Strategies for Collecting Quality Data in Psychiatric Clinical Trials

ABSTRACT

Sponsors of psychiatric clinical trials may face significant challenges in collecting robust, quality data to support the efficacy and safety of investigative compounds. Identifying and mitigating study design-, subject-, and site-related factors that may influence data quality as early as possible in program development can help to drive study success.
Ensuring that psychiatric clinical trial data accurately captures a compound’s safety and efficacy potential requires that sponsors account for the challenges inherent in working with a mentally ill population. Mental illness and its manifestations are almost as varied as the spectrum of human behavior. Understanding the interactions among the myriad genetic, biological, social, and environmental factors that give rise to mental illness is a complex task, which makes clinical trials involving psychiatry drugs quite a challenge.

Observing changes in the disease under study is, in part, a subjective process, and that subjectivity creates risk of undue influence that the patient and/or investigator may not recognize. To further complicate matters, not all symptomatic improvement in mental disorders can necessarily be tied to the product under investigation. Some changes may result from unrelated factors whose therapeutic effect erodes the efficacy signal of a potential treatment.

In this white paper, we explore a range of factors that, if identified and mitigated early in the development process, can maximize the potential for conclusive study results in psychiatric clinical trials.
Increased difficulty in demonstrating a treatment effect

Sponsors of psychiatric clinical trials may need to contend with a decreasing ability to demonstrate a treatment effect. In September 2007, a collaborative session between the International Society for CNS Clinical Trials and Methodology and the International Society for CNS Drug Development focused on the apparent reduction of drug-placebo differences in recent multicenter trials of antipsychotic medications for schizophrenia. During this joint session, presenters reported data from several recent trials that indicated higher rates of placebo response (see Figure 1) and lower rates of drug response – even to previously established comparator drugs – when compared with earlier trials. The consequent decrease in separation between treatment and control groups over time made it more difficult to obtain conclusive results.

These findings raise a host of questions:
+ Has study design or execution inadvertently encouraged these discouraging results?
+ Have study populations changed?
+ Have there been shifts in the natural course of the disease itself, or in our diagnostic abilities?
+ Is the efficacy of newer compounds simply less than earlier drugs?

During their discussion regarding the possible causes of this reduced drug-placebo difference, the working group covered a range of methodological factors, such as study design, site factors, subject selection, inclusion/exclusion criteria, and diagnostic specificity. The group also discussed potential solutions to proactively mitigate the risks associated with these factors, some of which we will discuss in more detail throughout this paper.

**Figure 1. Placebo response in acute schizophrenia trials**

*Placebo response in acute schizophrenia trials*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>1993</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1996</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1997</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2001</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2002</td>
</tr>
<tr>
<td>Sonepiprazole</td>
<td>~2000/1</td>
</tr>
<tr>
<td>Asenapine</td>
<td>2000/3</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>2004/5</td>
</tr>
<tr>
<td>Bifeprunox</td>
<td>~2004/6</td>
</tr>
</tbody>
</table>

- Mean change from baseline on PANSS total
Strategies for collecting quality data

Study design considerations

There is no tried-and-true template for psychiatric clinical trials. Each study has its own nuances and variables that make an impact on study design and the quality of the resulting data.

Subject and illness characteristics

The subject is the basic unit of any study. In any disease or disorder, certain characteristics of the subject or illness may affect the therapeutic response achieved or confound results. For example:

+ A meta-regression analysis of placebo response in 50 antipsychotic trials revealed that younger age, shorter duration of illness, and greater baseline symptom severity were significantly associated with greater placebo response.²

+ A review of 45 antidepressant studies demonstrated that the magnitude of symptom reduction was related to mean initial Hamilton Rating Scale for Depression (HAM-D) score. In the antidepressant-treated group, a higher initial HAM-D was linked to larger improvement from baseline. However, in the placebo group, a higher initial HAM-D was associated with a smaller improvement in symptoms.³

Understanding how subject and illness characteristics may impact treatment effect and placebo response for a specific disease or disorder can help inform study design. Sponsors should also take into account the natural course of the illness and the therapeutic setting provided by the site:

+ Does the illness normally wax and wane, regardless of treatment?

+ Will the increased attention associated with participating in a clinical trial (e.g., study visits, follow-up telephone calls, special medications) provide an unintended therapeutic benefit?

Subject expectations

Expectation is another unintended consequence of study design, as illustrated by how subject expectation – and treatment response – may be impacted by the percentage of study subjects randomized to placebo. If a subject knows that there is a 50 percent chance of being randomized to placebo in a two-arm study, his expectation of receiving active drug will be different than if he were to participate in a five-arm study or a comparator trial, where there is a lower likelihood he will be given placebo. This expectation may impact placebo response and, ultimately, trial outcome, particularly if the subject is familiar with medication side effects and tries to guess which study arm he is in. Not surprisingly, expectation response works in both directions. There is evidence that treatment effects to active drug are lower when placebo is used and that placebo responses are higher with decreasing ratios of placebo.

In addition, the expectation associated with the active drug – regardless of placebo – can be problematic. For example, the promise of a novel therapy to produce a ‘cure’ for depression can affect the outcome of both the placebo and treatment arms of a study. Sponsors should keep in mind that even the mode of drug delivery can influence subject expectations, with injections or infusions being perceived as more potent than pills.
Subject enrichment

Enrichment strategies may be used in clinical trials to select a subset of the population in which the effect of the investigative drug can more readily be demonstrated. In addition to increasing the likelihood of detecting a treatment effect, enrichment strategies may help to limit the number of subjects who are not appropriate for a particular trial.

Placebo run in is a relatively old study design where every participant is given placebo prior to randomization as a method for potentially eliminating placebo responders. Unfortunately, the evidence shows this enrichment strategy has not been successful in psychiatry trial. A meta-analysis of 101 antidepressant studies reveals that a placebo run-in does not lower the placebo response rate, increase the placebo-drug difference or affect the drug response rate post randomization.4

Adjunctive lead in for augmentation has been used in recent years, particularly in depression. In this study design, the target subject population is one that has had an inadequate response to an available treatment and is thus eligible for add-on therapy. Rather than relying on medical records or patient report, both of which can be incomplete or inaccurate, adjunctive lead-in studies give subjects an open-label medication and those who remain ill after an adequate course are allowed to continue on to the randomized portion of the study. The perceived advantage of this study design is that there is greater assurance that the subject was compliant with an adequate dose of a standard-of-care medication under monitored study conditions, confirming their eligibility as study participants.

Unfortunately, there are potential pitfalls to this design, as well. A lead-in period does not ensure compliance despite self report, and PK sampling to identify subjects who are taking no medication during this period is not uncommon. Also, there will be those who do respond to standard-of-care medication, as well as those who do not complete the open label period. As such, the number needed to recruit for an adjunctive lead-in study may be up to three times more than a study that relies on medical records or patient report, and this does not translate into better data. In fact, an analysis of randomized, double-blind, placebo-controlled trials of adjunctive pharmacologic strategies for major depressive disorder showed no advantage to a prospective lead-in over use of historical data only to define treatment resistance.5

Double randomization has been used for many years across multiple therapeutic areas and has been shown to be generally successful in depression. The sequential parallel comparison design (SPCD) popularized by Maurizio Fava, MD is just one of several common double-randomization designs. The first phase of randomization is used to identify and segregate subjects who may potentially confound the study because they report improvement on placebo. Placebo non-responders advance to Phase II of treatment.

One consideration for sponsors contemplating a double randomization study design is whether the Phase II treatment assignment for placebo non-responders is truly a re-randomization, or whether the treatment arm for placebo non-responders has already been pre-specified in Phase I of the study, as this leaves room for the introduction of bias during the enrichment process. Another consideration is the question of the ‘assumption of additivity’ which considers the difference between the observed treatment response and the observed placebo response to be the true medication effect.
As enrichment for placebo-nonresponders cannot account for this medication arm response due to the placebo effect, how does enrichment affect the magnitude of the calculated placebo-drug separation? A third consideration is whether the potential prolonged period of placebo exposure reasonable and ethical for the indication under investigation.

**Randomized withdrawal** study designs stabilize illness with the investigational drug before withdrawing the medication in a randomized fashion to compare the rate of relapse or increased symptomatology. Randomized withdrawal – also called relapse prevention in maintenance of effect studies – is often used to examine the long-term benefit of continued treatment, particularly with antidepressants and antipsychotics. An FDA review of antidepressant maintenance trials over a 25-year period found that these types of trials have a high rate of success. Randomized withdrawal is also commonly used in studies of attention-deficit/hyperactivity disorder (ADHD), where only those subjects who respond to the initial stabilization are allowed to randomize.

A downfall common to all enrichment strategies is time. Because the enrichment process happens during the study, the treatment period is longer and the subject number may significantly increase.

**Use of placebo**

The acceptability of placebo varies throughout the world, which may impact study design for global clinical trials. In North America, placebo-controlled studies are the norm, provided ethical safeguards in place. However, in South America, the majority of countries will not accept placebo-controlled studies. Western European countries typically require an active control, which tends to limit psychiatry trials in those countries to comparator studies, open label studies, or, with good justification, studies that include adjunctive treatment.
for all study arms. Eastern Europe is more accepting of placebo-controlled studies, but adequate justification is required and additional safety measures, e.g., study hospitalization for the full treatment period, may be needed. Similarly, Asia Pacific countries are likely to require substantiation for placebo design.

**Number of sites**
The number of sites in a study is dependent upon expected recruitment rate, desired timeline and available budget, and the risk associated with increasing the number of sites should not be taken lightly. Increasing the number of sites may decrease the separation from placebo. An analysis of 12 pediatric antidepressant studies showed that the single best predictor of the proportion of placebo responders was the number of study sites. This may be due to lower severity of illness, decreased site competence due to a lower subject volume, or decreased standardization, which naturally occurs when additional variables – in this case, sites – are introduced. Some studies attempt to mitigate this risk with the use of centralized raters to increase uniformity and consistency of assessment.

**Site factors**
Understanding study sites at a granular level can help to maximize the potential for conclusive study results. This involves taking a detailed look at the make-up of each site, including:

- Involvement and commitment of the principal investigator, which often defines the culture of the site
- Experience of the staff in the indication in a research setting
- Past performance of the site in the same indication, e.g., separation from placebo and reasons for screen failures or dropouts
- Research facility capabilities, including the feel of the waiting room, the process for securing facility use agreements for third-party hospital space, and how subjects will be cared for beyond study-specific procedures

If a study design utilizes site raters, putting in place a process to manage rater assessment is also important:

1. **Rater selection and availability** – establish requirements criteria, set baseline credentialing experience required, assess interview skills, and confirm availability
2. **Rater certification** – train raters on what to do and what not to do during the interview application
3. **Quality assurance and recalibration** – identify possible reversion to poor practices or unexpected changes in scoring from visit to visit and define process for recalibration or remediation, as needed

![Figure 5. Placebo response by number of study sites](image-url)
Subject selection and eligibility

When it comes to subject recruitment, speed and quality are equally important for study success. High quality subject selection and enrollment requires accurate classification and diagnosis, as well as assessment of a subject’s motivation and overall clinical profile. The process to screen and select subjects should include early evaluation of eligibility with these considerations:

+ Confirmation of symptom severity levels
+ Qualitative assessment of the appropriateness of the subject for the trial, including their home environment or other influences that could factor into the success of the subject in the study
+ Evaluation of therapeutic misconception, placebo response risk, and expectation of improvement or gain
+ Provision of results to Premier Research for incorporation into the central eligibility review, which helps the site identify potential areas of risk related to the patient profile which could negatively influence how the subject responds to study treatment (see Figure 6)

Data surveillance

We must identify, as early as possible, trends that may indicate issues with the quality of the data captured.

Targeted data surveillance

Employing a targeted data monitoring workflow helps ensure that data surveillance is accurate, precise, and ongoing:

1. Risk assessments – review all critical data and processes that could impact data quality and study results
2. Monitoring plan – identify on-site, off-site, and central monitoring activities for the study and define how the visit schedule can be altered based on data review
3. KRI programming – program key risk indicators (KRIs), (see Figure 7), and create analytics to support centralized monitoring
4. Monitoring execution – review analytics, visualizations, and execute monitoring activities; determine what actions to take based on the risk management plan; and conduct on-site monitoring per the Clinical Monitoring Plan (CMP)
### Figure 7. Sample key risk indicators

#### Risk level: study

<table>
<thead>
<tr>
<th>Category</th>
<th>Key risk indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study conduct</td>
<td>+ Systemic eCRF data entry issues</td>
</tr>
<tr>
<td></td>
<td>+ Enrollment (accrual vs. target)</td>
</tr>
<tr>
<td></td>
<td>+ Percent dropouts</td>
</tr>
<tr>
<td></td>
<td>+ Number of non-enrolling sites</td>
</tr>
<tr>
<td></td>
<td>+ Screen failure rate</td>
</tr>
<tr>
<td></td>
<td>+ Subject eligibility criteria challenges</td>
</tr>
<tr>
<td>Safety</td>
<td>+ SAE Rate</td>
</tr>
<tr>
<td>Treatment compliance</td>
<td>+ Reasons for Rx stops</td>
</tr>
</tbody>
</table>

#### Risk level: site

<table>
<thead>
<tr>
<th>Category</th>
<th>Key risk indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study conduct</td>
<td>+ Protocol deviation rate</td>
</tr>
<tr>
<td></td>
<td>+ Informed consent improperly obtained</td>
</tr>
<tr>
<td></td>
<td>+ Subject eligibility criteria not followed</td>
</tr>
<tr>
<td></td>
<td>+ IP improperly administered</td>
</tr>
<tr>
<td></td>
<td>+ Study blinding improperly broken</td>
</tr>
<tr>
<td>Safety</td>
<td>+ AEs/SAEs not properly/timely reported</td>
</tr>
<tr>
<td></td>
<td>+ AE grade 3/4 rate</td>
</tr>
<tr>
<td></td>
<td>+ Drug related AE</td>
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#### Risk level: patient

<table>
<thead>
<tr>
<th>Category</th>
<th>Key risk indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment compliance</td>
<td>+ Percent dose reductions</td>
</tr>
<tr>
<td></td>
<td>+ Percent dose delays</td>
</tr>
<tr>
<td></td>
<td>+ Missed PRO assessments</td>
</tr>
<tr>
<td></td>
<td>+ Missed visits, assessments</td>
</tr>
</tbody>
</table>

#### Risk level: study specific

<table>
<thead>
<tr>
<th>Category</th>
<th>Key risk indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study conduct</td>
<td>+ Under reporting of AEs</td>
</tr>
<tr>
<td></td>
<td>+ Patient follow up in compliance with visit windows</td>
</tr>
<tr>
<td></td>
<td>+ Proactivity in notifying sites when 24-month follow up for patients is due</td>
</tr>
<tr>
<td></td>
<td>+ Incomplete/missing CRF data</td>
</tr>
</tbody>
</table>

### Medical safety surveillance

There are three major facets to a medical monitor’s responsibilities in a study:

1. **Real-time medical review.** This involves evaluation of abnormal laboratory and ECG testing, as well as serious adverse events (SAEs) and other results, as the data is being generated. Real-time medical review allows the medical monitor to intervene when he or she detects a potential safety concern.

2. **Site guidance.** The medical monitor is also available to consult with the site on concerns related to the investigational drug. The medical monitor is well-positioned to do this because he or she sees the blinded data from all subjects at all sites.

3. **Study-wide safety interpretation.** This involves periodic review of aggregated safety data from all available subjects. The introduction of technology to help visualize trends and outliers is extremely valuable for medical monitors.

### Conclusion

The cornerstone of a successful clinical study is the ability to generate robust, quality data that yields conclusive results. However, sponsors of psychiatric clinical trials may face significant challenges in collecting the quality data needed to support the efficacy and safety of investigative compounds. Identifying and mitigating factors that may influence data quality early in the development process can help sponsors more accurately capture an investigative drug’s safety and efficacy potential. Collaboration among the sponsor, CRO, and sites is also critical to driving success in a psychiatric clinical trial, and alignment on study strategy and execution can help to maximize the quality of the data collected.
References


7. Massachusetts General Hospital Clinical Trials Network and Institute. SPCD. Available at http://mgh-ctrn.org/innovations/spcd/.


Krista Armstrong, Ph.D. | Vice President, Strategic Development

Krista Armstrong, Ph.D. has steadily taken on new responsibilities at Premier Research, and now oversees the overall execution of Premier’s Strategic Development Strategies. Dr. Armstrong is also responsible for oversight of the Executive Director Leadership Team for the company’s neuroscience, oncology, general medicine, pediatric, and rare disease portfolios. She ensures that Premier Research offers sponsors the best possible operational, regulatory, medical, and scientific advice.

Dr. Armstrong’s clinical research experience spans more than 20 years in both academia and the pharmaceutical industry. Her primary therapeutic and operational expertise is within neuroscience, with a specific emphasis in psychiatric indications and neurological conditions, such as ADHD, bipolar disorder, autism, addiction, Alzheimer’s disease, Parkinson’s disease, and stroke. At Premier Research, she has led the integration of six acquisitions and grown the clinical operations department from 60 to more than 500 employees globally.

Susan Kozauer, M.D. | Senior Medical Director, Medical Head of Psychiatry

Susan Kozauer, M.D. provides leadership to neuroscience strategy and oversees all medical operations within the psychiatry portfolio. With over 15 years’ experience in academia, clinical practice, and clinical research, Dr. Kozauer’s interests lie specifically in schizophrenia and treatment resistant depression. Dr. Kozauer’s work with Phase I-IV studies, regional and global programs, and protocol design and strategy allows her to provide valuable scientific guidance in the neuroscience operations space.

About Premier Research

Premier Research is a leading clinical development service provider that helps highly innovative biotech, medical device, and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional, and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, dermatology, medical devices, neuroscience, oncology, pediatrics, and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.