NetraAI: Understanding Patient Populations Beyond Disease Labels for De-Risking Clinical Trials with Large Language Models

NETRAMARK

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BACKGROUND

NetraAI, powered by its unique Attractor AI algorithms, provides pharmaceutical companies with actionable insights to de-risk clinical trials. This technology is unique in its ability to discover and learn from those subpopulations of patients from small data that are truly generalizable. NetraAI avoids overfitting by identifying which of the patients it can *truly* learn from and derives "Causal Clusters" of variables from these patients. It generates hypotheses, which are statistically significant collections of these causal clusters of variables along with the identified subpopulations of patients.

CHALLENGES:

- Within any clinical trial there are patients which harm the endpoint due to being poor responders to the drug, by being enhanced responders to placebo, and not being able to tolerate the drug candidate. Alternatively, there are patients which are excellent responders to the treatment.

NEED:

- The ability to identify which patients are benefiting the trial, which are harming the trial, and a clear explanation of why by integrating a variety of data.

OBJECTIVES

By fusing Attractor AI-based technologies with LLMs we seek to enhance the landscape of clinical trials, with a primary focus on heterogeneous disorders which includes schizophrenia, anxiety, and major depressive disorder (MDD). This innovative approach extracts those subpopulations of patients which are actually generalizable according to a set of causal variables (Causal Clusters) that can be used to derive clear exclusion/inclusion criteria in order to enrich clinical trials.

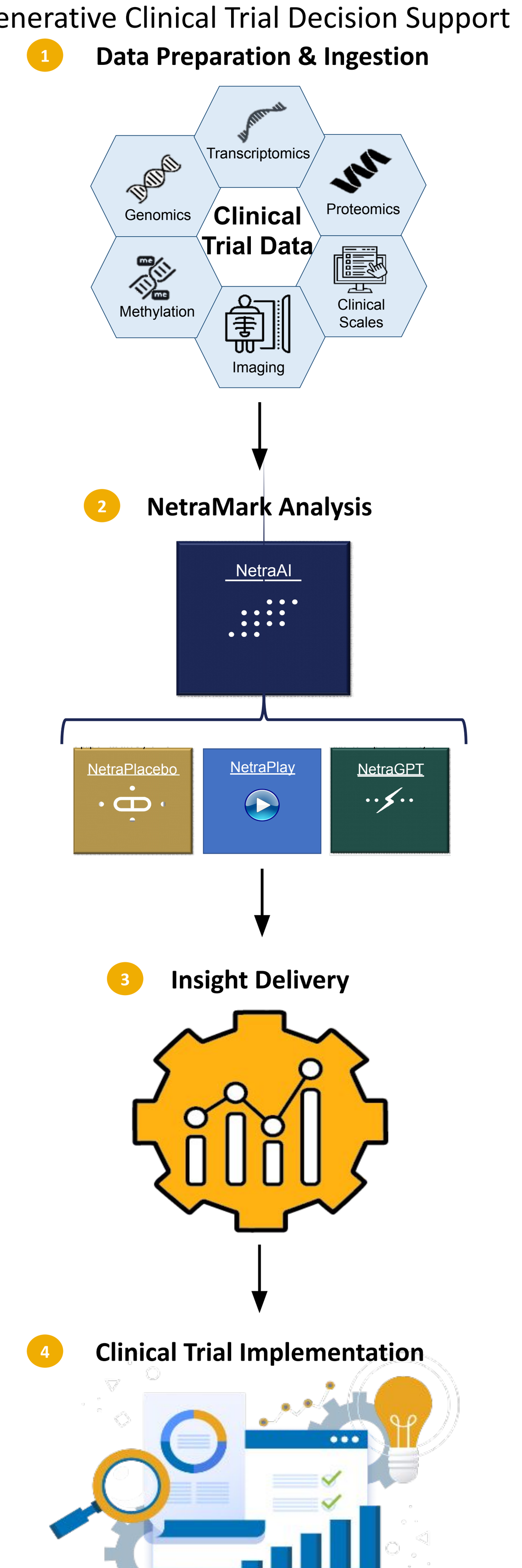
To achieve this objective, we aim to:

- Leverage the exceptional capabilities of Attractor AI to *decompose patient populations into explainable and unexplainable segments.* The explainable patient subpopulations are used to generate hypotheses to de-risk clinical trials. The large corpus of medical literature that LLMs have ingested provides a way to further enhance the discovered *personas* of these patient subpopulations, whether they are responders or non-responders.
- Identify key variables derived from the hypotheses generated, which can serve as inclusion and exclusion criteria to maximize the effect size of endpoints in subsequent, larger clinical trials by reducing placebo response while amplifying the drug response for improved trial outcomes.

METHODOLOGY & WORKFLOW

NetraMark Workflow

Generative Clinical Trial Decision Support



1 Data Preparation & Ingestion
Transcriptomics
Genomics
Clinical Trial Data
Proteomics
Methylation
Clinical Scales
Imaging
2 NetraMark Analysis
NetraAI
NetraPlacebo
NetraPlay
NetraGPT
3 Insight Delivery
4 Clinical Trial Implementation

DATASETS:

Multimodal data

- Demographic items
- Psychiatric scales, genetics, epigenetics, microbiome, etc.
- Safety measures

AI APPROACH:

- A unique *long-range memory mechanism reminiscent of attention mechanisms in LLMs* is utilized to cut through the monstrous number of combinations of multiple variables, facilitating the generation of hypotheses regarding patient subpopulations in the context of anxiety, schizophrenia, and MDD.

HYPOTHESIS GENERATION:

Hypotheses produced are a composite of various variables that describe drug and placebo responses, along with other events like toxicity. These hypotheses are designed to be clinically interpretable, providing actionable insights in the realm of psychiatric clinical trials, as well as for other heterogeneous disorders.

FAILED ANXIETY PHASE III TRIAL DETAILS:

- Clinical Scales (>100 variables)
- Placebo Response Propensity Scale (PRPS)
- 332 patients (161 placebo and 171 active)

SCHIZOPHRENIA PHASE IIa TRIAL DETAILS:

- Clinical Scales (138 variables):
  - CGI-S
  - LOF
  - Strauss Carpenter Level of Functioning
  - PANSS
  - Physiological measurements
- 87 patients randomized into placebo (n=39) and treatment arms (n=48)

MAJOR DEPRESSIVE DISORDER (MDD) SSRI CANBIND TRIAL):

- Clinical Scales (362 variables derived from over 30 scales including):
  - CGI
  - DARS
  - GAD7
  - SEXFX
  - SHAPS
  - YMRS
  - MINI
  - QIDS
  - QLESQ
- Endpoint was change in MADRS with a 50% response criteria
- 172 patients with only one arm that received an SSRI (no placebo arm)

RESULTS

Phase III Anxiety Trial

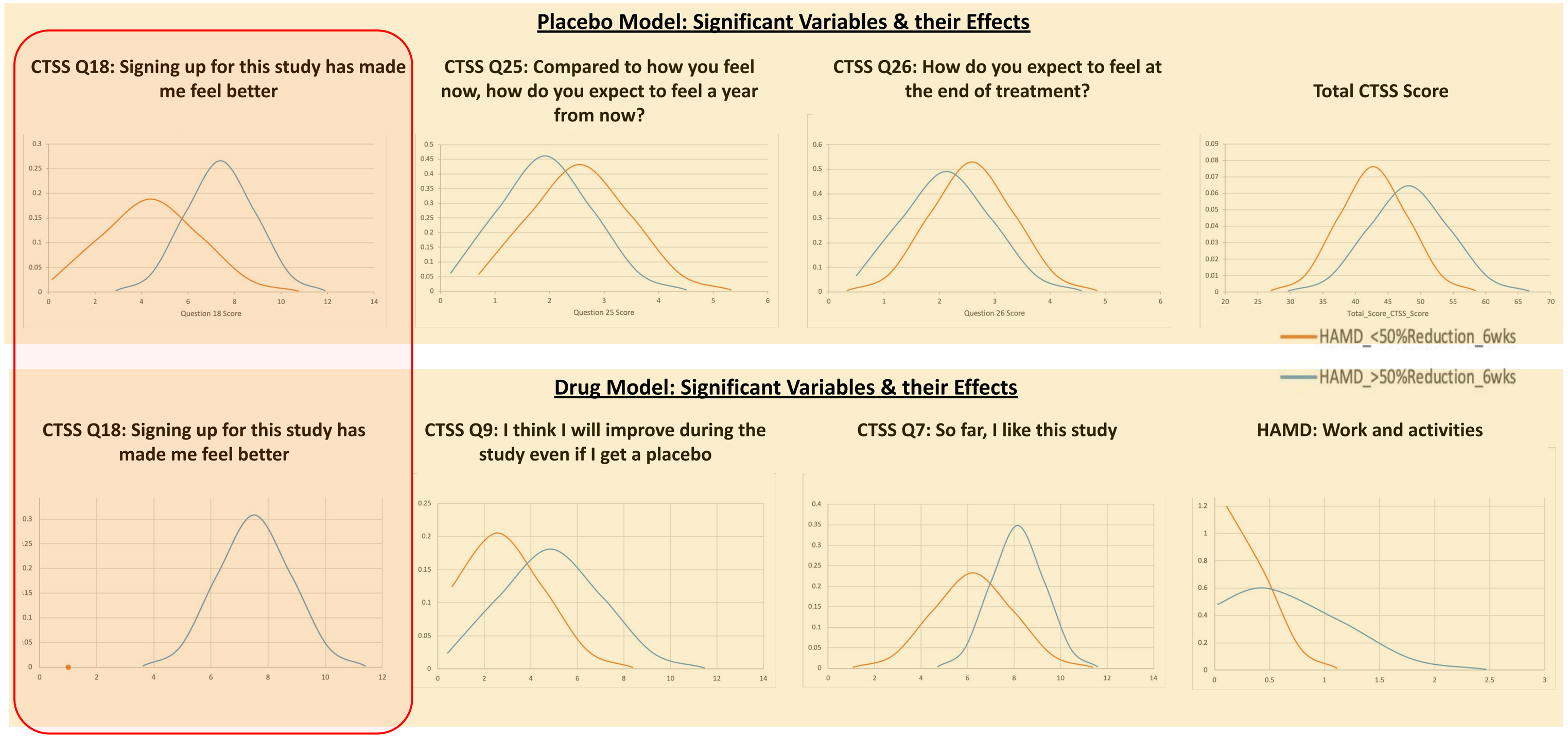
NetraAI uncovered markers of placebo and drug responders to attempt an improvement in the trial outcome.

Markers of Placebo Response:

- 73 responders, 88 non-responders
- CTSSQ18 and Total CTSS explain 55/73 responders
- CTSSQ26 and 27 explain 37/88 non-responders with 74% accuracy

Markers of Drug Response:

- 69 responders, 102 non-responders
- 10 drug non-responders came together according to a combination of variables



Placebo Model: Significant Variables & their Effects
CTSS Q18: Signing up for this study has made me feel better
CTSS Q25: Compared to how you feel now, how do you expect to feel a year from now?
CTSS Q26: How do you expect to feel at the end of treatment?
Total CTSS Score
HAMD_<50%Reduction_6wks
HAMD_>50%Reduction_6wks
Drug Model: Significant Variables & their Effects
CTSS Q18: Signing up for this study has made me feel better
CTSS Q9: I think I will improve during the study even if I get a placebo
CTSS Q7: So far, I like this study
HAMD: Work and activities

Figure 1. Significant variables extracted by NetraAI affecting placebo and drug response in a phase III anxiety trial. Top row represents significant variables in the placebo arm. Bottom row represents significant variables in the treatment arm. Note: CTSS Question 18 appears in both study arms which indicates a conflict if one were to try to enrich with this variable.

This information offers valuable insights for trialists on how the potential enrichment of certain scale item responses may positively affect the analysis of endpoints in future trials with this compound.

- Results suggest that the anxiety drug did not achieve its intended endpoint, but it did reveal a subtype of patients that may not respond in a predictable way. Identifying and excluding this subgroup from future trials is recommended to enhance the trial outcomes.
- Question 18 presents a challenge as it characterizes both placebo and drug response, highlighting the need to exercise caution when adding inclusion/exclusion criteria in clinical trials. By refining for placebo response, this would concurrently interfere with drug response and can skew the effect size.

Phase IIa Schizophrenia Trial

Shifting the effect size using NetraAI by identifying markers of placebo and drug response.

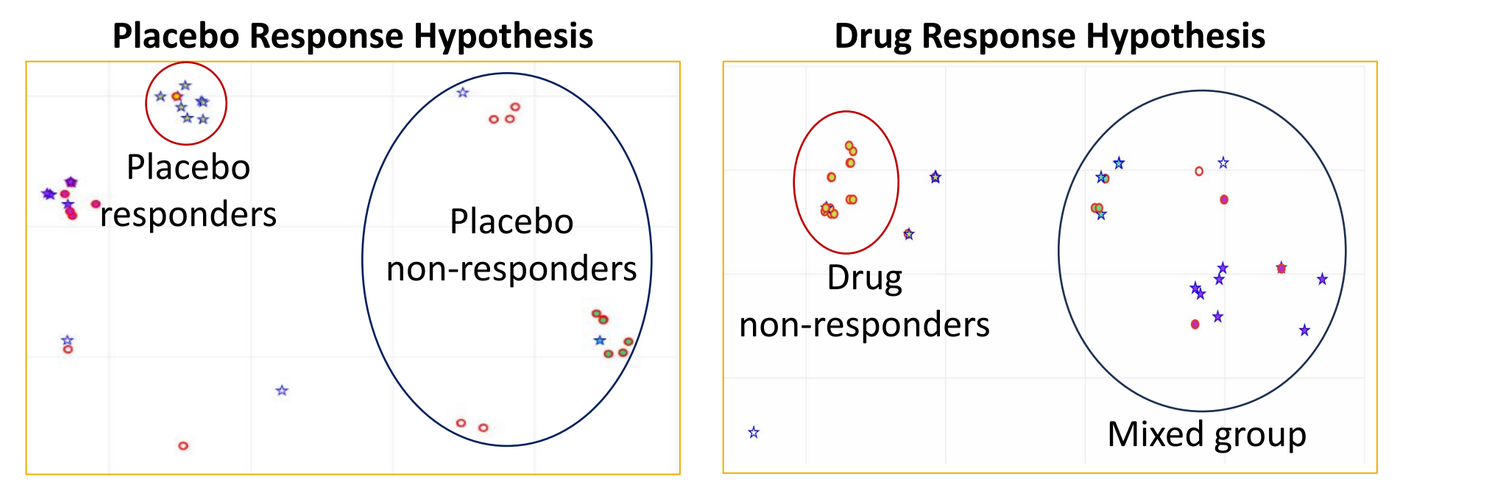
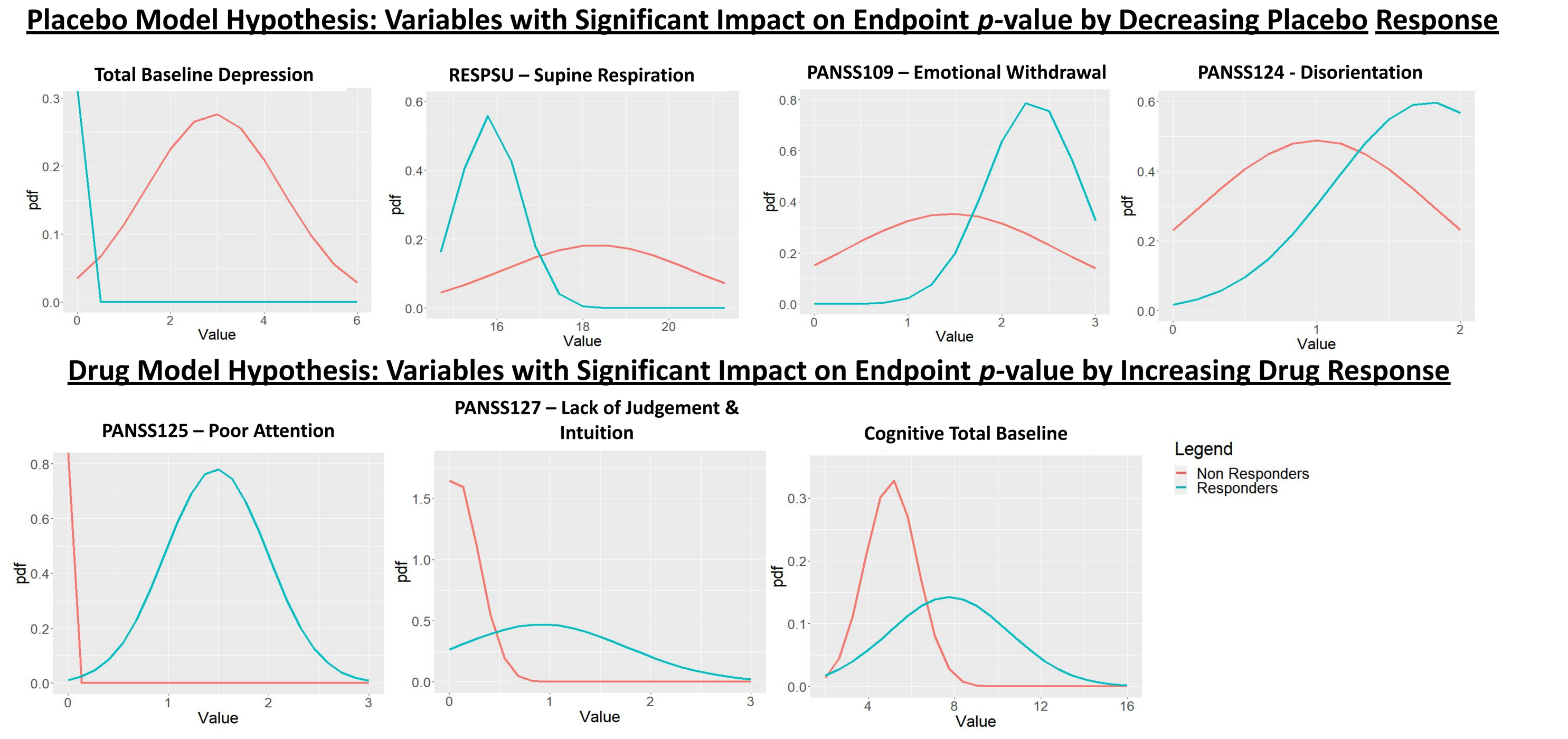


Figure 2. NetraMark hypotheses for phase IIa schizophrenia trial.

Explainable perspectives that can be used to enrich patient populations

- 50% of placebo responders defined
- 85% of drug responders can be explained
- 37.5% of drug responders are strongly explainable with 16/18 being drug non-responders



Placebo Model Hypothesis: Variables with Significant Impact on Endpoint p-value by Decreasing Placebo Response
Total Baseline Depression
RESPSU – Supine Respiration
PANSS109 – Emotional Withdrawal
PANSS124 - Disorientation
Drug Model Hypothesis: Variables with Significant Impact on Endpoint p-value by Increasing Drug Response
PANSS125 – Poor Attention
PANSS127 – Lack of Judgement & Intuition
Cognitive Total Baseline
Legend
Non Responders
Responders
Value
pdf

Figure 3. Significant variables extracted by NetraAI affecting placebo and drug response in a phase IIa schizophrenia trial. Top row represents significant variables in the placebo arm. Bottom row represents significant variables in the treatment arm.

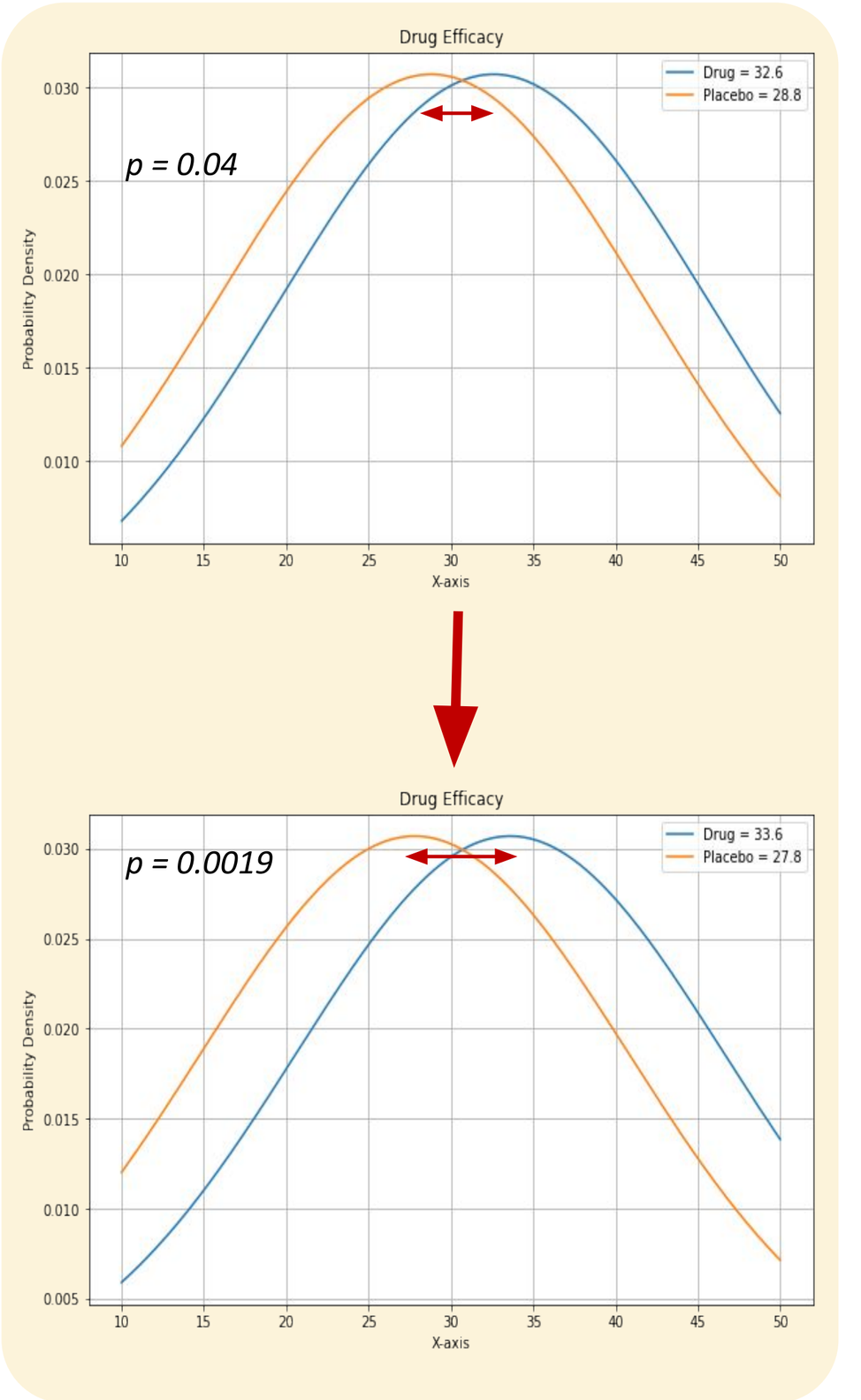


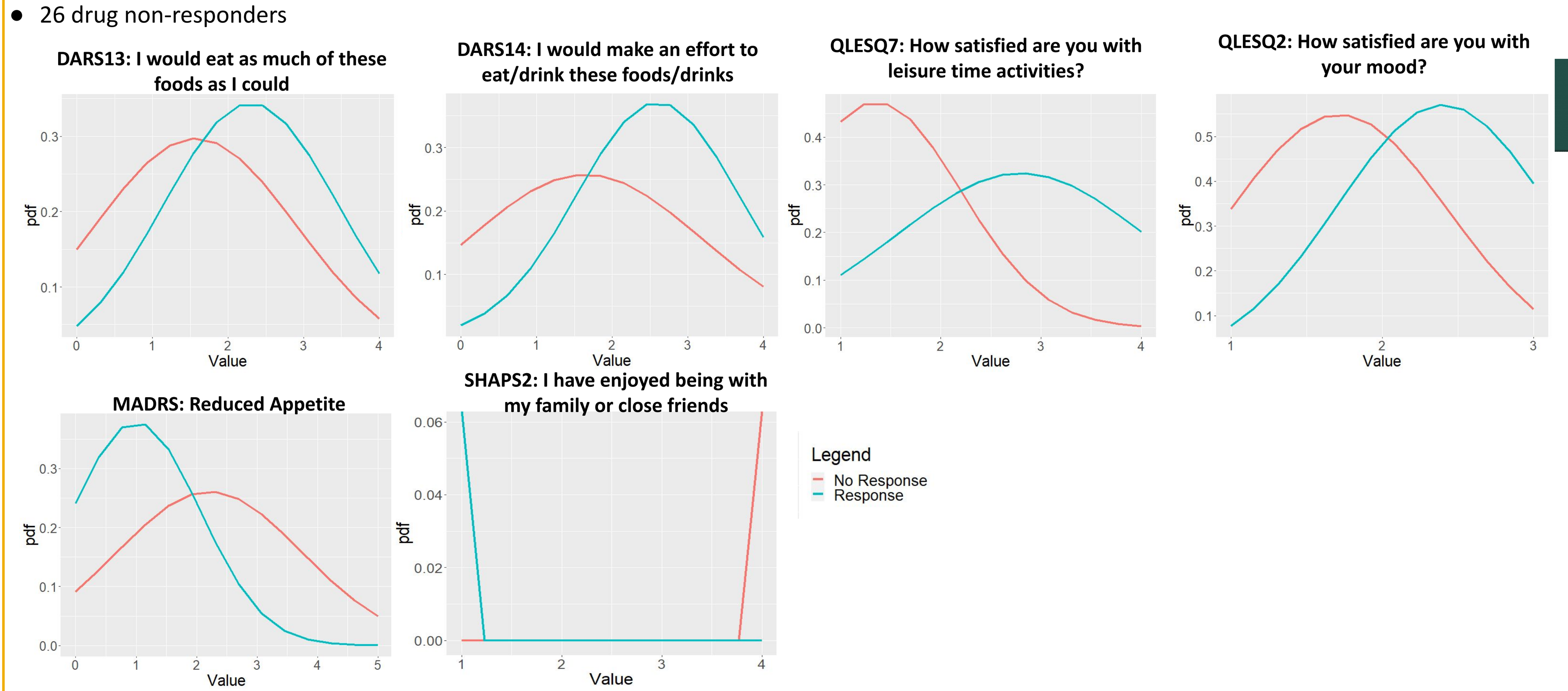
Figure 4. Maximizing endpoint effect size by combining both NetraAI hypotheses.

With our recommendations we are able to shift the p-value from 0.04 to 0.0019 by hypothetically improving response in less than 20% of each arm. (**Figure 4**)

CANBIND Major Depressive Disorder SSRI Investigation

NetraAI identified a group of patients highly characterized by a set of 6 variables that define a drug response persona

- 49/172 patients (~a third of patients)
- 23 drug responders
- 26 drug non-responders



DARS13: I would eat as much of these foods as I could
DARS14: I would make an effort to eat/drink these foods/drinks
QLESQ7: How satisfied are you with leisure time activities?
QLESQ2: How satisfied are you with your mood?
MADRS: Reduced Appetite
SHAPS2: I have enjoyed being with my family or close friends
Legend
No Response
Response
Value
pdf

Figure 5. Significant variables extracted by NetraAI affecting drug response in a major depressive disorder trial. These variables were hypothesized by the NetraAI to provide an actionable persona to improve response to SSRI for major depression subjects after enrichment.

These results show that this set of drug responders were characterized by an increased appetite, slightly higher satisfaction with their leisure time and mood, and a significant decrease in enjoyment with family and friends (**Figure 5**). Importantly, DARS15: "*I would actively try to get these foods/drinks*", was also a significant variable characterizing drug responders. Simultaneously, there was a set a drug non-responders that were characterized by the opposite effects.

NetraGPT

The NetraGPT Module: LLM Integration with Attractor AI offered the following for enhancing MDD trials:

1. <u>**Higher Desire for Food at Baseline**</u>
   Trial Design Insight: Consider incorporating appetite as an inclusion criterion. By selecting participants who have a higher baseline appetite, you may increase the proportion of subjects more likely to respond to the SSRI, potentially enhancing the drug's observed efficacy in the trial.
   Measurement: Use validated appetite assessment scales or questionnaires at the screening phase.
2. <u>**Satisfaction with Leisure Activities at Baseline**</u>
   Trial Design Insight: Evaluating the baseline satisfaction with leisure activities can help in stratifying participants based on their potential to respond. Including individuals who still derive pleasure from activities might lead to a higher overall response rate in the trial.
   Measurement: Use psychometrically sound scales assessing anhedonia or leisure activity satisfaction during participant screening.
3. <u>**Satisfaction with Mood at Baseline**</u>
   Trial Design Insight: It may seem counterintuitive to include patients with some degree of mood satisfaction in a MDD trial, these individuals may represent a segment that responds particularly well to SSRIs. Stratify participants based on their mood satisfaction scores to identify differential drug responses.
   Measurement: Implement standardized mood assessment tools at baseline, ensuring the tool captures nuances in mood satisfaction.
4. <u>**Less Enjoyment from Family at Baseline**</u>
   Trial Design Insight: Participants with significant familial or interpersonal stressors might represent a group where SSRIs demonstrate a pronounced effect, possibly due to the drug's buffering effect against these stressors. Consider creating a stratification analysis for participants with familial stressors or dissatisfaction.
   Measurement: Employ interpersonal relationship scales or family-related quality of life assessments during the screening phase.

<u>**Integrated Trial Strategy:**</u>

To enrich your clinical trial, utilize these predictors as stratification or subgrouping factors. This approach can help in identifying specific segments of the depressed population where the SSRI demonstrates maximum efficacy. Furthermore, these predictors can aid in patient selection, ensuring a higher likelihood of observing positive treatment outcomes, and consequently enhancing the power and validity of the trial results. Additionally, understanding these factors upfront can assist in post-hoc analyses and interpretations, helping to delineate why certain participants responded better and informing future trial designs or post-market strategies.

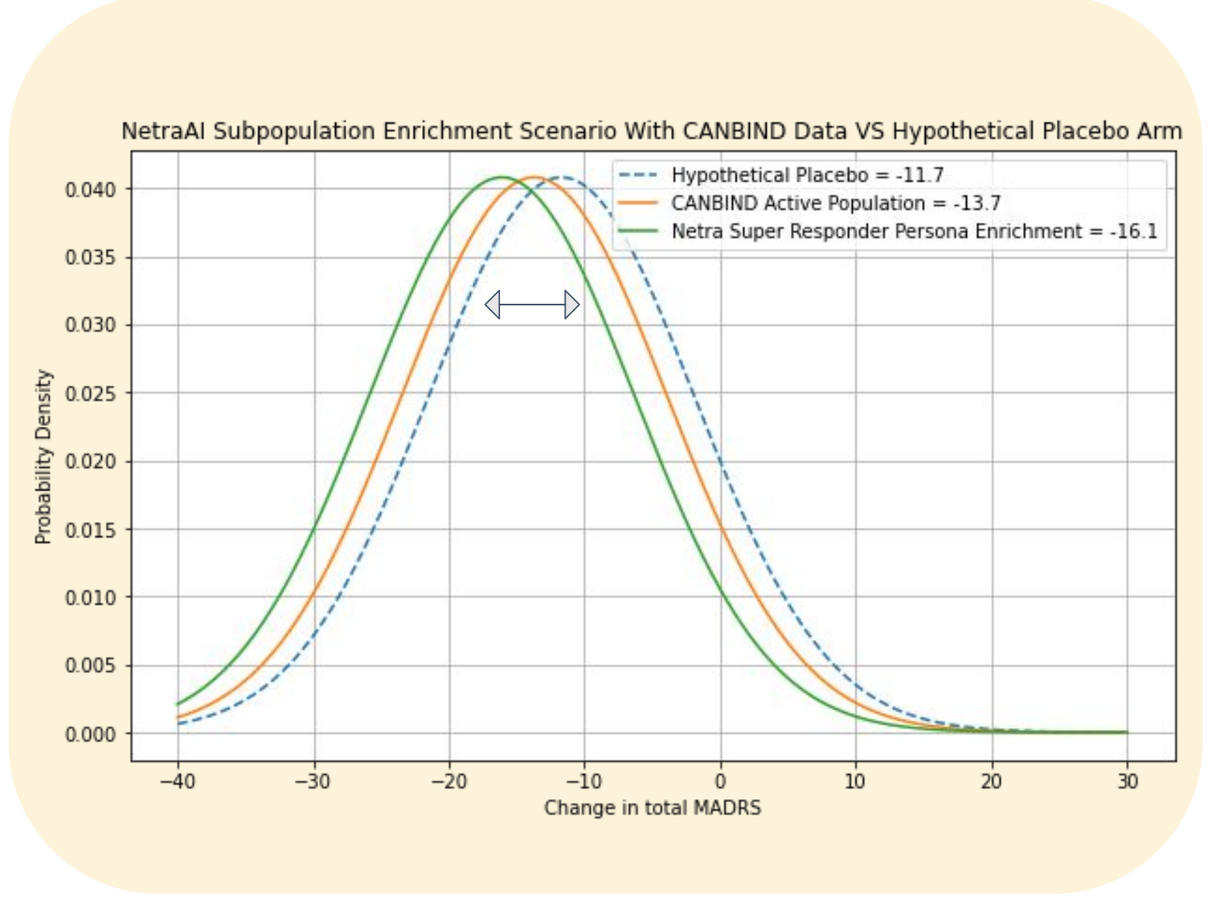


Figure 6. Using NetraAI inclusion and exclusion criteria to improve clinical trial endpoints.

Using this subset of patients and the inclusion/exclusion criteria identified by NetraAI, we were able to create a model where the change in MADRS went from -13.7 to -16.1 by assuming that we can improve response in ~a third of the population. By comparing the active arm against a hypothetical placebo group whose average change in MADRS was -11.7, this process was able to improve the *p*-value from 0.056 to just under 0.0001. (**Figure 6**)

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS

1. **Identifying Markers of Placebo and Drug Response in a Phase III Anxiety Trial**
   - 8 clinical scale items explaining 25% of placebo responders and 5 clinical scale items explaining a small group of drug non-responders, highlighting the importance of identifying variables that affect placebo and drug response. The trial is unlikely to be rescued.
2. **Shifting the Endpoint Effect Size in a Phase IIa Schizophrenia Trial**
   - Hypotheses for placebo and drug response with variables that have a significant impact on endpoint *p*-value by decreasing placebo response or increasing drug response.
3. **Identifying Markers of Drug Response based on a collection of items from a variety of clinical scales**
   - A 6 variable persona that characterizes a third of patients in the CANBIND MDD investigation with respect to drug response was found. This persona was used to create a model that predicted a scenario that can increase the average change in MADRS by over 2 points. This can have a significant impact for clinical trial efficacy for major depression.

CLINICAL TRIAL SIGNIFICANCE OF METHODOLOGY AND FINDINGS:

This research underscores the powerful synergy of Attractor AI and LLMs in dissecting patient population responses in clinical trials. Identifying causal variables ensures optimized participant selection, fortifying trial efficacy. By providing clear decompositions of patient populations ***into explainable and unexplainable subpopulations***, we can derive generalizable insights that can help evaluate the chance of success of future trials from past trial data, and simultaneously provide exclusion and inclusion criteria to enhance endpoints.

FUTURE USE AND APPLICATIONS:

Using variables derived from *explainable subpopulations,* as identified through this hypothesis generation technology, to impact clinical trial endpoint outcomes by adding inclusion and exclusion criteria to improve efficacy in the active drug arm and reduce response in the placebo arm that can be applied to subsequent clinical trials.

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