Principal Investigator

First Name: Jose
Last Name: Rubio
Degree: MD
Primary Affiliation: Northwell Health Feinstein Institutes for Medical Research
E-mail: JRubio13@northwell.edu
State or Province: NY
Country: United States

General Information

Key Personnel (other than PI):
First Name: Mehrdad
Last name: Sadri
Degree: MD
Primary Affiliation: Northwell Health Feinstein Institutes for Medical Research
SCOPUS ID:
Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/10/SV_57KskaKADT3U9Aq-R_611iOdsMvZMVDPr.pdf
https://yoda.yale.edu/wp-content/uploads/2025/10/YODA_COI_Mehrdad_Sadri.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. NCT03345342 - R092670PSY3015 - A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation
2. NCT02713282 - R092670SCH3015 - A 52-Week, Open-Label, Prospective, Multicenter, International Study of a Transition to the Paliperidone Palmitate 3-Month Formulation In Patients With Schizophrenia Previously Stabilized on the Paliperidone Palmitate 1-Month Formulation
3. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
4. NCT01515423 - R092670PSY3011 - A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects With Schizophrenia
5. NCT01281527 - R092670SCH3010 - A 6-month, Open Label, Prospective, Multicenter, International, Exploratory Study of a Transition to Flexibly Dosed Paliperidone Palmitate in

Patients With Schizophrenia Previously Unsuccessfully Treated With Oral or Long-acting Injectable Antipsychotics

6. NCT01258920 - PALM-JPN-5 - A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Patients With Schizophrenia
7. NCT01157351 - R092670SCH3006 - A Fifteen-month, Prospective, Randomized, Active-controlled, Open-label, Flexible Dose Study of Paliperidone Palmitate Compared With Oral Antipsychotic Treatment in Delaying Time to Treatment Failure in Adults With Schizophrenia Who Have Been Incarcerated
8. NCT01081769 - R092670SCH3005 - A 24-month, Prospective, Randomized, Active-Controlled, Open-Label, Rater-Blinded, Multicenter, International Study of the Prevention of Relapse Comparing Long-Acting Injectable Paliperidone Palmitate to Treatment as Usual With Oral Antipsychotic Monotherapy in Adults With Schizophrenia
9. NCT00378092 - CR011992, RISSCH3024 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia
10. NCT00369239 - RISSCH4043 - Is Premorbid Functioning a Predictor of Outcome in Patients With Early Onset Psychosis Treated With Risperdal Consta?
11. NCT00299702 - RISSCH4060 - A 2-year, Prospective, Blinded-rater, Open-label, Active-controlled, Multicenter, Randomized Study of Long-term Efficacy and Effectiveness Comparing Risperdal(R) Consta(R) and Abilify(R) (Aripiprazole) in Adults With Schizophrenia
12. NCT00297388 - RIS-SCH-401 - A 52-wk Prospective, Randomized, Double-blind, Multicenter Study of Relapse Following Transition From Oral Antipsychotic Medication to 2 Different Doses (25 or 50 mg Every 2 Wks) of Risperidone Long-acting Microspheres (RISPERDAL CONSTA) in Adults With Schizophrenia or Schizoaffective Disorder
13. NCT00236457 - RIS-INT-62 - Randomized, Multi-center, Open Label Trial Comparing Risperidone Depot (Microspheres) and Olanzapine Tablets in Patients With Schizophrenia or Schizoaffective Disorder
14. NCT00236379 - RIS-USA-275 - A Six-month, Double-blind, Randomized, International, Multicenter Trial to Evaluate the Glucoregulatory Effects of Risperidone and Olanzapine in Subjects With Schizophrenia or Schizoaffective Disorder
15. NCT00216671 - RISSCH4045 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode
16. NCT00216632 - RISSCH4026 - Treatment Success in Patients Requiring Treatment Change From Olanzapine to Risperidone Long Acting Injectable (TRESOR)
17. NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal(R) Consta(R) Trial of Relapse Prevention and Effectiveness
18. NCT00589914 - R092670PSY3006 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia
19. NCT00604279 - R092670PSY3008 - A Randomized, Open-Label, Parallel Group Comparative Study of Paliperidone Palmitate (50, 100, 150 mg eq) and Risperidone LAI (25, 37.5, or 50 mg) in Subjects with Schizophrenia
20. NCT00590577 - R092670PSY3007 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
21. NCT00111189 - R092670PSY3001 - A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia. Placebo Consists of 20% Intralipid (200 mg/mL) Injectable Emulsion
22. NCT00210717 - R092670PSY3002 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With Schizophrenia
23. NCT00119756 - R092670PSY3005 - A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients With Schizophrenia
24. NCT00210548 - R092670PSY3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
25. NCT00101634 - R092670PSY3004 - A Randomized, Double-blind, Placebo-controlled, Parallel-

group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia
26. NCT00074477 - R092670-SCH-201 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia
27. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
28. NCT01051531 - R092670SCH3009 - Safety, Tolerability, and Treatment Response of Paliperidone Palmitate in Subjects With Schizophrenia When Switching From Oral Antipsychotics
29. NCT01527305 - R092670SCH4009 - An Open-Label, Prospective, Non-Comparative Study to Evaluate the Efficacy and Safety of Paliperidone Palmitate in Subjects With Acute Schizophrenia
30. NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia
31. NCT00495118 - RIS-INT-80 - Risperidone Depot (Microspheres) in the Treatment of Subjects With Schizophrenia or Schizoaffective Disorder - an Open-label Follow-up Trial of RIS-INT-62 and RIS-INT-85
32. NCT00236587 - RIS-USA-265 - An Open Label, Long Term Trial of Risperidone Long Acting Microspheres in the Treatment of Patients Diagnosed With Schizophrenia

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

Research Proposal

Project Title

Predicting Next Visit Outcomes in Antipsychotic Clinical Trials: A Data-Driven Approach to Individualized Forecasting

Narrative Summary:

For this analysis, we will include only randomized clinical trials of antipsychotics that lasted at least six months and had monthly or more frequent assessments of symptom severity. Individual predictive models are emerging in psychiatry and a very relevant actionable individual prediction is for outcomes of interest at the next visit based on the information learned about a given patient so far. We propose to use visit-by-visit data to build predictive models that forecast the next visit's outcomes for each patient. By incorporating cumulative information up to each assessment, this framework aims to maiximize the information that can be used to make predictions and present it in an actionable way. The project's deliverable will be a validated modeling strategy for individualized prediction of visit to visit outcomes in schizophrenia.

Scientific Abstract:

Background: In long-term studies of schizophrenia, researchers usually look at whether patients get better overall by the end of the trial. However, clinicians need more immediate predictions on whether a given outcome will occur before the next visit, so that they can modify interventions accordingly. We argue that these predictions may get better as more data about the trajectory for a given patient accumulates.
Objective: We want to test whether we can use detailed visit-by-visit data to predict what a patient's symptoms will look like at the next visit.

Study Design: We will use clinical trial data where patients with schizophrenia or schizoaffective disorder were treated with antipsychotics for at least six months, and where there were monthly check-ins or more frequent assessments. We will build models that use all the information collected up to each visit to predict what will happen at the following visit.
Participants: People in schizophrenia clinical trials that meet the criteria above.
Primary Outcome: Study defined relapse, treatment disengagement, emergence of side effects.
Statistical Analysis: At each visit t, we will predict next-visit (t+1) occurrence of any of three events - study defined relapse, treatment disengagement, or a new adverse event - using only information available up to t. (See more in supp. materials)

Brief Project Background and Statement of Project Significance:

While many patients initially respond to antipsychotics, a subset experiences progressive symptom worsening despite continued treatment. Current analytic strategies emphasize overall perceived response and neglect visit-level dynamics. Our inclusion criteria (>=6-month duration, monthly or more frequent assessments) ensure sufficient longitudinal density to study trajectories. Building prediction models that forecast outcomes at the next visit mirrors real-world clinical decision making and can identify high-risk patients earlier. This work will refine how long-term trial data are analyzed and inform adaptive treatment strategies.

Specific Aims of the Project:

Specific Aims
1. Develop predictive models that use cumulative visit-level information to forecast next-visit symptom outcomes.
2. Identify predictors of such predictions

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research on clinical prediction or risk prediction

Research Methods

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

Study Design
- Data Source: Patient-level data from schizophrenia trials available via the YODA Project.
- Inclusion Criteria:
o Trial duration >=6 months.
o At least monthly study visits.
o Participants with schizophrenia or schizoaffective disorder randomized to active antipsychotic treatment.

- Exclusion Criteria: None beyond failing inclusion requirements.

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

Primary and Secondary Outcomes
- Primary: Study defined relapse by next visit
- Secondary: treatment disengagement by next visit, new AE by next visit

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

Predictors
- Baseline features: All available information (demographic, medical and psychiatric illness, baseline AE, psychopathology)

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

n/a

Statistical Analysis Plan:

1. Preprocessing
We'll line up all trials on the same timeline (days on study) and include only trials that last at least six months with monthly or more frequent visits. Within each training split (to avoid information leaks), we will fill in missing values, standardize numeric variables to the same scale, and build "at-this-visit (t)" features using only information collected up to that visit: last PANSS score, change since baseline and since the prior visit, short short-term trend over the last 2--3 visits, a person-specific slope and fitted level estimated from their own history so far, symptom volatility (moving average and rolling variability), time on treatment and dose, adherence flags, recent adverse events, and site/trial indicators.
2. Modeling approaches
a) Linear mixed-effects (primary): logistic models that predict whether an event will happen at the next visit (t+1), with participant-level random effects (and optional site effects) to

account for repeated measures.
b) Autoregressive models: include the most recent outcome level(s) plus other features to capture the "from-visit-to-visit" dependence. (We will also frame this as a discrete-time survival model to estimate interval risk between visits.)
c) Machine learning: elastic-net logistic regression (for robust feature selection) and a gradient-boosted tree model (for non-linear patterns and interactions).
3. Validation
We will test generalizability by leaving one site out each time: train on all other sites, test on the held-out site, and rotate through all sites. (Where relevant, we will also leave one trial out.) Inside every training split, all preprocessing and hyperparameter tuning happen only on the training data. We also enforce a rolling-origin rule--predictions for t+1 can use data only up to t. If events are rare, we will use class weights so the model does not ignore them.
4. Stratification
After we get predicted next-visit risk for each person, we will sort everyone and split them into three groups: Low, Medium, and High risk. If any group is too small (less than 10% of participants), we will merge it with the nearest group to keep results stable. We will then check that these groups truly differ over time by testing a group x time interaction and by plotting cumulative event rates for each group.
5. Feature importance
For regression models, we will report standardized coefficients (with confidence intervals) to show direction and strength. For tree-based models, we will use SHAP values to show which variables most influence the predicted next-visit event risk in an interpretable way.

Software Used:

R

Project Timeline:

We will need for the analyses both R (through RStudio) and Python (through Jupyter Lab or Jupyter Notebook).
We plan to start as soon as we are granted access to the data. We anticipate 3 months for data preprocessing, 6 for analyses, and 3 for manuscript preparation and submission.

Dissemination Plan:

Findings will be submitted to high-impact psychiatry and psychopharmacology journals and presented at national conferences. Code and analytic pipelines will be shared in line with YODA's open-science principles.

Lancet Psychiatry as potential journal.

Bibliography:

James, Gareth, et al. "An introduction to statistical learning: With applications in Python." Cham: Springer International Publishing, 2023. 15-67.

Poldrack, Russel A., Grace Huckins, and Gael Varoquaux. "Establishment of best practices for evidence for prediction: a review." JAMA psychiatry 77.5 (2020): 534-540.

Rubio JM, Schoretsanitis G, John M, Tiihonen J, Taipale H, Guinart D, Malhotra AK, Correll CU, and Kane JM. "Psychosis relapse during treatment with long-acting injectable antipsychotics in individuals with schizophrenia-spectrum disorders: an individual participant data meta-analysis." Lancet Psychiatry. 2020 Sep; 7(9): 749-761.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2025/10/Statistical-Analysis-.docx