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General Information

Key Personnel (in addition to PI):

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: UK Medical Research Council
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_yoda_5.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. NCT00249158 - RIS-AUS-5/CR006010 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia (BPSSD): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial
2. NCT00249145 - RIS-INT-24/CR006046 - Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference
3. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia

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

Research Proposal

Project Title

Symptom severity and minimal clinically important differences for agitation outcome scores in Alzheimer's disease clinical trials

Narrative Summary:

Testing a new drug involves comparing changes in outcome scores in drug versus placebo groups in a clinical trial. In a 'positive' trial, where the drug performs better than placebo, we need to understand the smallest change in score that equates to clinically meaningful change (also known as the minimal clinically important difference, MCID). We aim to evaluate MCIDs for agitation scales (NPI and CMAI) by assessing mean score changes in individuals judged by raters to have experienced minimal global improvement. We will also investigate factors that influence MCIDs, including symptom nature and severity. Findings will be relevant to interpreting agitation clinical trial findings.

Scientific Abstract:

Background
Agitation, one of the most common, distressing and difficult-to-treat neuropsychiatric symptoms in AD dementia, is the treatment target of several drug trials. It is important to understand the smallest change in any clinical outcome assessment (COA) score that is judged to be clinically meaningful, i.e. the minimal clinically important difference (MCID), to interpret the clinical relevance of trial findings and design studies with adequate power to detect such differences. No studies have so far reported MCID estimates for neuropsychiatric or agitation symptom scales, such as the Cohen-Mansfield agitation inventory (CMAI) and Neuropsychiatric Inventory (NPI).

Objective
To assess the MCIDs for CMAI and NPI score change, and their specificity for minimal clinical improvement. To explore whether agitation symptoms with high or low clinical impact (taking into account symptom nature, severity and/or frequency) differentially influence MCID magnitude.

Study Design
The retrospective study will use data from three randomized clinical trials of risperidone to treat behavioral disturbance in AD, comprising participants scoring >= 8 points on the BEHAVE-AD scale at baseline. We will use an 'anchor-based' approach to calculate the MCID for each dataset. Outcome measures (NPI subscales and/or the CMAI), will be 'anchored' to clinicians' perception of meaningful change (Clinician's Global Impression-Severity (CGI-S) or CGI-change (CGI-C) scores) over the two earliest consecutive assessments for each participant during the trial.

Participants
Participants will be included if they had at least two assessments during the trial period, each including at least one of NPI and CMAI measures, which correspond to a CGI-S rating or CGI-C score.

Primary and secondary outcome measure(s)
Primary outcomes will be the MCIDs, i.e. mean changes on NPI and/or CMAI scores in individuals judged to have experienced a minimal clinically relevant improvement in symptoms, as indicated by a one-category improvement on CGI-S, or a 'minimal' improvement on the CGI-C, compared to the previous assessment.

Secondary outcomes will be the MCIDs in participant subsets, i.e. those who had high impact symptoms (defined e.g. as >=1 aggressive behavior occurring at least once a day on the CMAI, or had 'severe' agitation on the NPI), versus those with low impact symptoms (the remaining participants from the main analysis).

Statistical analysis
We will report baseline sociodemographic and clinical characteristics of included participants. We will estimate mean agitation COA score changes for the overall cohort who experienced a minimal improvement, as defined above, for each dataset, and compare the MCIDs to mean scores corresponding to zero or moderate clinical improvement. We will compare MCIDs for the clinical (high vs low) impact subsets within the cohort as described above. If there is sufficient power, we will compare mean MCIDs corresponding to minimal improvement and

minimal worsening. We will assess statistically significant differences between subsets or cohorts using chi-squared tests for categorical measures and t-test or Wilcoxon-rank sum tests for continuous measures. Sensitivity analyses will be conducted after excluding participants who had psychotic symptoms at baseline or restricting NPI analyses to agitation subscales.

Brief Project Background and Statement of Project Significance:

In Alzheimer's disease (AD) clinical trials, the efficacy of a drug targeting cognitive or behavioral symptoms is confirmed if there is a treatment-related difference on a clinical outcome assessment (COA) score change. However, a statistically significant difference does not mean that the difference is clinically meaningful, as even very small and clinically imperceptible differences can be statistically significant with a large enough sample size 1. To interpret the clinical relevance of trial findings, it is important to understand the smallest change in any COA score that represents a clinically meaningful difference, i.e. the minimal clinically important difference (MCID). This has implications for trial design, as studies need to be powered to detect clinically significant differences.

Agitation is one of the most common, distressing and difficult-to-treat neuropsychiatric symptoms in dementia due to AD. Although several phase 3 pharmacological treatment trials for agitation in AD are ongoing, with one recently announcing positive results 2, no studies have yet investigated MCID estimates for agitation COA scales. Although the three trial datasets we requested were designed to investigate 'behavioral disturbance' in AD, rather than agitation per se, they used the Cohen-Mansfield agitation inventory (CMAI) 3 and Neuropsychiatric Inventory (NPI) 4, which are commonly employed as primary or secondary outcomes in agitation AD trials. In addition, the inclusion criteria for the three trials included a score of >=8 on the BEHAVE-AD scale, which lists symptom categories consistent with the recent consensus definition of agitation5. We plan to conduct additional sensitivity analyses to explore the degree to which our findings are specific to agitation symptoms.

Due to the design of the NPI and CMAI scales, where the total score comprises measures of severity and/or frequency for a number of (agitation) symptoms, there is likely to be a non-linear relationship between change in agitation behavior and total score. It is therefore important to evaluate the specificity of the MCID for minimal change (as opposed to no or moderate change), and the influence of symptom severity on the MCID, to improve the interpretation of trial findings. For example, a 5 point improvement on the CMAI may indicate a reduction in aggressive behavior (such as kicking) occurring several times an hour to once a week, which would be judged as clinically significant. Alternatively, the cessation of aimless wandering and trying to get to a different place, occurring up to several times a week, also resulting in a 5 point improvement, may be less likely to be perceived as a clinically meaningful improvement if distress and risk levels were low.

This study will report MCIDs for COAs commonly employed to assess agitation, which will improve our understanding of the clinical relevance of agitation trial outcomes. Findings will be relevant for clinicians, payors, and regulators when deciding on clinical and cost-effectiveness, and for sponsors when planning recruitment and sample sizes for trials.

Specific Aims of the Project:

Aim: Investigate the MCID for the CMAI and NPI, which are commonly employed primary COAs in agitation clinical trials, in AD.

Objectives:
1. Assess the mean COA score change in individuals who were judged to experience a minimal (i.e. a one category) improvement on the Clinician's Global Impression-Severity (CGI-S) scale (or a 'minimal' improvement relative to baseline on the CGI-C scale if available) between two assessment points during the trial. We will assess the specificity of the MCIDs to minimal improvement by analyzing whether the MCIDs are significantly different to mean scores corresponding to either zero or moderate meaningful change.
2. Subject to sufficient statistical power, explore whether the clinical impact of agitation influences MCID magnitude, and to compare MCIDs corresponding to minimal improvement vs worsening.

Hypotheses: MCIDs for NPI/CMAI will be specific to minimal improvement in behavioral disturbance, and that it will be influenced by symptom severity.

What is your Study Design?:

Other

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

Research on clinical trial methods

Research Methods

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

Data from three pharmacological treatment trials of behavioral disturbances in AD will be analyzed retrospectively. Recruited participants had a diagnosis of AD and a total score on the BEHAVE-AD scale of >= 8.

Inclusion criteria will be participants who had a global clinician rating (CGI-S at both or CGI-C at the second assessment), and corresponding neuropsychiatric or agitation COA scores (NPI and/or CMAI) on at least two consecutive assessments during the trial.

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

Primary outcomes:
Mean changes on NPI and CMAI scores in individuals who were judged to have experienced a minimal clinically relevant improvement in 'behavioral disturbance' symptoms, as indicated by a one-category improvement on CGI-S, or 'minimal' improvement on the CGI-C, compared to the previous assessment.
We will compare whether the mean score in this group, i.e. the MCID, is significantly different to the mean scores in individuals judged to have experienced either no meaningful change or a moderate degree of improvement, to assess its specificity to minimal clinical improvement.

Secondary outcomes:
Comparing the MCIDs between two participant subsets, i.e. those defined as having clinically impactful agitation symptoms, e.g. >=1 aggressive behavior occurring at least once a day on the CMAI, or 'severe' agitation on the NPI, versus a group defined as having less clinically impactful agitation (the remaining participants from the main sample). If there is sufficient power, we will also compare mean MCIDs corresponding to minimal improvement and minimal worsening.

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

The main independent variable will be the group-defining degree of meaningful clinical improvement in 'behavioral disturbance', as measured by the CGI-S or CGI-C. We are primarily interested in the MCID for the CMAI and NPI, and its specificity for minimal improvement compared to no change or moderate improvement.

As multiple assessments were completed throughout the trial, the earliest two timepoints where all relevant measures were obtained will be used, as participants are more likely to have clinically relevant neuropsychiatric/agitation symptoms earlier in the trial and the influence of dropout will be minimized.

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

Secondary grouping variables will include high versus low clinical impact of agitation symptoms, as defined by study researchers using the CMAI +/- NPI, as described above. Depending on statistical power, we may also group the sample according to minimal improvement vs worsening.

Statistical Analysis Plan:

For each trial dataset, we will report baseline characteristics of included participants, including sociodemographic variables (age, race/ethnicity, gender) and clinical characteristics (cognitive status/MMSE, NPI [agitation subscale]

and CMAI scores, and CGI-S ratings). We propose to analyze each trial dataset separately, but we will also explore the feasibility of combining two or more datasets to optimize statistical power if needed. If this is the case, we will take into account the fact that one of the three datasets used the CMAI (rather than BEHAVE-AD) as the primary outcome measure. We will assess statistically significant differences between subsets or cohorts using chi-squared tests for categorical measures and t-test or Wilcoxon-rank sum tests for continuous measures.

To estimate the MCID for CMAI and NPI scales, we will calculate mean (and 95% confidence interval) score scores for the cohort who experienced a one category improvement on the CGI-S, or 'minimal' improvement on the CGI-C, between two consecutive timepoints in each dataset. We will assess whether the MCID obtained is significantly different to the mean scores corresponding to either zero meaningful change or moderate clinical improvement.

Sensitivity analyses
To assess the extent to which the MCID is specific to agitation symptoms, we will:
Repeat the main analysis after excluding any participants who had psychotic symptoms (hallucinations and delusions) at baseline, as measured by the BEHAVE-AD, and compare this MCID to that from the primary analysis.
Examine the MCID for participants who had NPI agitation subscale(s) (agitation/aggression +/- irritability, disinhibition and motor disturbance) marked as present, compared to the MCID obtained from the total NPI score.

Secondary analyses
If there is sufficient power, we will conduct secondary analyses.
We will divide the MCID sample for each dataset into two groups: one where agitation symptoms at the initial assessment likely had relatively high clinical impact (defined e.g. as >=1 aggressive behavior occurring at least once a day on the CMAI, or 'severe' agitation subscale(s) on the NPI), versus a group where they likely had relatively low clinical impact (comprising the remaining participants). We will compare the MCIDs from each group to test if they are significantly different.
We will generate a new group that represents minimal worsening in 'behavioral disturbance' symptoms, comprising participants who experienced a one category worsening on the CGI-S, or 'minimal' worsening on the CGI-C, between two consecutive timepoints. We will then compare the MCIDs for improvement and worsening to assess if there is a significant difference.
Software Used:
R
Project Timeline:

We aim to start the data analysis as soon as the data is made available, predicted to be early 2023. The analysis will likely take 6-8 months so preliminary findings should be available by the end of 2023. First draft of manuscript by January 2024 and submission for publication by February 2024. We will aim to report results to the YODA project at the time of initial manuscript submission.

Dissemination Plan:

We anticipate this to be the first study to report MCIDs for common neuropsychiatric/agitation symptom scales, evaluating their specificity for minimal change and whether symptom severity influences MCID magnitude. This will be relevant for clinicians, dementia researchers and trialists/sponsors. We therefore expect to submit the manuscript to relevant high-impact journals such as the Alzheimer's & Dementia journal.

Bibliography:

1. Liu, K. Y., Schneider, L. S. & Howard, R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry (2021) doi:10.1016/S2215-0366(21)00197-8.
2. Otsuka Pharmaceutical and Lundbeck announce positive results showing reduced agitation in patients with Alzheimer's dementia treated with brexpiprazole?News Releases. Otsuka Pharmaceutical Co., Ltd. https://www.otsuka.co.jp/en/company/newsreleases/2022/20220627_1.html.
3. Cohen-Mansfield Agitation Inventory (CMAI). Int. Psychogeriatr. 8, 519–519 (1997).
4. Cummings, J. L. et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44, 2308–2314 (1994).
5. Cummings, J. et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int. Psychogeriatr. 27, 7–17 (2015).