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How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2026/07/COI_FLORIAN_NAUDET-1.pdf
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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

Exploratory IPD Meta-analysis of Esketamine Trials: Heterogeneity of Treatment Effects, Super-Responders, and Rating Bias in MADRS and PHQ-9 Outcomes

Narrative Summary:

This study uses individual participant data from randomized, placebo-controlled trials of esketamine in adults with major depressive disorder. We will reanalyse the data to assess whether treatment effects are consistent across patients or whether some individuals show much larger benefits ("super-responders").

We will also compare clinician-rated depression scales with patient self-reports and explore whether measurement differences or potential rating biases may influence results.

The aim is to improve understanding of who benefits from esketamine and how reliably its effects are measured, to support better interpretation of antidepressant trials and clinical decision-making.

Scientific Abstract:

Background: Esketamine shows modest average effects in randomized trials of major depressive disorder, but it is unclear whether benefits are consistent across patients or driven by subgroups. Differences between clinician-rated and patient-reported outcomes may also affect interpretation.

Objective: To assess heterogeneity of treatment effect (HTE) and potential "super-responders" in esketamine trials, and to compare clinician- and patient-reported outcomes.

Study Design: Secondary individual participant data (IPD) analysis of randomized, double-blind, placebo-controlled esketamine trials from the YODA platform.

Participants: Randomized adults (>=18 years) with major depressive disorder.

Primary and Secondary Outcome Measure(s): Primary outcome is MADRS score; secondary outcome is PHQ-9 where available, including comparisons between clinician- and patient-rated effects.

Statistical Analysis: ANCOVA models adjusted for baseline and trial will estimate treatment effects. HTE will be explored using variance-ratio meta-analysis and finite mixture models. Predictive models (interaction models, PITE-LASSO, BART) will further assess individual-level variation. Agreement between outcomes will be evaluated using correlations, ICCs, and calibration analyses. Analyses are exploratory and focus on effect sizes and uncertainty.

Brief Project Background and Statement of Project Significance:

Esketamine has been shown to be statistically superior to placebo in reducing depressive symptoms measured by the MADRS. However, the average treatment--placebo difference is small (around 3 points; SMD ≈ 0.3), smaller than in early ketamine trials and likely below conventional thresholds for clinical relevance, with only modest advantages over standard antidepressants.

Despite this, treatment effects may differ substantially across patients. Some individuals may experience much larger benefits ("super-responders"), which is central to precision psychiatry. Identifying such subgroups could improve targeting of treatment and improve the risk--benefit balance. However, robust and clinically useful predictors of antidepressant response have not been identified despite extensive research. Heterogeneity of treatment effect (HTE) can be explored through IPD interaction analyses, which have previously (and inconsistently) shown isolated significant moderators in esketamine trials, though these may reflect false positives due to multiple testing. Alternatively, HTE can be assessed at the distribution level: true super-responders should alter outcome distributions or increase variance in the treatment arm. Mixture models have suggested latent response subgroups in antidepressant data, but findings are inconsistent and may reflect measurement or rating artefacts. Variance-ratio meta-analyses have similarly not provided consistent evidence for meaningful HTE. In this study, both approaches are applied to esketamine IPD to estimate plausible bounds of heterogeneity, acknowledging limited power to detect subtle effects.
Most trials rely on clinician-rated outcomes such as the MADRS, but evidence suggests self-reported outcomes often yield smaller treatment effects than clinician ratings. This raises concerns about measurement differences and potential rating bias. Bias may arise when unblinding or expectancy influences clinician judgments, particularly when symptoms are ambiguous. This is especially relevant for esketamine, where psychoactive effects make blinding difficult and treatment assignment may often be guessed correctly by clinicians, patients, and raters. Clinicians may also unintentionally harmonize ratings under uncertainty or time pressure, reducing variability relative to patient self-reports. Comparing clinician- and patient-reported outcomes may therefore help assess potential rating bias and differences in measurement properties. In this study, we will compare treatment effects across clinician- and patient-reported outcomes and examine agreement, variability, and calibration between them. Prior analyses have only partially compared these outcomes across esketamine trials, and cross-trial patterns remain underexplored. Blinding was not systematically assessed in the original studies; adverse events, particularly dissociation, may serve as indirect indicators of functional unblinding, although prior work suggests limited impact on overall efficacy. Further details are provided in the attached protocol.

Specific Aims of the Project:

The overall objective is to use shared IPD from randomized esketamine trials to investigate whether the average treatment effect conceals clinically relevant variation between patients, whether treatment effects differ between clinician-rated and patient-reported outcomes, whether previous depression trial data can be used responsibly for historical borrowing.

The analyses are exploratory and hypothesis-generating. They are intended to clarify methodological questions, identify signals worthy of future confirmation, and support transparent analysis strategies for secondary use of clinical trial data.

Further details are provided in the attached protocol.

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 only data from the YODA Project

Research Methods

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

Trial Eligibility Criteria
Eligible trials must meet all of the following criteria:
1. randomized, double-blind, placebo-controlled clinical trial;
2. evaluation of esketamine as an intervention;
3. adult participants aged 18 years or older;
4. diagnosis of major depressive disorder;
5. availability of individual participant data;
6. availability of baseline depression severity and randomized treatment assignment;
7. availability of at least one post-baseline depression severity assessment.
Trials will be classified according to clinical population and design characteristics. In particular, trials in treatment-resistant depression and trials in patients with acute suicidality will be analysed separately unless pooling is clinically and methodologically justified.

Participant Eligibility Criteria
Eligible participants are randomized adults with known treatment assignment and available baseline depression severity assessment. Endpoint-specific analyses will include participants with the relevant outcome observed or derivable within the predefined visit window. Participants without endpoint data will be included in descriptive summaries of missing data and in longitudinal or joint modelling analyses where appropriate.

Intervention and Comparator
The intervention is esketamine administered according to the trial-specific protocol. Esketamine may have been administered as augmentation to standard-of-care antidepressant therapy or, where applicable, as monotherapy.
The comparator is placebo administered according to the trial-specific protocol, either as augmentation to standard of care or as monotherapy.

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

Primary Clinician-Rated Outcome
The primary clinician-rated outcome is the Montgomery--˚Asberg Depression Rating Scale (MADRS) total score at the main endpoint.

For treatment-resistant depression trials, the main endpoint is Day 28, defined as the assessment closest to Day 28 within a Day 25--28 window. If multiple assessments are available within this window, the latest assessment will be used.
For trials in patients with acute suicidality, the main endpoint is 24 hours after the first dose. If an exact 24-hour assessment is not available, the assessment closest to 24 hours after first dose will be used.
Because these populations and endpoint timings address different clinical questions, treatment-resistant depres- sion trials and acute suicidality trials will not be pooled in the primary analysis unless there is a clear justification.

Patient-Reported Outcome
The main patient-reported outcome is the Patient Health Questionnaire-9 (PHQ-9) total score at the corresponding endpoint, where available. Other patient-reported depression outcomes may be included if they can be harmonized across trials and measured at comparable time points.

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

Treatment group (esketamine / placebo)

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

In exploratory analyses, candidate variables may include age, sex, race, employment status, education level, number of previous depressive episodes, duration of the current depressive episode, family history of psychiatric disorders, past substance use disorder, and baseline depression severity. See the full protocol for more details.

Statistical Analysis Plan:

This paragraph provides a condensed version of the full Statistical Analysis Plan (SAP) described in the protocol attached to the proposal. The complete SAP includes more detailed methodological specifications, modeling approaches, and sensitivity analyses that could not be fully reproduced within the application template due to space limitations.

General Statistical Principles

All analyses will account for the multi-trial structure. Trial effects will be handled as fixed effects in basic models and as random or hierarchical effects in meta-analytic or Bayesian frameworks where appropriate.
Continuous outcomes will be summarized by treatment arm and trial using standard descriptive statistics (means, SDs, medians, IQRs, minima, maxima) and distribution plots. Binary outcomes will be summarized using counts and percentages.

Treatment effects and related measures (e.g., correlations, regression coefficients, ICCs) will be reported with confidence or credible intervals. Analyses are exploratory. Emphasis will be on effect sizes, uncertainty, between-trial consistency, and robustness.

No formal multiplicity adjustment will be applied.

Statistical Analysis

Module 1: Heterogeneity of Treatment Effect and Super-Responders

For this module, the primary endpoint is MADRS total score at prespecified time points (Day 28 for treatment-resistant depression trials and Day 2 for acute suicidality trials, depending on design). The main analysis uses ANCOVA adjusting for baseline MADRS and trial to estimate the average treatment effect of esketamine versus placebo. Outcomes will be summarized and visualized by trial

and arm.
-> Variability ratio analysis
Treatment-effect heterogeneity will be assessed by comparing variability of adjusted outcomes between arms. Trial-specific estimates will be combined using random-effects meta-analysis. Greater variability in the esketamine arm will be interpreted as compatible with heterogeneity.
-> Mixture model analysis
Finite mixture models will be used to explore latent response distributions in adjusted outcomes. Competing models will be compared using fit criteria and stability across trials. A "favourable response" component will be defined if it is consistently more frequent in the esketamine arm and not driven by a single trial.
-> Item-level sensitivity analysis
If available, MADRS item data will be analysed using item response theory to assess whether observed heterogeneity is consistent across symptoms or driven by specific items, floor effects, or measurement properties.
-> Exploratory covariate analyses
If heterogeneity is detected, treatment-covariate interactions will be tested for prespecified variables. Multivariable predictive models will further explore individual-level treatment effects using penalised regression and flexible machine learning methods.

Module 2: Clinician- vs Patient-Reported Outcomes and Functional Unblinding

The objective of this module is to compare treatment effects estimated from clinician-rated and patient-reported depression outcomes and to explore whether discrepancies between these outcomes are associated with treatment assignment, adverse events suggestive of functional unblinding, or trial characteristics. It compares treatment effects between clinician-rated MADRS and patient-reported PHQ-9 outcomes where available.

Outcomes will be analysed on original or standardized scales, with descriptive summaries and distribution plots. Treatment effects will be estimated separately for each outcome type using regression models adjusted for baseline and trial.

Agreement will be assessed using correlations, ICCs, discrepancy measures, and calibration analyses relating MADRS and PHQ-9 across trials. Differences between clinician and patient ratings will be explored using discrepancy models.

Adverse events, especially dissociation, will be examined as potential indicators of functional unblinding and explored in relation to outcomes and discrepancies.

Sensitivity Analyses
Sensitivity analyses will include stratification by clinical population, exclusion of non-comparable trials, alternative covariate adjustments, leave-one-trial-out analyses, restriction to complete cases, and exclusion of protocol deviations where applicable.

Results will focus on effect sizes, uncertainty, consistency across trials, and graphical summaries. Planned outputs include trial flow, baseline characteristics, outcome distributions, variance-ratio and mixture-model summaries, and comparisons between clinician- and patient-reported outcomes (including agreement and discrepancy analyses such as Bland--Altman plots). Interpretation will clearly separate average treatment effects, evidence of heterogeneity, prediction of response, and exploratory signals of potential rating bias.

Further methodological details (including the full details of the statistical approach) are provided in the attached protocol.

Software Used:

R

Project Timeline:

This project is part of SHARE-CTD Datathon 3, in which three independent teams have developed three distinct research questions. The present submission is made by the Principal Investigator on behalf of the datathon. Each team will conduct its analyses separately and in isolation, ensuring independence of research questions, analytical approaches, and interpretation of results across teams.

This project will be conducted during September 2026 as part of the SHARE-CTD Datathon 3. The main analyses will be carried out between Monday, 7 September 2026, and Friday, 11 September 2026, during the datathon. Additional analyses, quality checks, and finalisation of the statistical analyses may continue later in September, if required. Manuscript preparation is expected to take place between September and October 2026.

Dissemination Plan:

Results will be disseminated through peer-reviewed scientific publications, presentations at national and international conferences, and communication activities conducted as part of the SHARE-CTD project.

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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2026/07/SHARE_CTD_Datathon_3_Team2_SAP_final-1.pdf