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Requires Data Access? Yes

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: Share CTD is funded by the European Union under the grant agreement Horizon-MSCA.2022-DN 101120360.

How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/10/COI_FLORIAN_NAUDET-1.pdf

https://yoda.yale.edu/wp-content/uploads/2025/10/COI_han-1.pdf

<https://yoda.yale.edu/wp-content/uploads/2025/10/COI-GIULIA.pdf>

https://yoda.yale.edu/wp-content/uploads/2025/10/COI_Minoo-Matbouriahi.pdf

https://yoda.yale.edu/wp-content/uploads/2025/10/COI_YAZID_ZALAI.pdf

<https://yoda.yale.edu/wp-content/uploads/2025/10/Ploederl-COI-YODA.pdf>

<https://yoda.yale.edu/wp-content/uploads/2025/10/COI-FORM-UM.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. [NCT04599855 - 54135419TRD4005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Esketamine Nasal Spray Administered as Monotherapy, in Adult Participants With Treatment-resistant Depression](#)
2. [NCT04338321 - 54135419TRD3013 - A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment Resistant Major Depressive Disorder \(ESCAPE-TRD\)](#)
3. [NCT03434041 - ESKETINTRD3006 - A Randomized, Double-blind, Multicenter Active-controlled Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression](#)
4. [NCT02497287 - ESKETINTRD3004 - An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression](#)
5. [NCT02493868 - ESKETINTRD3003 - A Randomized, Double-blind, Multicenter, Active-Controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for Relapse Prevention in Treatment-resistant Depression](#)
6. [NCT01998958 - ESKETINTRD2003 - A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression \(SYNAPSE\)](#)
7. [NCT02918318 - 54135419TRD2005 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Doses of Intranasal Esketamine in Japanese Subjects With Treatment Resistant Depression](#)
8. [NCT01627782 - KETIVTRD2002 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression](#)
9. [NCT01640080 - ESKETIVTRD2001 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression](#)
10. [NCT03097133 - 54135419SUI3002 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive](#)

- [Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide](#)
11. [NCT02133001 - ESKETINSUI2001 - A Double-blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Subjects Who Are Assessed to be at Imminent Risk for Suicide](#)
 12. [NCT03039192 - 54135419SUI3001 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide](#)
 13. [NCT02422186 - ESKETINTRD3005 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects With Treatment-resistant Depression](#)
 14. [NCT02418585 - ESKETINTRD3002 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression](#)
 15. [NCT02417064 - ESKETINTRD3001 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression](#)

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

Research Proposal

Project Title

Multi-Analyst Reanalysis of IPD on Esketamine and Suicidality (team two)

Narrative Summary:

This study explores if and how different analytical choices may affect the results of meta-analyses using individual participant data (IPD) from clinical trials. Three independent research teams will separately analyse data on esketamine's effect on suicidal thoughts in depression, shared through the Yale Open Data Access (YODA) project. By comparing their methods, results, and interpretations, the study will test whether analytic flexibility changes scientific conclusions. The project promotes transparency, reproducibility, and more trustworthy clinical research.

Scientific Abstract:

Background: The reproducibility of meta-analyses can be affected by analytical flexibility, especially in individual participant data (IPD) meta-analyses, which require complex data management and methodological decisions. The effect of such flexibility on outcomes remains underexplored.

Objective: To assess the reproducibility of independent IPD meta-analyses evaluating esketamine's efficacy in reducing suicidality among patients with major depressive disorder.

Study Design: Three independent teams from the SHARE-CTD network will conduct parallel IPD meta-analyses using a common dataset, working in isolation until a collaborative datathon, where results and methods will be compared.

Participants: IPD from all esketamine clinical trials available via the YODA project, encompassing patients with major depressive disorder.

Primary and Secondary Outcome Measure(s): Primary: Change in suicidality, assessed using standardised scales or adverse event reporting. Secondary: Variability in analytical decisions,

observed results, and conclusions across teams.

Statistical Analysis: Teams will define and preregister their own analysis plans. Reproducibility will be evaluated by comparing methodological choices, quantitative results (effect sizes, p-values, confidence intervals), and interpretations. Based on the forking path diagram, all possible combinations of analytic decisions will be run in a vibration of effects (VoE) exercise.

Brief Project Background and Statement of Project Significance:

Meta-analyses are often placed at the top of the evidence-based medicine (EBM) hierarchy. Yet, they are published in large numbers, frequently overlapping or redundant, and sometimes producing contradictory results [1]. Such inconsistencies are concerning, given that meta-analyses are expected to be exhaustive and reproducible syntheses of the literature. However, they are retrospective exercises that involve many degrees of freedom, making them prone to vibration of effects (VoE) [2]. This phenomenon has been observed using multiverse analyses of 1/ head-to-head meta-analyses [3], 2/ indirect comparisons [4], and--though to a lesser extent--3/ individual participant data (IPD) meta-analyses [5]. However, multiverse meta-analyses rely on many meta-analyses to evaluate result variability, often taking an overly agnostic approach, with sometimes very arbitrary analytical choices. Less is known about how specific analytical scenarios and decisions--especially in data management, statistical modelling, and interpretation--can shape findings within a single research question.

IPD meta-analyses are a particularly relevant context for exploring this phenomenon, as they involve numerous analytical choices--not only in defining the research question, selecting inclusion criteria, and analyzing outcomes, but also during data management. Because IPD must be harmonized across studies, and outcomes are sometimes reconstructed when they were not originally collected for the specific purpose of the meta-analysis, these additional steps introduce further degrees of freedom that may influence results.

To explore this question, we selected the case study of esketamine's effect on suicidal ideation, drawing on our prior experience with this topic [6]. This clinically significant outcome exemplifies the many degrees of freedom involved in IPD meta-analyses making it an ideal example to investigate how analytical decisions can influence results.

The SHARE-CTD datathons provide a unique opportunity to investigate these issues in a many-analyst framework [7], helping to better understand the role of analytical flexibility in IPD meta-analysis.

Specific Aims of the Project:

To explore the reproducibility of independent analyses conducted by three teams performing an individual participant data (IPD) meta-analysis assessing the efficacy of esketamine in reducing suicidality among patients with major depressive disorder. Clinical trial data will be sourced via the YODA project.

Reproducibility of those analyses will be assessed along three key dimensions, as defined by Fanelli et al. [8]:

- Methods reproducibility (consistency in analytic procedures),
- Results reproducibility (consistency in quantitative outcomes), and
- Inferential reproducibility (consistency in interpretation and conclusions).

Structure and Recruitment of Analysis Teams

- Composition: Three independent teams from the SHARE-CTD network, each consisting of 3--4 analysts (including at least one with biostatistical expertise), and one senior researcher with domain expertise in psychiatry or psychopharmacology (IAC, FN, MP).
- Rationale: IPD meta-analyses demand diverse competencies spanning data management, statistical methodology, and clinical knowledge. Senior researchers will serve as independent advisors--providing methodological and clinical input--but will not engage in data handling or analysis.
- Recruitment: All analysts will be SHARE-CTD doctoral candidates. Teams must commit to working independently until the datathon in February 2026.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Develop or refine statistical methods

Other: Many-analyst study

Research Methods

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

Datasets: IPD from all esketamine trials available via the YODA project, accompanied by study protocols, variable dictionaries, and relevant metadata.

All available studies are listed here: <https://yoda.yale.edu/trials-by-generic-name/>

"Does esketamine reduce suicidality in patients with depression?"

This research question is intentionally broad to allow for variation in analytic strategies. It addresses a clinically relevant issue, given esketamine's U.S. approval for patients depression and suicidal ideation. The dataset offers substantial analytical flexibility, with potential variability in:

- . Population: e.g., inclusion of patients with or without suicidal ideation at baseline; baseline depression; history of suicide

- . Intervention: different dosing regimens

- . Outcome: suicidality assessed through specific scales, standardisation to a Z-score or adverse event reporting

- . Comparator: placebo vs. active comparators (e.g., quetiapine)

- . Study design: double-blind, single-blind, or open-label trials

Despite these degrees of freedom, feasibility is enhanced by the homogeneity of the dataset: all studies originate from a single manufacturer and drug development program.

Independence of Analyses

- Before the Datathon: Teams must work in isolation, with no inter-team communication regarding data analysis until the February 2026 datathon.

- During the Datathon: Teams will present their results, compare methods, identify discrepancies, and collaboratively assess methodological variability.

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

Primary outcome: Each team's analysis will assess the change in suicidality, measured using standardized scales or adverse event reports.

Secondary outcomes: The results from all teams will be compared to explore variability in (i) analytical decisions (methods reproducibility), (ii) observed results (results reproducibility), and (iii) conclusions across teams (inferential reproducibility). In addition, using the forking paths diagram, all possible combinations of analytic decisions will be executed in a vibration of effects (VoE) exercise. A volcano plot will display effect sizes on the x-axis and p-values on the y-axis.

We will quantify the VoE by calculating:

- The range of p-values (RP);
- The difference between the 99th and 1st percentiles of $-\log(p\text{-value})$;
- The range of effect sizes;
- The Janus effect (when the 1st and 99th percentiles of the effect size are in opposite directions).

Reporting Requirements

- Teams will prepare a comprehensive research report detailing their SAP (including deviations), analytic decisions, results, commented code, and final conclusions.
- All code and methodological documentation will be made openly accessible upon publication.

Inclusion of Analyses

- All analyses submitted by the three teams will be included in the final synthesis, regardless of their methodology or findings.
- Teams may update their analyses before the February 2026 datathon, provided all changes are transparently documented.
- During the datathon, analyses will be finalised, presented, compared, and discussed with other teams and SHARE-CTD principal investigators. No further modifications will be permitted after this meeting.

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

Except for the effect of esketamine, no main independent variable is prespecified, as this is not a modeling exercise. Given the nature of this IPD meta-analysis project, it is expected that some teams may encounter heterogeneity and wish to explore it further by adjusting for several baseline variables (e.g., but not limited to, depression severity or the presence of suicidal thoughts).

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

Not applicable

Statistical Analysis Plan:

Each team is required to prepare its own analysis plan in accordance with the template outlined below (as this is a multi-analyst project allowing analytical degrees of freedom, only a template is provided at this stage).

1. Objectives

- Primary objective: State the main objective of the meta-analysis.
- Secondary objective(s): State the secondary objective(s) of the meta-analysis.

2. Study Methods

2.1. Design

- Specify the type of meta-analysis being conducted (e.g., IPD meta-analysis).
- Introduce the PICOS framework, which will be detailed in the next section.

2.2. Participants, Interventions, Comparators, Outcomes, and Study Design (PICOS)

2.2.1. Participants

- Define participant selection criteria at the study level.
- Define participant selection criteria at the individual level (if only specific subgroups are analyzed within a trial).

2.2.2. Interventions

- Describe the intervention in detail (e.g., esketamine), including dose, route of administration, and any relevant characteristics.

2.2.3. Comparators

- Describe the comparator(s) used in the IPD meta-analysis (e.g., placebo, or any other relevant comparator).

2.2.4. Study Outcomes

Detail the outcomes selected to address the research question. For each outcome, specify:

- Outcome Measure Type:
 - o Primary

- o Secondary

- o Other pre-specified / post-hoc

- Outcome Measure Title: Name of the specific outcome measure.
- Outcome Measure Description: Additional information about the outcome measure, including a description of the metric used, if not already included in the title.
- Outcome Measure Time Frame: Time point(s) at which the measurement is assessed, specific to each outcome (e.g., "change from baseline to week 4").
- Outcome Type: Type of data (e.g., continuous, binary, time-to-event, censored).

2.2.5. Study Design

- Define the design of the studies included in the IPD meta-analysis (e.g., randomized controlled trials, crossover studies, double-blind studies, etc.).

3. Statistical Analysis

3.1. General Context

- Describe the context of the meta-analysis project, including a reference to the master protocol submitted to YODA.

3.2. Software

- All analyses will be performed using R.

3.3. Meta-analysis (for each outcome)

For each outcome, specify:

1. Type of IPD meta-analysis (one-stage or two-stage).
2. Statistical method used.
3. Exploration and handling of statistical heterogeneity.
4. Plots to be produced (e.g., forest plot, funnel plot, other visualizations).
5. Association measures used and approach to assessing uncertainty (e.g., confidence intervals, prediction intervals).
6. Any other relevant analytical considerations not covered above (including exploration of moderators).

Then, each team will provide the lead team (team 1) with:

- Final results regarding the research question.
- Cleaned and annotated code.
- A narrative linking findings to conclusions

By the end of the datathon, the lead team will archive the (aggregated) data and results with restricted access. All materials will be publicly released afterward as part of post-datathon activities.

Submitted analyses will be compared along three dimensions of reproducibility:

- Methods Reproducibility:

- o All methodological choices will be qualitatively analyzed and described, for instance using a "forking path diagram." This will include:

- a) Defined PICOS (Population, Intervention, Comparator, Outcomes, Study design);
- b) Statistical analysis plans and methods;
- c) Tools and software used;
- d) Any additional options that may be identified.

- Results Reproducibility:

- o Consistency across analyses will be assessed using the following approach. Each analysis will be summarized in terms of (i) its conclusion (positive or negative), (ii) p-value, (iii) effect size (with outcome details), and (iv) any deviations from the initial protocol regarding the primary outcome. (v) uncertainty estimate (e.g., Confidence Interval).

- o Based on the forking path diagram, all possible combinations of analytic decisions will be run in a vibration of effects (VoE) exercise. A volcano plot will display effect sizes on the x-axis and p-values on the y-axis. We will quantify the VoE by calculating:

- a) The range of p-values (RP);
- b) The difference between the 99th and 1st percentile of the $-\log(p\text{-value})$;
- c) The range of effect sizes;
- d) The Janus effect (if the 1st and 99th percentiles of the effect size are in opposite directions).

- Inferential Reproducibility:

- o Differences in interpretation and clinical implications will be explored collaboratively during the datathon. As interpretation of a meta-analysis involves clinical judgment and cannot rely solely on

quantitative metrics, a structured discussion among co-analysts and SHARE-CTD PIs will take place. This discussion, grounded in both quantitative results and expert clinical perspectives, will assess whether observed differences in results could meaningfully lead to different conclusions or clinical recommendations.

Software Used:

R

Project Timeline:

- Before the Datathon (December 2025 - February 2026) : Teams must work in isolation, with no inter-team communication regarding data analysis until the February 2026 datathon (9-13 February).
- During the Datathon (9-13 February 2026) : Teams will present their results, compare methods, identify discrepancies, and collaboratively assess methodological variability.
- During and after the Datathon (up to June 2026) : The lead team (team 1) will perform the VoE analysis and draft the final paper ;

Dissemination Plan:

- Results of the datathon will be published in a research article (e.g. BMJ Medicine or BMJ Evidence Based Medicine, journal of clinical epidemiology, BMC medical research methodology).

Inclusion of Analyses

- All analyses submitted by the three teams will be included in the final synthesis, regardless of their methodology or findings.

Authorship and Attribution

- Analysts' names will be publicly linked to their team's work, with individual contributions denoted by initials.
- All co-analysts will be included as co-authors of the final publication, provided they also meet the other criteria (approval, accountability) for being listed as an author, with contributions described using the CRediT taxonomy.

Bibliography:

1. Ioannidis JP: **The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses.** *Milbank Q* 2016, **94**(3):485-514.
2. Vinatier C, Hoffmann S, Patel C, DeVito NJ, Cristea IA, Tierney B, Ioannidis JPA, Naudet F: **What is the vibration of effects?** *BMJ Evid Based Med* 2025, **30**(1):61-65.
3. El Bahri M, Wang X, Biaggi T, Falissard B, Naudet F, Barry C: **A multiverse analysis of meta-analyses assessing acupuncture efficacy for smoking cessation evidenced vibration of effects.** *J Clin Epidemiol* 2022, **152**:140-150.
4. Vinatier C, Palpacuer C, Scanff A, Naudet F: **Vibration of effects resulting from treatment selection in mixed-treatment comparisons: a multiverse analysis on network meta-analyses of antidepressants in major depressive disorder.** *BMJ Evid Based Med* 2024, **29**(5):324-332.
5. Gouraud H, Wallach JD, Boussageon R, Ross JS, Naudet F: **Vibration of effect in more than 16 000 pooled analyses of individual participant data from 12 randomised controlled trials comparing canagliflozin and placebo for type 2 diabetes mellitus: multiverse analysis.** *BMJ Med* 2022, **1**(1):e000154.
6. Naudet F, Pellen C, Fodor LA, Gastaldon C, Barbui C, Turner EH, Le Pabic E, Cristea IA: **Efficacy and safety of esketamine for "treatment resistant depression": registered report for a Systematic Review with an Individual Patient Data Meta-analysis of Randomized, Double-Blind, Placebo-Controlled Trials.** *medRxiv* 2025:2025.2007.2017.25331696.
7. Mansmann U, Locher C, Prasser F, Weissgerber T, Sax U, Posch M, Decullier E, Cristea IA,

- Debray TPA, Held L *et al*: **Implementing clinical trial data sharing requires training a new generation of biomedical researchers**. *Nature Medicine* 2023, **29**(2):298-301.
8. Goodman SN, Fanelli D, Ioannidis JP: **What does research reproducibility mean?** *Sci Transl Med* 2016, **8**(341):341ps312.
9. Aczel B, Szaszi B, Nilsson G, van den Akker OR, Albers CJ, van Assen MALM, Bastiaansen JA, Benjamin D, Boehm U, Botvinik-Nezer R *et al*: **Consensus-based guidance for conducting and reporting multi-analyst studies**. *eLife* 2021, **10**:e72185.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2025/10/PROTOCOL_TEAM2.pdf

https://yoda.yale.edu/wp-content/uploads/2025/10/SAP_TEMPLATE_ALL_TEAMS-1.pdf