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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.
Project Funding Source: McMaster University (MacDATA Institute)
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/jet_coi.pdf
https://yoda.yale.edu/system/files/as_coi.pdf
https://yoda.yale.edu/system/files/sf_coi.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. 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
2. NCT00660179 - AC-055-302 - A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel Group, Event-driven, Phase III Study to Assess the Effects of Macitentan (ACT-064992) on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension

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

Research Proposal

Project Title

Minimax regret for data analysis with application to clinical treatment decisions

Narrative Summary:

Conventional /frequentist statistical theory often applied to clinical trials is not ideally suited for decision making. E.g., it ignores the magnitude of losses given treatment errors. Also, it is commonly limited to pair-wise comparisons, and asymmetrically prioritizes mistakenly concluding outcomes are different when they are not (false positives) over failing to observe differences (false negatives). Using historical trial data with multiple treatments, we will assess the performance of the minimax regret criterion as an alternative that chooses a decision rule that performs uniformly well across all states of the world. It also frequently requires smaller samples for credible decisions.

Scientific Abstract:

Background: The data from randomized clinical trials have been predominantly analyzed using classical frequentist statistical theory. In particular, utilization of inferential methods such as hypotheses testing has become a convention in treatment decision-making. However, As Manski (2021), Manski and Tetenov (2016) note, conventional approaches such as hypothesis testing ignore the magnitude of (welfare) losses when errors occur. Moreover, these frequentist approaches treat type I and type II errors asymmetrically and are limited to pair-wise comparisons. Starting from seminal works by Wald (1939, 1945, 1950), Haavelmo (1944), Savage (1951), and extending to more recent research such as Manski (2004, 2007a, 2007b, 2019a, 2019b) and Manski and Tetenov (2016, 2019, 2021), minimax regret has been proposed as a useful approach for addressing the limitations of hypothesis testing – although it has not been widely used in practice.

Objective: Using data from clinical trials each comparing three treatments, we will access the performance of minmax regret, including an empirical rule that approximates it, in sub-samples with treatment arms sizes proposed by Manski and Tetenov's (2016). We will also compare the performance of minimax-regret to conventional approaches such a z-tests.

Study Design: Using two clinical trials with three treatments and sufficient treatment arm sizes, we compare different decision-making rules/criteria and their performance in terms of maximum regret in different contexts.

Participants: We use the following trials including at least two treatment arms: NCT00968812 and NCT00660179.

Main Outcome Measures: Change in HbA1c from Baseline to Week 52 (for NCT00968812); Time to First Confirmed Morbidity or Mortality Event up to the End of Treatment (for NCT00660179). Based on these outcomes, the maximum regret is calculated.

Statistical Analysis: We are going to perform a simulation study using actual clinical data assessing the performance of minimax regret (exactly) optimal rules and the empirical success rule. The idea is to draw samples from the initial dataset with treatment arm sizes recommended by the Manski and Tetenov's (2016) sufficiency bounds. We are also going to compare maximum regrets, z-tests and minimax-regret rules. We are also going to assess the epsilon-optimality (i.e., exactly estimate epsilon as opposed to using sufficiency bounds) of the empirical success rule.

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Brief Project Background and Statement of Project Significance:

As Manski (2021), Manski and Tetenov (2016) note, the data from randomized clinical trials have been predominantly analyzed using classical frequentist statistical theory. Utilization of inferential methods such as hypotheses testing has become the convention in treatment decision-making. However, as Manski and Tetenov (2016) point out, these methods have several limitations. First, hypothesis testing is poorly suited for decision-making since it ignores the magnitude of losses when type I and II errors occur. Second, in practice hypothesis testing is often accompanied by the asymmetric use of type I and type II error probabilities, that is the probability of type I error is usually fixed at some level, often at 5%, while the probability of type II error is fixed at 10-20%. However, there is no clear rationale for treating them asymmetrically in decision-making. Third, the conventional theory of hypothesis testing is usually limited to a pairwise comparison of treatments while, in reality, many treatment options are available even within the same treatment type (e.g., doses). Finally, utilization of these inferential methods has had an impact on how clinical trials are designed. In particular, Manski and Tetenov (2016, 2018) note that the size of each treatment arm is set to achieve the aforementioned conventional probabilities of type I and II errors. There is a clear need to consider alternatives to hypothesis testing theory that can accommodate the needs of clinical decision-making.

Starting from seminal works of Wald (1939, 1945, 1950), Haavelmo (1944), Savage (1951), and extending to more recent research such as Manski (2004, 2007a, 2007b, 2019a, 2019b) and Manski and Tetenov (2016, 2019, 2021), minimax regret has been proposed as a useful approach for addressing the limitations of hypothesis testing – although it has not been widely used in practice. In addition, the minimax regret criterion allows choosing a decision rule that performs uniformly well across all states of the world. This is because a rule chosen according to the minimax-regret criterion minimizes the maximum possible regret across all states of nature.

Our research contributes to this topic in several ways which combine the aforementioned cutting-edge data-analysis technique with data from actual clinical trials. First, the minimax-regret application literature is limited to cases with binary treatments and/or binary outcomes. We aim to fill in this gap by considering continuous bounded outcomes such as time to the first event occurrence as well as multiple treatments. Moreover, we are going to compare maximum regrets from empirical success rule and z-tests based on the clinical trial data. We are also going to assess the optimality of the empirical success rule using the data. In addition, we are going to account for attrition following Horowitz and Manski (2000). Finally, we are going to perform a simulation study using actual clinical data assessing the performance of minimax-regret (exactly) optimal rules and the empirical success rule in the samples with treatment arm sizes recommended by the Manski and Tetenov's (2016) sufficiency bounds.

Specific Aims of the Project:

Main aim: assess performance of a novel statistical decision-making method (minimax regret) in real clinical trial data.

Specific aims:
- Assess performance of an empirical rule (which approximates minimax-regret) and minimax-regret itself in cases with continuous bounded outcomes and multiple treatments.
- Compare maximum regrets from empirical success rule and z-tests based on the actual clinical trial data; assess the optimality of the empirical success rule using the data (if applicable).
- Perform a simulation study using clinical data assessing the performance of minimax-regret (exactly) optimal rules and the empirical success rule in the samples with treatment arm sizes recommended by the Manski and Tetenov's (2016) sufficiency bounds.

Our analysis does not seek to validate the original results but assess/contrast the performance of different methods using actual trial data.

What is the purpose of the analysis being proposed? Please select all that apply.
Develop or refine statistical methods

Research Methods

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

All participants of NCT00968812 and NCT00660179 trials.

In particular, we are going to use two and/or three treatment arms of the trials (both trials have three arms).

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

Change in HbA1c from Baseline to Week 52 (for NCT00968812);
Time to First Confirmed Morbidity or Mortality Event up to the End of Treatment (for NCT00660179).

The outcomes might be categorized by age and gender (available for both trials), and World Health Organization functional class (only for NCT00660179).

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

Treatment allocation is our main independent variable.

In NCT00968812 treatment includes: Canagliflozin 100 mg; Canagliflozin 300 mg; Glimepiride (protocol-specified doses).
In NCT00660179 treatment includes: Placebo; Macitentan (ACT-064992) 3mg; Macitentan (ACT-064992) 10mg.

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

Age and gender (available for both trials), and for NCT00660179 only World Health Organization functional class.

Secondary outcomes:

Percentage of Patients Experiencing at Least 1 Hypoglycemic Event from Baseline to Week 52 (for NCT00968812);
Percent Change in Body Weight from Baseline to Week 52 (for NCT00968812);
Change in HbA1c from Baseline to Week 104 (for NCT00968812).

Time to Death Due to PAH or Hospitalisation for PAH up to the End of Treatment (for NCT00660179);
Time to Death Due to Any Cause up to the End of Treatment (for NCT00660179).

Statistical Analysis Plan:

Methods summary: (1) accessing the performance of minimax regret (complex modeling and simulations; cross-validation; bootstrap); (2) comparison of minimax regret to other conventional statistical methods (complex modeling; cross-validation; bootstrap; bivariate and multivariate analysis; propensity score and other matching techniques are also likely)

Details:

We are going to perform a simulation study using actual clinical data assessing the performance of minimax regret (exactly) optimal rules and the empirical success rule. The idea is to draw samples from the initial dataset with treatment arm sizes recommended by the Manski and Tetenov's (2016) sufficiency bounds. This way the initial full clinical dataset is assumed to be a pseudo-population and the draws are pseudo-experimental samples. The baseline for comparison of the decision rules will be based on the treatment decisions produced by those rules in the full sample. Moreover, special attention is going to be given to the attrition issues. We are going to consider the performance of Horowitz and Manski's (2000) sharp bounds. In particular, we are going to evaluate the performance of the bounds for the empirical success rule using the false dominance rate, i.e., when the dominance ordering produced using sample draws is different from the ordering in the full sample. This requires having three or more treatment arms and a sufficient number of observations relative to that recommended by the sufficiency bounds.

In addition, we are going to compare maximum regrets from an empirical success rule and z-tests used in the original study based on these clinical trial data. We are also going to assess the ?-optimality (i.e., exactly estimate ?

as opposed to using sufficiency bounds) of the empirical success rule using the data. In addition, as a robustness check for the empirical success rule, we are going to account for missing data by deriving sharp bounds for the mean treatment response following Horowitz and Manski (2000). This approach does not place any assumptions on the treatment response of missing trial subjects.
Software Used:
STATA
Project Timeline:

Project start date: January 2022 or when data received
Analysis completion: July 2022
Manuscript draft completion: August 2022
Manuscript draft presentation at scientific meeting(s): August/fall 2022
Manuscript submission to a journal: December 2022

Dissemination Plan:

(1) Scientific meeting at MacData Institute (McMaster University) to present early results, August 2021; perhaps also external scientific meetings.
(2) Submission to a journal such as: 'Journal of Health Economics' or 'Statistical Methods in Medical Research' or 'Journal of the American Statistical Association'

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