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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
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How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_form_jw.pdf
https://yoda.yale.edu/system/files/yoda_coi_form_xz.pdf
https://yoda.yale.edu/system/files/yoda_coi_cherlin.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. NCT01077362 - CNTO1275PSA3002 /// PSUMMIT II - A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis With and Without Prior Exposure to Anti-TNF Agents
2. NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled,

Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy
3. NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis
4. NCT01645280 - CNTO1275ARA2001 - A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Study Evaluating the Efficacy and Safety of Ustekinumab (STELARA®) and CNTO 1959 Administered Subcutaneously in Subjects With Active Rheumatoid Arthritis Despite Concomitant Methotrexate Therapy

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

Research Proposal

Project Title

Improving efficiency of immune-mediated inflammatory disease trials through better design and analysis

Narrative Summary:

Some diseases are caused by the body's immune system incorrectly attacking itself and causing damage through inflammation. This leads to serious symptoms. These immune-mediated inflammatory diseases (IMIDs) include rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and many others.

Clinical trials testing new drugs are vital for improving the health of IMID patients. However, they are very expensive and time-consuming to do. New statistical methods can help to improve efficiency of trials. This research will investigate how basket trial approaches and improving the analysis of responder outcomes can improve the efficiency of IMID trials.

Scientific Abstract:

Background
Immune-mediated inflammatory diseases (IMIDs) are a group of conditions that share common inflammatory and immunity pathways. They affect >5% of the population and cause serious impact on patients and healthcare services.
Clinical trials are essential for improving treatment of IMID patients but are expensive and time-consuming, especially for rare IMIDs. To address these issues, there is a need for improved methods that are tailored to the nature of IMIDs.

Objective
We aim to develop new statistical methods to improve the efficiency of IMID trials, using data from rheumatoid arthritis (RA), psoriatic arthritis (PSA), ulcerative colitis (UC), and Crohn's disease (CD) as proof-of-concept applications of the methods. Specifically we will: 1) develop methods that can more efficiently model the probability of remission in UC and CD; 2) extend basket trial methods to allow more powerful analysis of response outcomes in RA and PSA; 3) develop methods for borrowing information in basket trials where there is a common secondary outcome but different primary outcomes.

Study design
This is a methodological research study. We will develop on previous methods published by the research team in efficient analysis of responder outcomes and borrowing of information in basket trials. Simulation studies will be used to assess the statistical properties of the methods developed. The data being requested in this application will be used as proof-of-concept applications of the methods.

Participants
For all the four trials being requested we will use the primary analysis population in the proof-of-concept application

of methods.

Primary and secondary outcome measure(s)
NCT02407236: Remission (defined by Mayo score)
NCT00771667: Remission (defined by CDAI)
NCT01645280: ACR20 response
NCT01077362: ACR20 response

Statistical analysis
Each objective will have a method (or methods) developed that will be applied to the relevant dataset. This will be done in R, using a Bayesian software package where required.

Brief Project Background and Statement of Project Significance:

Over three million people in the UK have one or more diseases where the body's immune system incorrectly attacks itself and causes damage through swelling (inflammation). The damage from inflammation leads to serious symptoms. These diseases are called immune-mediated inflammatory diseases (IMIDs), which include rheumatoid arthritis, psoriasis, inflammatory bowel disease, and many others. IMIDs harm the activities, health, and wellbeing of affected individuals.

Clinical trials are vital for improving the health of IMID patients. They are used to test if new drugs are beneficial and the best ways of using existing treatments. However, they are very expensive and time-consuming to do. New statistical methods can help to improve efficiency of trials. This research will investigate how basket trial approaches and improving the analysis of responder outcomes can improve the efficiency of IMID trials.

Grayling et al(1) shows IMID trials often use complex response/relapse endpoints that are analysed in an inefficient way. Previous work has developed methods that can be used to considerably improve the efficiency for certain responder outcomes, such as those used in rheumatoid arthritis(2,3). However, these methods require extension to be applicable for some IMIDs, such as Chrohn's Disease and Ulcerative Colitis.

Basket trials have been proposed as a way of improving efficiency of drug development when a drug may show promise for multiple related conditions (such as IMIDs that share a mechanism or symptoms). They have huge potential for evaluating biological therapies that target a common immune or inflammatory pathway implicated in multiple IMIDs(1). Nevertheless, they have been used most often in single-arm oncology trials(4). In particular, methodology development is required to utilise basket trial approaches to their full potential in trials that use responder outcomes.

This research would use data from several trials that tested ustekinumab in different IMIDs to provide proof-of-concept of the proposed methodology.

Specific Aims of the Project:

The project aims to show that:

1. through application of a modified version of the augmented binary method (1), it is possible to improve the power of Inflammatory Bowel Disease trials that use remission and response outcomes formed from the Crohn's Disease Activity Index (CDAI) or the Mayo score as the primary endpoint.
2. through application of a method combining the augmented binary method with information borrowing, it is possible to improve the efficiency of basket trials of IMIDs that use the same responder outcome.
3. through considering a mechanistic endpoint in common, it is possible to improve the efficiency of basket trials of IMIDs that use different primary outcomes.

What is your Study Design?:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Develop or refine statistical methods

Research on clinical trial methods

Research Methods

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

NCT02407236 (6): 18 years or older diagnosed with UC 3 or more months before screening, classified as having moderate-to-severe UC (Mayo score of 6–12 and an endoscopy subscore of >=2) and (1) inadequate responders or intolerant to conventional therapy and/or biologic therapy, (2) naïve to biologic therapy, or (3) no history of failing to respond to, or tolerate, a biologic therapy.

NCT00771667 (7): 18 years or older, >3-month history of CD; CDAI score 220-450 who met specified criteria for a primary nonresponse, a secondary nonresponse, or unacceptable side effects after receiving a TNF antagonist at an approved dose.

NCT01645280 (8): Age 18–80 years, diagnosis of RA, according to ACR criteria, for ?6 months with persistent disease activity despite treatment with methotrexate. Patients who received approved or investigational biologic agent are not eligible.

NCT01077362 (9): Adult patients with active PsA for ?6 months, despite ?3 months of disease-modifying antirheumatic drug (DMARD) therapy, ?4 weeks of non-steroidal antiinflammatory drugs (NSAIDs) therapy and treatment with TNF-antagonist were eligible.

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

NCT02407236 (6):
Primary: Remission at 8 weeks defined by Mayo score. For the augmented analysis each of these components would be separately modelled; for the standard analysis the outcome is whether or not the total Mayo score is <=2 (with no individual score >1). For objective 3 we would model the change in c-reactive protein level from baseline to week 8 in addition to the Mayo score.
Secondary: Change in CRP from baseline to week 8.
NCT00771667 (7):
Primary: Clinical remission at week 6 defined by Crohn's Disease Activity Index (CDAI). For augmented analyses we would use the actual CDAI values; for the standard analysis we would use whether CDAI is below 150 at week 6.
Secondary outcomes: Clinical response and change in CRP (if available)
NCT01645280 (8) and NCT01077362 (9):
Primary: Response at 28 weeks and 24 weeks respectively, defined by ACR20. For the augmented analysis the ACR-N would be calculated and modelled; for the standard analysis we would use whether there was an ACR20 response or not.
Secondary outcomes: Change from baseline in CRP

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

For each study, the main independent variable would be the treatment arm indicator.

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

We would also include the baseline measure of the relevant disease activity score in the model. We would explore whether it is possible to include additional baseline variables, such as Sex, in the analysis.

NCT02407236: Mayo score at baseline
NCT00771667: CDAI score at baseline

NCT01645280+NCT01077362: components that are used to form the ACR20 which are measured at baseline (e.g. tender joint count, swollen joint count).

Statistical Analysis Plan:

Objective 1:
For remission defined by Mayo score we will explore four different approaches to estimating the treatment effect of ustekinumab compared to placebo:
a) Standard analysis treating remission as binary and using a logistic regression.
b) Extending the method of Suissa(10) to count outcomes and estimating the difference between arms in probability of remission, treating Mayo score as a Poisson variable.
c) Fitting an ordinal regression model to Mayo score and using this to estimate the odds ratio representing difference in arms.
d) Extending previous work(11) that would model the component of Mayo score as correlated ordinal variables, and using the augmented binary approach to estimate the difference in remission probability between arms.
It is anticipated that approaches b), c) and d) may be advantageous in terms of efficiency compared to the standard approach represented by a). Efficiency of approaches will be compared in terms of precision represented by the confidence interval
Objective 2:
We would extend methods that have been developed for borrowing information in basket trials, e.g. (5) to multivariate latent variable models. This would allow borrowing of information across distinct components of the ACR20 outcome and estimating the treatment effect in each basket.

Objective 3:
We would extend the model used in objective 2 to allow for a common mechanistic outcome (e.g. change in CRP) and distinct clinical primary outcomes. Through allowing suitable information sharing on treatment effects via the common mechanistic outcome, we anticipate that it would be possible to improve the precision of the trial.

As methodology development is the main focus of the research, it is difficult to provide fuller details of the statistical analysis. However, we have a strong track record for both responder outcomes and basket trials and are fully confident that the methods described above would be successfully developed.
Software Used:
RStudio

Project Timeline:

Start of study: 1st June 2023
Completion of work for objective 1 and 2: 31st Dec 2023
Submission of publications for objective 1 and 2: 28/02/2024
Completion of work for objective 3: 30/04/2024
Submission of publication for objective 3: 31/05/2024
We note it is likely that completing objective 3 may require an extension to the data access agreement to allow for revising of papers based on reviewer comments.

Dissemination Plan:

For each of the three objectives, we plan to publish a paper in a peer-reviewed journal. Objective 1's paper would be written for a gastroenterology journal; objectives 2 and 3 would be written for biostatistical journals. In each case the trial data would be used to show the results from using the method on a real dataset.
As well as publications, we have funding to disseminate the research at academic journals. The overall research project also has a public advisory group who will advise on how to best communicate the work to the public.
If the sponsor of the trial would like, we would also be happy to provide a presentation of the results at a suitable internal meeting or event.

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