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## General Information

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**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/system/files/coi\\_heinz\\_0.pdf](https://yoda.yale.edu/system/files/coi_heinz_0.pdf)

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[https://yoda.yale.edu/system/files/coi\\_lasse\\_brandt.pdf](https://yoda.yale.edu/system/files/coi_lasse_brandt.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

### Associated Trials:

1. [NCT00488319 - R076477PSZ3002 - A 2-Year, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release \(1.5-12 mg/day\) in the Treatment of Adolescents \(12 to 17 Years of Age\) With Schizophrenia](#)
2. [NCT01009047 - R076477PSZ3003 - A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Prolonged Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age](#)
3. [NCT00645099 - R076477SCH3020 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia](#)
4. [NCT00518323 - R076477PSZ3001 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age](#)
5. [NCT01606228 - R076477SCH3033 - An Open-Label Prospective Trial to Explore the Tolerability, Safety and Efficacy of Flexibly-Dosed Paliperidone ER among Treatment-Naive and Newly Diagnosed Patients with Schizophrenia](#)
6. [NCT00334126 - R076477SCH3015 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia](#)
7. [NCT00086320 - R076477-SCH-301 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia](#)
8. [NCT00650793 - R076477-SCH-703 - A Randomized, DB, PC and AC, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS Paliperidone \(6, 9, 12 mg/Day\) and Olanzapine \(10 mg/Day\), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia - Open Label Phase](#)
9. [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](#)
10. [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](#)
11. [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](#)
12. [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](#)
13. [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](#)
14. [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](#)
15. [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](#)
16. [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](#)
17. [NCT00391222 - RISBMN3001 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable \(LAI\) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I Disorder](#)
  18. [NCT00034749 - RIS-USA-231 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone](#)
  19. [NCT00076115 - RIS-BIM-301 - Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children \(REACH\): A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Risperidone for the Treatment of Acute Mania in Bipolar I Disorder](#)
  20. [NCT00132678 - RISBIM3003 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension](#)
  21. [NCT00094926 - RIS-BIP-302 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder](#)
  22. [NCT00397033 - R076477SCA3001 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder](#)
  23. [NCT00412373 - R076477SCA3002 - A Randomized, Double-blind, Placebo-controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder](#)
  24. [Multiple NCT#s - Multiple - OPTICS Trial Bundle](#)
  25. [NCT00249132 - RIS-INT-3 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)
  26. [NCT00216476 - RISSCH3001 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness](#)
  27. [NCT00216580 - RIS-PSY-301 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis](#)
  28. [NCT00253162 - RIS-INT-69 - The Efficacy And Safety Of Flexible Dose Ranges Of Risperidone Versus Placebo Or Haloperidol In The Treatment Of Manic Episodes Associated With Bipolar I Disorder.](#)
  29. [NCT00378092 - CR011992, RISSCH3024 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)
  30. [NCT00299715 - R076477-BIM-3001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response, Multicenter Study to Evaluate the Efficacy and Safety of Three Fixed Doses of Extended-Release Paliperidone in the Treatment of Subjects With Acute Manic and Mixed Episodes Associated With Bipolar I Disorder](#)
  31. [NCT00309699 - R076477-BIM-3002 - A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed, Extended-Release Paliperidone Compared With Flexibly-Dosed Quetiapine and Placebo in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder](#)
  32. [NCT00309686 - R076477-BIM-3003 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed Extended-Release Paliperidone as Adjunctive Therapy to Mood Stabilizers in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder](#)
  33. [NCT00752427 - R076477-SCH-702 - 24 week extension of NCT00085748: A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia](#)
  34. [NCT00077714 - R076477-SCH-304 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia](#)
  35. [NCT00083668 - R076477-SCH-305 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release \(ER\) Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia](#)
  36. [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](#)
  37. [NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-](#)

- [Release \(ER\) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia](#)
38. [NCT00085748 - R076477-SCH-302 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia](#)
  39. [NCT00249236 - RIS-IND-2/CR006064 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Or Mixed Episodes Associated With Bipolar I Disorder](#)
  40. [NCT00250367 - RIS-INT-46/CR006058 - The Safety And Efficacy Of Risperdal \(Risperidone\) Versus Placebo As Add-On Therapy To Mood Stabilizers In The Treatment Of The Manic Phase Of Bipolar Disorder](#)
  41. [NCT00088075 - RIS-SCH-302/CR003370 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents](#)
  42. [RIS-USA-1 \(RIS-USA-9001\) - Risperidone versus haloperidol versus placebo in the treatment of schizophrenia](#)
  43. [NCT00253149 - RIS-USA-102/CR006040 - The Safety And Efficacy Of Risperdal \(Risperidone\) Versus Placebo Versus Haloperidol As Add-On Therapy To Mood Stabilizers In The Treatment Of The Manic Phase Of Bipolar Disorder](#)
  44. [NCT00253136 - RIS-USA-121/CR006055 - Risperidone Depot \(Microspheres\) vs. Placebo in the Treatment of Subjects With Schizophrenia](#)
  45. [NCT00257075 - RIS-USA-239/CR006052 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Episodes Associated With Bipolar I Disorder](#)
  46. [RIS-USA-240 - The efficacy and safety of flexible dose ranges of risperidone vs. Placebo or divalproex sodium in the treatment of manic or mixed episodes associated with bipolar 1 disorder](#)
  47. [RIS-USA-72 - The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia](#)
  48. [NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia](#)
  49. [NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)
  50. [NCT01662310 - R076477-SCH-3041 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study](#)
  51. [NCT00490971 - R076477BIM3004 - A Randomized, Double-Blind, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Extended-Release Paliperidone as Maintenance Treatment After an Acute Manic or Mixed Episode Associated With Bipolar I Disorder](#)
  52. [NCT00524043 - R076477SCH4012 - A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/Day of Paliperidone Extended Release \(ER\) in the Treatment of Subjects With Schizophrenia](#)
  53. [NCT00105326 - R076477-SCH-1010/CR002281 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia](#)
  54. [NCT00645307 - R076477-SCH-701 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase](#)
  55. [NCT00246246 - RIS-BIP-301 - A Randomized, Open-label Trial of RISPERDAL® CONSTA™ Versus Oral Antipsychotic Care in Subjects With Bipolar Disorder](#)
  56. [NCT00249223 - RIS-INT-61 - Risperidone Depot \(Microspheres\) vs. Risperidone Tablets - a Non-inferiority, Efficacy Trial in Subjects With Schizophrenia](#)
  57. [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](#)
  58. [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](#)
  59. [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](#)
  60. [NCT01051531 - R092670SCH3009 - Safety, Tolerability, and Treatment Response of Paliperidone](#)

- [Palmitate in Subjects With Schizophrenia When Switching From Oral Antipsychotics](#)
61. [NCT01527305 - R092670SCH4009 - An Open-Label, Prospective, Non-Comparative Study to Evaluate the Efficacy and Safety of Paliperidone Palmitate in Subjects With Acute Schizophrenia](#)
  62. [NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 \(Paliperidone Palmitate\) in Patients With Schizophrenia](#)
  63. [NCT01258920 - PALM-JPN-5 - A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Patients With Schizophrenia](#)
  64. [NCT00216671 - RISSCH4045 - Early Versus Late Initiation of Treatment With Risperdal Consta in Subjects With Schizophrenia After an Acute Episode](#)
  65. [NCT00369239 - RISSCH4043 - Is Premorbid Functioning a Predictor of Outcome in Patients With Early Onset Psychosis Treated With Risperdal Consta?](#)
  66. [NCT00216632 - RISSCH4026 - Treatment Success in Patients Requiring Treatment Change From Olanzapine to Risperidone Long Acting Injectable \(TRESOR\)](#)
  67. [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](#)

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

## Research Proposal

### Project Title

Prediction of outcome and adverse events in antipsychotic treatment

### Narrative Summary:

The two main factors guiding the choice of a specific antipsychotic treatment are its outcome and risk of adverse events. A personalized therapeutic strategy would be based on prediction of these factors, where the treatment effect should ideally outweigh potential adverse events. However, in clinical routine, prediction of these two factors remains elusive. We intend to predict outcome and adverse events in patients with schizophrenia, schizoaffective disorder, and bipolar disorder treated with antipsychotics in randomized controlled trials using a machine learning approach trained on individual demographic, clinical, and laboratory parameters.

### Scientific Abstract:

**Background:** Outcome and adverse events are the two primary factors when planning a safe and successful antipsychotic therapy. However, evidence is scarce regarding the prediction of outcome and adverse events in an individual patient.

**Objective:** Our aim is to predict the outcome and adverse events in antipsychotic treatment.

**Study Design:** We plan to predict the outcome and adverse events by implementing a machine learning approach in an individual participant data meta-analysis of randomized controlled trials (RCTs).

**Participants:** Schizophrenia, bipolar disorder, and schizoaffective disorder.

**Main outcome measure:** Our main outcome measure will be reduction of major symptoms (i.e. psychosis or mania).

**Statistical analysis:** Non-linear regression of the above-mentioned outcome measures will be carried out using state-of-the-art artificial neural networks. The model's accuracy will be compared with alternative approaches including linear regression models and support vector regression.

### Brief Project Background and Statement of Project Significance:

Providing the appropriate antipsychotic substance in psychiatric disorders is a complex process that involves prediction of at least two key factors: outcome and adverse events<sup>1</sup>. The desired outcome should ideally outweigh potential adverse events. However, in clinical routine, prediction of these two factors in individual remains elusive<sup>2</sup>. Predictors of outcome have been investigated in different clinical, social, and genetic domains<sup>2</sup>. Focussing on the clinical history, Kinon et al. investigated early response to an antipsychotic medication as a predictive factor for a

later response<sup>3</sup>. Using data from five randomized controlled trials (n = 1077 schizophrenia patients), they showed that early non-response was a robust predictor of continued later lack of response<sup>3</sup>. Similarly, social factors likely influence the functional outcome in antipsychotic treatment. For instance, Köhler-Forsberg et al. reported that living with a partner was the strongest predictor of social functioning (assessed by Global Assessment of Functioning – GAF) after clozapine initiation in schizophrenia patients<sup>4</sup>. Pharmacogenetic investigations showed that a combination of six polymorphisms in neurotransmitter-receptor-related genes resulted in a significant 76.7% prediction of clozapine response and a sensitivity of 95% for satisfactory response<sup>5</sup>. Taken together, these findings indicate that multifactorial variables from different domains contribute to the outcome of antipsychotic treatment. In addition to outcome, prediction of adverse events (AEs) is the other key factor when planning a safe and successful therapy. Even though AEs are frequent in antipsychotics<sup>6</sup>, little is known about their prediction according to individual patient characteristics<sup>7</sup>. Polypharmacy is a known risk factor for the occurrence of adverse events<sup>8</sup>. Furthermore, the risk for increased weight gain during treatment with olanzapine was reported to be threefold in subjects with at least one allele at each locus of leptin and leptin receptor<sup>8</sup>. Polymorphisms (A1 allele) of the dopamine D2 receptor gene Taq1 in females were associated with increased prolactin levels during treatment with bromperidol<sup>9</sup>.

The scarce literature highlights the need for research to optimize prediction of outcome and adverse events in antipsychotic treatment. Importantly, both measures depend on multiple variables (e.g. demographic, genetic, and clinical) most likely in a complex non-linear interaction, which cannot be captured in conventional linear regression models, where the dependent variable is predicted as a weighted sum of individual predictors. Neural networks represent the most advanced technique to tackle such non-linear regression problems. Employing these techniques, we aim at identifying complex patterns of predictors of treatment outcome and adverse events. This study could have a major impact on health of patients and help to identify crucial predictors of outcome and adverse events and may help to promote the development of personalized and precise therapeutic strategies.

### Specific Aims of the Project:

Primary objective: A. Identify patterns of predictors for outcome during antipsychotic treatment.

Secondary objective: B. Identify patterns of predictors for adverse events during antipsychotic treatment.

Endpoints: The following two groups of endpoints (1A-4A and 5B-10B) are clustered according to the two groups of objectives (A and B).

Primary endpoint:

1A. Pattern of predictive variables for symptom reduction during antipsychotic treatment (all antipsychotics pooled).

Secondary endpoints:

2A. Pattern of predictive variables for symptom reduction during antipsychotic treatment (assessed for each antipsychotic individually).

3A. Pattern of predictive variables for increase in global functioning during antipsychotic treatment (all antipsychotics pooled).

4A. Pattern of predictive variables for increase in global functioning during antipsychotic treatment (assessed for each antipsychotic individually).

5B/6B/7B. Pattern of predictive variables for occurrence/severity/duration of adverse events during antipsychotic treatment (all antipsychotics pooled).

8B/9B/10B. Pattern of predictive variables for occurrence/severity/duration of adverse events (assessed for each antipsychotic individually).

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

Participant-level data meta-analysis

Participant-level data meta-analysis using only data from 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:

Participant-level data provided from randomized controlled trials (RCTs) on antipsychotic treatment in patients with schizophrenia, bipolar disorder, and schizoaffective disorder will be included. All routes of antipsychotic administration (e.g. oral and injection) will be included. The primary endpoint is six weeks treatment duration but durations from 4 to 12 weeks will also be included<sup>10</sup>.



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

The main outcome is reduction in the total score of major symptoms (psychosis or mania) from baseline to endpoint of six (four to twelve) weeks post-baseline. All assessment time points in this timeframe will be included. We aim to implement the same score for each disorder:

- Psychosis: Positive and Negative Syndrome Scale (PANSS)<sup>11</sup>
- Mania: Young Mania Rating Scale (YMRS)<sup>12</sup>

Oral and long-acting injectable antipsychotics will be calculated separately.

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

Potential predictors include variables derived from demographic data, clinical examinations, and laboratory investigations. Specifically, we aim at determining predictive combinations (patterns) of these predictors using artificial neural networks. We will investigate if these predictive combinations are similar for all investigated psychiatric disorders / medications or unique to specific disorders / medications.

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

We will include additional variables / characteristics potentially associated with outcome and AEs. Global functioning (endpoint 3A and 4A) will be measured on the Clinical Global Impression (CGI) – scale<sup>13</sup>. Occurrence of AEs (Yes / No) will be measured according to trial documentation. Duration of AEs is defined as cumulative number of days the AE occurred. Severity of AEs is measured as mild / moderate / severe.

### **Statistical Analysis Plan:**

We will merge individual patient data from the RCTs provided by The YODA Project. Separate analyses will be made for each diagnosis (i.e. schizophrenia, bipolar disorder, and schizoaffective disorder). We will use Deep Learning neural network methods with emphasis on uncertainty quantification and robustness against outliers. Uncertainty quantification does not just allow to predict the expected treatment outcome and risk for adverse events, but also confidence intervals of the prediction<sup>14,15</sup>. To choose a specific treatment option together with a patient in the sense of informed consent and shared decision making, it is crucial to have a measure of the prediction's certainty on hand. Hence, applying and refining techniques for certainty quantification of individualized treatment predictions might constitute a substantial advance on the road to individualized treatment recommendations based on multiple patient characteristics from different domains. Outlier robustness is important since real-life data is always noisy and contains contaminated learning data, which might impede the proper learning of predictive patterns.

We plan to compare the predictions of the neural networks with other established machine learning regression techniques such as support vector regression and random forests. We will construct multiple test-train folds for repeated cross-validation through partition of the original cohort into a subset for training purposes and a subset for testing<sup>16</sup>. Model performance is captured by the root mean squared error (e.g. deviance between predicted and real treatment outcome) and data likelihood and will be examined in an independent cohort subset.

Missing data will be treated as recommended by Little et al.<sup>17</sup>: First we will register if reasons for missing data were documented and develop a primary set of assumptions about the cause for missing data<sup>17</sup>. Then the primary set of assumptions will be followed by multiple imputation by chained equations and robustness tested with a sensitivity analysis<sup>17</sup>.

### **Project Timeline:**

- Milestone 1 at 0 months: Data preparation and implementation of Deep Learning neural network methods starts.
- Milestone 2 at 12 months: Analysis of objective A starts.
- Milestone 3 at 24 months: Analysis of objective B starts.
- Milestone 4 at 36 months: Analyses of objectives are completed and papers drafted.

The YODA project will be informed about the completion of each milestone and reports will be made available.

### **Dissemination Plan:**

To benefit both health professionals and patients we will present the study at internationally accredited conferences

(e.g. symposia at the WPA) and make the study available in major medical journals (e.g. JAMA Psychiatry, American Journal of Psychiatry, Lancet Psychiatry).

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5. Arranz, M. J. et al. Pharmacogenetic prediction of clozapine response. *Lancet* 355, 1615–1616 (2000).
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