaussian likelihood). The main effects for treatments and covariates will have independent priors for each trial, while the priors for the covariate-treatment interactions will have hyper-priors, to allow sharing of information. We have successfully fit such models on simulated data.

For each covariate-treatment interaction we will report the mean effect for each drug-class and drug grouping, along with the between drug-class variance. We will first model each comorbidity in turn, after which we will simultaneously model multiple comorbidities. We will separately examine associations for datasets comprising trials where a trial drug is compared with placebo, an agent from a different drug-class, and an agent from the same drug-class.

An assumption of this modelling approach is that comorbidity-treatment interactions are exchangeable for trials within drug-classes, and for drug-classes within wider drug groupings. This assumption makes use of the structure inherent in the anatomic therapeutic classification system; thereby allowing borrowing of information across drug-classes (eg antithrombotic agents).

If there is no similarity in treatment-comorbidity interactions within our drug-groupings, the predicted comorbidity-treatment interaction for an unknown drug-class will have a wide uncertainty interval, indicating that little can be learned about one drug class comorbidity-treatment interaction based on knowledge about such an interaction for another drug-class within that grouping.

These models will be fit in the JAGS package. Alternative model specifications will be explored and compared using the deviance information criterion (DIC) and the Bayesian information criterion (BIC). Model convergence and autocorrelation will be assessed using diagnostic plots as well as summaries such as the Gelman-Rubin statistic.

Project Timeline:
1. Defining covariates (age, sex and sex-treatment interactions) , identifying treatment allocation and outcome variables and standardising the latter - 6 months.
2. Modelling covariate-treatment interactions and obtaining coefficients and variance-covariance matrices - 6 months.
Analysing summaries (2) with summaries from other trial repositories - 2-years.

Dissemination Plan:
The protocol will be registered on the PROSPERO register for systematic reviews (or similar) prior to accessing the data. An abstract summarising these results will be submitted to a relevant international conference within one year of completing the analysis and summary results will be made available via our institutional website. A manuscript reporting these findings will be submitted to an appropriate scientific journal such as Medical Decision Making, the Journal of Clinical Epidemiology or Trials.

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