# A.1 Title of the Proposed Research

Assessing heterogeneity in relative treatment efficacy by age, sex and comorbidity.

# A.2 Lay Summary

Less than half of patients with a chronic condition have only a single disease. Most have multiple diseases – or multimorbidity. People with multimorbidity are less likely to receive recommended treatments; Partly because clinical practice guidelines, which make treatment recommendations, rarely provide specific treatment recommendations for people with multimorbidity.

This rarity reflects uncertainty as to whether standard treatment recommendations should apply to multimorbidity. Clinical trials usually resolve such uncertainties, but it is not feasible to conduct trials large enough to examine the most common patterns of multimorbidity, even for the most important treatments. Analysing data from large healthcare databases is a feasible alternative, but such analyses have in several cases led to inaccurate conclusions.

Therefore, individual clinicians have to estimate treatment effectiveness in people with multimorbidity unsupported by guidance or high quality evidence. There is therefore a need to develop novel methods, for determining treatment effectiveness in multimorbidity.

Evidence synthesis (ES), where modellers combine data from multiple sources, is a promising approach. Using ES, results from clinical trials may be combined with other data to estimate treatment effects for particular groups. However, ES has not yet been developed for the problem of multimorbidity and there are a number of additional challenges.

In a project funded by the Wellcome Trust we plan to develop and validate an approach to determine treatment effectiveness in people with multimorbidity. As part of that project we aim to determine whether and how, for different groups of related drug-classes, relative treatment effects differ according to the presence or absence of specific co-existing diseases.

We have identified 201 suitable trials. We will use these to ‘survey’ how treatment effects vary according to the presence of co-existing diseases for different types of drug and treatment outcome (eg blood pressure, mortality).

Rather than focusing on individual drugs we will summarise this variation for drug-classes and groupings of related drug classes. We will use statistical models similar to those outlined in the NICE Technical Support Documents for ES.

This work will improve the health of people with multimorbidity. If we find that there is very little variation, it will considerably simplify the challenge of determining treatment effectiveness in multimorbidity. If instead we discover substantial variation, this knowledge may be incorporated into ES, resulting in more robust valid estimates of treatment effectiveness.

# A.3 Study Design

The study design is meta-analysis/evidence synthesis.

However, rather than meta-analysing the treatment effect we will meta-analyse the treatment-comorbidity interaction. We intend to produce summaries of the treatment-comorbidity interactions at the level of drug-class and drug-grouping (WHO ATC drug classes combined into clinically meaningful groups) rather than at the trial or drug level.

The planned modelling approach is to use Bayesian generalized linear models. The models will be extensions of those described in Dias, Sofia, Nicky J. Welton, Alex J. Sutton, and A. E. Ades. “NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials.” NICE, 2011. http://www.nicedsu.org.uk. The main difference in the models we propose to use is that there will be additional parameters for comorbidities and comorbidity-treatment interactions, and that these will have shared hyper-priors across trials.

# A.4 Studies Selected and Study Populations

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. The covariates of interest being comorbidities, age and sex. We intend for these summaries to be used in models examining treatment effects in people with multimorbidity, either as informative priors, or in probabilistic sensitivity analyses.

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). Therefore, we excluded trials where the indication was for neoplastic, infectious, affective, psychotic or developmental disorders. Topical eye and primary prevention trials conducted in the general adult population were also excluded.

Examples of some groupings of the 201 selected trials are shown in the table below. We will finalise the groupings within our steering committee prior to starting analyses.

### Table - Example drug groupings

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Trials | Participants | Group name |
| A02 | 10 | 9098 | drugs for acid related disorders |
| A10 | 18 | 22676 | drugs used in diabetes |
| B01 | 23 | 123772 | antithrombotic agents |
| C09 | 26 | 24801 | agents acting on the renin-angiotensin system |
| G04B | 8 | 14099 | drugs for urinary frequency and incontinence |
| G04B | 7 | 3836 | drugs used in erectile dysfunction |
| L01 and L04 | 22 | 16938 | antineoplastic agents |
| M04 | 4 | 5187 | antigout preparations |
| M05 | 7 | 15415 | drugs for treatment of bone diseases |
| N04 | 11 | 4469 | anti-parkinson drugs |

In order to obtain trials likely to include at least some participants with one or more comorbid diseases, we selected phase 3 and phase 4 trials for which people aged over 60 were not explicitly excluded (as recorded on clinicaltrials.gov). We selected trials with at least 300 participants to avoid problems with very small numbers, and parallel group designs to avoid additional complexity.

We will use the intention to treat rather than the per protocol population in order to maintain the instrument. Where a trial has more than 2 arms we will select the most extreme comparison – eg a placebo arm versus the highest dose arm.

# A.5 Primary and Secondary Endpoints for the Study

As part of this wide-ranging examination of heterogeneity in treatment effect by comorbidity, we will examine outcomes within each trial, appropriate to the original disease of interest, which might plausibly have a causal relationship with the original study drug.

Our aim, is to ‘survey’ many trials to determine how much variation in treatment effect by comorbidity is plausible within different clinically-meaningful groupings. As such, 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, all of the trials for rheumatoid arthritis (except one) included both the American College of Rheumatology Criteria and Disease Activity Score 28 endpoints (listed on clinicaltrials.gov). Similarly, of 34 trials in chronic obstructive pulmonary disease, 33 included a measure of forced expiratory volume in one second and 21 included a measure of exacerbations. As an example of a categorical variable, for cardiovascular trials, we will use all-cause mortality as well as major adverse cardiovascular events (MACE).

In order to simplify comparisons within indications, and to make qualitative statements about the relative heterogeneity in treatment effect in different drug-groupings (eg is there more variation in chronic obstructive pulmonary disease than in rheumatoid arthritis), we will scale continuous outcomes and will also use log-transformation in order to examine heterogeneity by comorbidity on the relative scale.

After having examined the trial documentation and datasets to identify which data are available, but prior to performing any comparisons by treatment allocation, we will with our steering group agree on the final outcomes, transformations etc.

For each trial, the definitive analysis, as included in clinical study report submitted to the regulatory agencies, will have included the measure felt to best capture the specific aim of the trial. Our aim, instead is to derive similar measures across multiple trials for the purpose of assessing the overall plausibility of variation in treatment efficacy by comorbidity. Hence we recognise that our approach is not likely to be optimal for estimating the main effect for each trial. For that reason, we will not report main effects from individual trials (ie marginal effects across sub-groups), drug-classes or drug groupings.

# A.6 Statistical Analysis Plan

## Rationale

The wider rationale for this research is given more fully in the lay summary section, but is outlined briefly below.

Multimorbidity is common and increasing. Less than half of patients with a chronic condition have only a single disease.[1,2] As multimorbidity is commoner in older people,[2] it is likely to become more prevalent as the population ages, making the provision of optimal care increasingly complex.[3–5]

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]

The complexity and prevalence of multimorbidity is increasing,[26] hence the question of how treatment effectiveness differs for people with comorbidity is becoming increasingly important. Currently, individual clinicians must estimate treatment effectiveness in older, sicker people with multimorbidity unsupported by guidance or high-quality evidence. 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 based around 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) treatment efficacy was found to be similar across patient groups; 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.

## Aim

Therefore, in this proposal we aim to examine and quantify the variation in relative treatment efficacy by comorbidity. We intend to do so by modelling such variation within clinical trials, then summarising this for drug-classes and wider groupings of related drug classes, for a range of comorbidities.

## 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 – eg (B01 – antithrombotic drugs)

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 and selected comorbidities

Stage Two – Analyse trial-level aggregated estimates

5. In Bayesian hierarchical generalized linear models, use the estimates from 4 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

## Study design

The study design involves first producing trial-level summary estimates (Objectives 1-4), and then meta-analysing these across studies (Objectives 5-6).

## Stage One

### Objective 1 Assign drugs to wider drug-classes

The trial inclusion/exclusion criteria are described in previous sections. We have already allocated all trial drugs for 202 selected trials to both an RXNORM code and, where a suitable code exists, a 7-digit WHO ATC code. We have then assigned each code to a less specific 5-character ATC code.

### Objective 2 Related drug-classes to wider drug-groupings

Using clinical judgement, we have made a preliminary assignment of each 5-character drug-class to a wider drug-grouping (see relevant section). We will finalise the groupings within our steering committee prior to starting analyses.

### Objective 3 Identify comorbidities within individual clinical trials according to the Clinical Classification Software scheme (similar to Elixhauser)

Comorbidities will be categorised using the Agency for Healthcare Research and Quality clinical classifications system (CCS). Having similar groupings to those used in the Elixhauser comorbidity scheme,[30] the CCS collapses WHO international Classification of Diseases (ICD-10) codes into groups. The CCS was originally developed in order to produce as clinically homogenous groupings as possible,[29] has been updated for ICD-10 and is used in research and health services reporting.[31] Having excluded those CCS groupings which are unlikely to have any impact on treatment effectiveness (eg code 200 “Other skin disorders” will be excluded), we will attempt to define in the trial datasets comorbid conditions from each of the 94 remaining grouping.

The majority of trials were not set-up to record comorbidities. As such, 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 will, where possible, assign an ICD-10 code as well as CCS group. However, for some trials and comorbidities only the latter, broader, definition will be feasible. We anticipate that it will frequently not be possible to arrive at an operational definition for many of the comorbidities.

As a sense check, we will also examine summary statistics for characteristics not included in the definition, but nonetheless related to the disease. For example, we would expect people with inflammatory arthropathy to have a higher prevalence of chronic pain than people without inflammatory arthropathy (except where collider-bias is an issue).

Where trials do clearly define and record comorbidities (eg the presence of spirometry-confirmed chronic obstructive pulmonary disease as a comorbidity), the sensitivity and specificity of our operational definitions will be estimated and reported.

This approach to defining variables is commonly used in routine-data research, a field in which members of our team have considerable expertise. While imperfect, this approach is an important first step in examining comorbidity-treatment interactions. We will take the following steps to make this process as robust as possible. First, each operational trial definition will be approved by our steering committee comprising clinicians, epidemiologists and statisticians. Secondly, we will not perform any statistical modelling or analyses including the outcome until these definitions have been agreed. Thirdly, we will maintain a database showing how each variable in the final dataset relates to the original trial variables, and will make this available to consumers of the research findings (along with the complete analysis code). Fourthly, we will categorise each trial (using published eligibility criteria) as regards their inclusiveness with respect to the defined comorbidities, and will conduct sensitivity analyses after excluding moderately restrictive trials. Finally, we will make explicit the limitations arising from this approach, particularly the possibility of non-differential misclassification bias, in all study reports.

For each drug grouping we will model treatment effects by age and sex. The latter will be defined as per the study documentation.

### Objective 4 Estimate interactions

For each outcome, we will model main effects and interactions with treatment allocation for age, sex, and up to 6 comorbidities. The comorbidities selected will be the 6 commonest for each drug-grouping. Where a particular trial does not have a comorbidity variable defined we will record that variable as missing.

For between-trial heterogeneity, the effect of scale and different transformations (logistic, log etc) has been extensively studied. However, 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 event outcome data we will model outcomes on the log-odds ratio log-rate ratio scales and log-risk ratio as well as log-hazard ratios 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.

All analyses will be conducted in R. We will obtain the coefficients and variance covariance matrices from each of these models. These model summaries will allow subsequent modelling of differences in treatment efficacy, by comorbidity, for drug classes and wider drug-groupings.

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 diagnosis.

Where trials are missing definitions for particular comorbidities these will be encoded as missing and estimated within the Bayesian modelling. This is equivalent to assuming that data are missing at random.

### Summary of outputs from stage one

In summary, therefore, the following results, all of which are trial-level aggregates/summaries, will be obtained from the above analyses:-

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 Cox proportional hazard and generalized linear models described above.

## Stage Two

### Objective 5 Subsequent modelling

All subsequent modelling will be conducted on aggregated trial-level data.

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 using Markov Chain Monte Carlo Methods in the JAGS package (<http://mcmc-jags.sourceforge.net/>) and using approximate methods in the R package, INLA package (<http://www.r-inla.org/>).

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).

The modelling is sufficiently flexible that, if there is no similarity in treatment-comorbidity interactions within our drug-groupings, the predicted comorbidity-treatment interaction for an unknown drug-class will simply have a wide uncertainty interval. This would indicate that little can be inferred 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, using the GLM module. 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.

## Objective 6 – summarise comorbidity-treatment interactions as probability distributions

For all analyses, after convergence, a random sample from the model chains for the parameters of interest at the drug-class and drug-grouping level will be obtained. A model will be fit to these samples in R using non-linear least squares. Adequacy of the fit will be confirmed graphically. We will choose a distribution with not more than 3 parameters. In pilot analyses a t-distribution fit the MCMC samples very well.

We will retain these diagnostic plots to allow consumers of our research to check on the fit.

## Sample size calculations

We have not conducted a formal power calculation for estimating comorbidity-treatment interactions as we not aware of any analytical method for doing so, and analysing a large number of simulated datasets would have been impractical.

Instead we explored the feasibility of using a similar model to that shown above to estimate the mean comorbidity-treatment interaction across multiple drug-classes for both a categorical and continuous outcome. For both, an unspecified comorbidity was assumed to have a 20% prevalence, and for the continuous outcome the logit link and binomial distribution were substituted for the identity link and normal distribution.

We simulated null interactions for a categorical and continuous outcome and a 1.2-fold comorbidity-treatment interaction for the categorical outcome and a 2.5-unit comorbidity-treatment interaction for the continuous outcome. We recovered the original simulated effects. Additional assumptions are shown in the following table.

|  |  |  |
| --- | --- | --- |
| Outcome | Categorical | Continuous |
| Number trials | 23 | 68 |
| Number participants | 132,358 | 103,774 |
| Baseline | Risk = 0.2 | Mean = 70 |
| Treatment | RR ~ unif(0.65 | Diff ~ N(10, 1) |
| Comorbidity | RR ~ unif (1.2 | Diff ~ N(5, 0.5) |
| Null interaction – result | OR 0.96; 95%CI | Diff -0.01; 95%CI -0.8 to 0.77 |
| Interaction present – result | OR 1.22; 95%CI | Diff 2.52; 95%CI 1.68 to 3.35 |

OR – odds ratio, RR relative risk, diff – difference on the absolute scale

Moreover, although clinicaldatarequest.com is the largest repository, we are applying to additional clinical trial data repositories. As such, for those drug-grouping where data are sparse, we are likely to be able to gain improvements in precision for the estimated comorbidity-treatment interactions by combining the summary estimates from these analyses with additional data.

## Bias and confounding

Patients cannot be randomised to having or not having specific comorbidities. Hence, any observed differences in treatment efficacy by comorbidity may be caused by confounding. We will adjust these associations by age and sex but other variables, such as lifestyle factors, may confound the observed associations.

Moreover, clinical trials use double-blinding and other methods to ensure that follow-up and measurement not differential by randomisation status; no such steps are used to prevent differential misclassification by the presence/absence of comorbidity. As such, apparently weaker treatment effects could be due to greater misclassification in recording outcomes among people with specific comorbidities (eg in people with chronic obstructive pulmonary disease the presence of affective disorders may make exacerbations more difficult to diagnose).

We will therefore make these limitations clear in reporting of our findings. Nonetheless, these limitations are also features of pharmacoepidemiological approaches, the main alternative methodology which has been used to address this question. Moreover, pharmacoepidemiological approaches have the added problem of confounding by indication.

A further caveat around causation is to note that, if treatment efficacy does differ by comorbidity, we will be unable to identify the specific mechanisms underlying this process. Differences in treatment concordance, pharmacokinetics (eg in absorbance), the presence of drug-drug and drug-disease interactions and/or psychological factors modifying experience of certain outcomes (eg pain) could modify treatment efficacy in the presence of comorbidity.

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# A.7 Publication Plan

The protocol will be registered on the PROSPERO register for systematic reviews (https://www.crd.york.ac.uk/PROSPERO/) 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.