Outcome Solutions in Medical Research

By using a hypothetical protocol in CNS clinical research, it is possible to illustrate new approaches to common real world study challenges that research teams face

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In central nervous system (CNS) clinical research, pharmaceutical sponsors pursuing CNS indications encounter numerous challenges stemming from the subjective nature of many CNS endpoints, variability of placebo response, and from measurement errors due to inconsistency in a site investigators' assessment processes. CNS clinical trial sites also face formidable challenges related to recruiting and retaining appropriate patients, tight budgets, and increasing respondent burden due to the increasing number of endpoints, measures, and techniques required by modern protocols. Variability in rater experience, patient eligibility requirements, and the task of integrating multiple vendors and technology applications create additional hurdles to trial success.

A key challenge facing clinical trials in many CNS indications is in designing studies to optimise the opportunity to demonstrate efficacy by obtaining a true drug-placebo difference. For example, high placebo response rates in Parkinson's disease, depression, mania, anxiety, and negative symptoms of schizophrenia are suspected to be a key reason for study failure.

Becker and colleagues describe sources of clinical trial unreliability that are not widely acknowledged, but have the potential to compromise CNS drug development (1). **Table 1** demonstrates some of the sources of this unreliability and representative examples.

Inaccurate ratings, perilous mistakes, bias, and, of course, protocol violations and falsified data are very important. We can consider these problems in four broad categories:

- Eligibility
- Outcomes
- Placebo response
- Patient engagement

Other topline challenges include the growing number of endpoints and outcome measures that trials seek to capture, how best to capture robust reliable data, and how to avoid overburdening patients and raters. Every study confronts these challenges, but some study teams (such as in CNS) grapple with them more directly than others. Finding the best solution requires a thoughtful approach, considerable therapeutic expertise and operational experience, as well as excellent technical capabilities.

State-of-the-Art Solutions in eCOA

Electronic clinical outcomes assessment (eCOA) solutions are increasingly commonplace in global CNS clinical trials due to the numerous advantages over traditional paper-based methods, and they greatly increase a trial's chance of success. eCOA technology can be used for collecting patient reported outcomes measures (PROMs), observer reported outcomes, clinician or rater reported outcomes, and performance outcomes. The same technology can also incorporate electronic solutions for collecting and managing informed consent in clinical trials and provide enhanced, ongoing patient engagement solutions.

Capturing clinical outcomes assessments in CNS studies can be difficult due to two main problems:

1. The unique requirement to elicit key information from patients whose capacity to perceive, judge, and report are often impacted by the condition under study
2. The reliance on an error-prone process in which site staff must cope with the complex directions and criteria embedded in the dense text of multiple paper scales, consistently processing the patient's responses to make a rating, record it correctly, and eventually transcribe it into the database

eCOA utilises technology built into smartphones, tablets, personal computers, and mobile apps to create

Sources of clinical trial unreliability	Representative examples
Clinical trial subject samples	Heterogeneity
	Nonrepresentative sampling
	Sensitivity and specificity of diagnostic criteria
	Sponsors and investigators relax criteria
Clinical trial design and implementation	Inaccuracies in observations
	Imprecision in observations
	Excessively large numbers of subjects in sight required to provide subjects
	Inadequate training and monitoring and research sites
	Lack of protocols control and systematised practice
Protocol deviations	Diagnostic criteria disregarded
	Clinical ratings without protocols to control administration of scales
	Clinical raters not extensively experienced with the disorder under study
Inadequate clinical instruments and rater skills	No prior use of clinically rated outcome measures by the investigator
	Inaccurate ratings/imprecise rating
	Careless mistakes
Placebo group improvements	Possible bias by raters
	Non-specific responses of trial subjects to attention and other aspects of participation
Undocumented hazards	Falsified data
	Protocol violations

Table 1: Not widely acknowledged potential compromises to CNS drug development

a simpler and more user-friendly experience for patients, clinicians, and their caregivers. eCOA guides the process and allows outcomes to be recorded directly into the clinical trial data system during a visit. This improves fidelity to the protocol as well as assuring the capture, transparency, integrity, and quality of data. If deployed effectively, eCOA ultimately helps speed up the path to approval.

Using a hypothetical protocol, it is possible to illustrate the potential benefits of eCOA in CNS clinical research. In an imaginary global trial, the clinical team proposes to study the efficacy and safety of the company's novel compound Beta-Mar-X for Parkinson's disease.

Parkinson's disease is one of the most common progressive neurodegenerative disorders, where patients experience motor dysfunction and non-motor symptoms, such as sensory loss, depression, sleep disruption, dysautonomia, psychosis, and dementia. It is associated with progressive disabilities that, at present, can be slowed, but not halted, by treatment. Most patients do respond to initial treatment with L-DOPA/Carbadopa, but the response diminishes as the disease progresses, and there is significant room for improvement.

The symptoms of Parkinson's disease are distressing, not just for patients, but for their caregivers as well. There are vast costs associated with this disorder, estimated globally to exceed $50 billion a year.

In this hypothetical protocol, Beta-Mar-X is a novel small molecule that is well absorbed orally and demonstrates neuroprotective effects *in vitro*. Beta-Mar-X binds to adenosine receptors, lessens aggregation of alpha-synuclein, and inhibits progression of neuronal atrophy in animal models. The Phase II study is a double-blind, placebo-controlled trial with aggressive timelines, designed to evaluate Beta-Mar-X's potential to ameliorate both the motor and the non-motor symptoms, as well as slow the progression of the disease. An overview of the study can be seen in **Table 2 (page 54)**.

The study is looking to enrol 600 patients, randomising them to six months of treatment in one of three treatment arms, two doses of Beta-Mar-X and one of placebo. The trial is open to patients who have a confirmed diagnosis, based on the typical criteria in Parkinson's disease studies. The main eligibility criteria can be seen in **Table 3 (page 55)**.

The study will commence with a screening phase for consenting patients. There will be a two-week single blind placebo lead-in, then, at baseline, those eligible will start placebo or 450 mg Beta-Mar-X. After a month, those patients on the study drug will be split into those who will continue at 450 and those who will go off to 900. Those patients will continue for six months. The outcomes will be evaluated, and they will be eligible to go into either a safety study or an open label continuation.

The primary endpoint is typical for studies like this, where a change from baseline to the six-month point on the unified Parkinson's disease rating scale is of interest, including typical general health outcomes and safety outcomes. There are also a number of secondary endpoints that are of interest. In addition to motor symptom outcomes at various times, the sponsor is interested in sleep, quality of life, depression, and discovering the full range of activities the compound may exhibit, including exploring various destinations of response or remission and positive symptoms. The sponsor is also enthusiastic about using technologies such as wearable sensors for tremor analysis, gait analysis, and the potential

Clinical study synopsis: Study PD-001	
Study number	PD-001
Title of study	A randomised, double-blind, placebo-controlled, multicentre study of Beta-Mar-X as in patients with Parkinson's disease
Study centres (country)	Approximately 70 study centres in US, Asia, and Latin America
Development phase	Two
Objective	To evaluate the efficacy, safety, and tolerability of adjunctive Beta-Mar-X treatment in patients with Parkinson's disease
Methodology	Multicentre, randomised, six-month double-blind, placebo-controlled, parallel-group study in patients with Parkinson's disease
Test product and dosage	450 mg Beta-Mar-X tablets PO BID 900 mg Beta-Mar-X tablets PO BID Matched placebo PO BID
Number of patients	Approximately 600 planned to be enrolled

Table 2: Study overview

for other smartphone assessments – such as vocal analysis.

Protocol Challenges

This protocol relies on the completion of a Parkinson's disease motor diary, so it is crucial to make sure that this is filled in accurately by the right type of patients. Another challenge also applies to the quality of the ratings and assessments performed.

Completing the motor diary requires intensive effort and is a challenging instrument to incorporate. To limit patient burden, it is normally employed for just a few consecutive days at periods throughout the study. The diary requires assessments at half-hour intervals throughout the day by indicating on/off periods when the treatment is effective in alleviating motor symptoms (on) and when it is not (off). Electronic diaries are important for ensuring data integrity as they provide time stamps to demonstrate that assessments have been recorded in a timely manner when the patient is able to accurately recall their symptoms and prevent retrospective entries outside suitable recall intervals. This measure of data integrity is important when motor symptom diaries are used to derive important study endpoints. There are a lot of scales that not all the investigators and raters may be fully confident in using, and identifying problematic ratings may need to be addressed.

When considering the example protocol, there are various challenges that spring to mind. Firstly, there are multiple study-related obligations for the patient. The primary outcome measure must be optimised while accurately assessing other key outcomes. Creating programming to enable the patient and care partner to be successful, to meet all the data collection obligations and study visits, etc., is crucial, along with simplifying the process and making it more engaging for the patients to participate. Additionally, as with any protocol, it is key to get the right patients into the study.

Protocol Solutions

What are some of the best approaches to help the study achieve its aims? For this hypothetical protocol, PROMs can be handled in a number of ways, including home-based completion. **Table 4** demonstrates some of the scales.

Other scales include those to monitor depression, suicidality, improvement, and quality of life. For Parkinson's patients, one of the most common scales is the Hauser diary, and there are some ePRO design considerations that could be considered from a usability perspective:

- Stylus use is unpopular: Finger/knuckle navigation is easier to use to select items on screen, especially when experiencing tremors
- Large, well-spaced buttons separated by white space and kept as far apart as possible to aid selection/navigation
- Simplified PIN entry keyboard
- Handheld device must be large enough to handle comfortably
- Ability to define snooze periods to prevent being disturbed by diary prompts during rest times

The design should be simple and easy to use, as it is an intensive assessment, and should allow an appropriate period of time for retrospective entry and completion, ensuring good usability is balanced with acceptable recall ability.

Other remote assessments to consider include mobile sensors and wearable devices, something that may be suitable in a Parkinson's trial to assess tremor and gait. Certain challenges for activity monitoring in Parkinson's patients include measurement challenges due to shortened stride length, shuffling gait, increased variability of stride, reduced walking speed, and freezing of gait. These are important factors to consider when selecting accelerometers for such studies as additional evidence may be needed to ensure algorithms provide valid measurements in this population. Additionally, a wrist-worn device may be appropriate to measure sleep in a Parkinson's study.

Clinical study synopsis: Study PD-001	
Main criteria for inclusion	Male and female outpatients who are 18 to 75 years of age
	Meet diagnostic criteria for Parkinson's disease (based on confirmation from the UK Brain Bank criteria at least six months before study entry)
	Disease stage corresponding to II-IV according to classification of modified Hoehn and Yahr (while 'on')
	Have CGI-S score of ≥ four at screening and baseline
	Stable regimen including L-DOPA at adequate dose and duration (> four weeks)
	Experiences > 2.5 hours of off time/day on diary
	Mini mental state examination > 24 at screening visit
Duration of treatment	Two week screening and single-blind placebo lead in
	Followed by a six-month double-blind treatment period
	Followed by a one-month safety follow-up period (for patients who do not roll over into the open label extension study)

Table 3: Main criteria for inclusion

Patient Engagement

In the outlined protocol, the sponsor is expecting a lot from the site and subjects. If patients are not engaged, drop outs can become a problem and data quality suffers. Patient engagement is like the glue that serves to keep patients and their partners active and participating in clinical trials. Patient engagement elements that could be utilised in a study are intended to enable, inform, and encourage patients in multiple ways, and to tie them to critical metrics such as protocol adherence, medication compliance, and, importantly, study retention. Crucially, patient engagement should begin at recruitment.

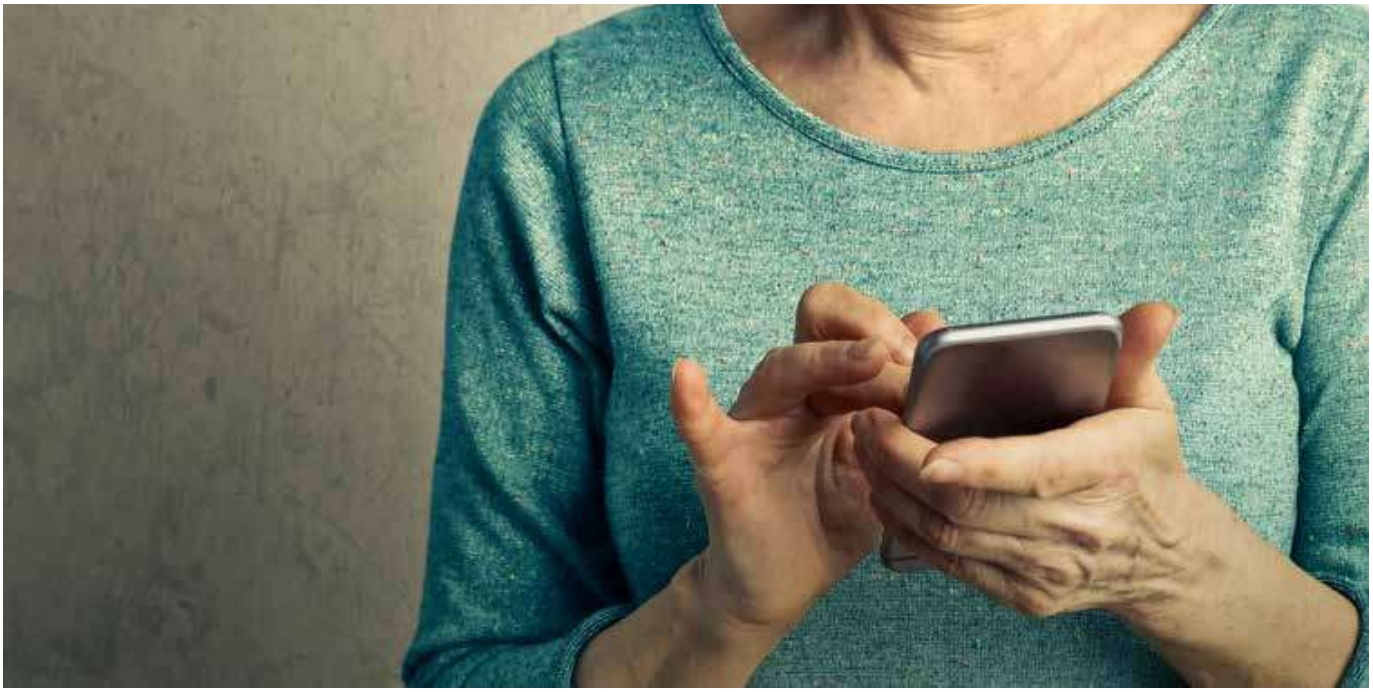
Thinking through a patient's experience from screening all the way through to study completion is critically important for the overall study success, and certainly in the context of Parkinson's. In the outlined study, the expectations placed on the patients are fairly overwhelming; they already have the burden of their daily regimen to contend with. Therefore, engagement needs to be as straightforward as possible. It will be crucial to equip the patients with the information and instruction necessary to be successful in gathering data for this protocol.

Mobile engagement apps and SMS engagement are intended to support patients in getting to visits on time, taking their medication, and completing their diaries. Engagement should also include encouragement and possibly recognition. Those are important elements to acknowledge the patient's contribution and keep them feeling as though they are a part of something beyond their own daily disease regimen.

Engagement app elements include protocol obligations, a library of instructions, eDiaries, and retention programming. Content should help the patient understand their progress through the trial, what they need to do, associated timeframes, instructions, information, and study-related materials.

Name	Acronym	Description	Scale type(s)	Recall period
Parkinson's disease questionnaire	PDQ-39	Mobility, activities of daily living, emotional wellbeing, stigma, social support, cognition, communication, and bodily discomfort – 39 items	LIK-5	One month
The self-assessment Parkinson's disease disability scale	SPDDS	Activities of daily living for patients at home – 24 items	VRS-5	
The Parkinson's fatigue scale	PFS-16	Physical aspects of fatigue and their impact on patient functioning – 16 items	LIK-5	Two weeks
Parkinson's disease sleep scale	PDSS	Nocturnal sleep and sleep disturbance – 15 items	NRS-11	Seven days
Hauser on/off diary		On/off symptoms	SSL-5	At this moment

Table 4: PROMs – Parkinson's disease



The use of video is also important; for example, instructions on how to use the wearable device and collect data using the sensor in the patient's phone. If you can enable a patient to be more on track, to be successful, to understand what they need to do to participate in a given trial, then these can effectively deliver an improved return on investment and better data in the trial overall.

What does the Future Hold?

eCOA solutions are already being used successfully in many global studies examining CNS conditions. Roche is pioneering a smartphone-based monitoring system for patients with Parkinson's (2). This will complement the conventional physician-led assessments, which are limited by availability of expert centres, are resource intensive, and represent only a snapshot in time. Additionally, a recent *Nature* review article demonstrated that the touchscreen of smartphones can help evaluate motor function remotely by monitoring finger tapping and reaction times (3). With mobile technology everywhere, smartphone-based monitoring of patients will undoubtedly hold great promise for use in future CNS trials.

With today's eCOA and cloud computing allowing an almost immediate availability of data, there has been a paradigm shift in data analytics. Analyses can be conducted unobtrusively in the background in almost real-time, facilitating immediate intervention determined by identified issues. Data analytics can identify sites and raters that are statistical outliers from the study population as a whole and, by identifying such patients/raters at risk, it becomes possible to prevent errors before they occur.

Similarly, a lack of familiarity with instruments can be determined and rapidly addressed with data analytics. It can identify potentially fraudulent sites, and issues can be remediated before randomising any patients into the study. Symptom fluctuation can also pose problems, especially in Parkinson's trials, leading to inconsistencies and variabilities. Analytics can help identify anomalous patterns of change in patients, which could be due to inconsistent timings of assessments, such as only conducted when a rater is available. If, despite remedial action, the site continues to provide poor quality data, the sponsor will be aware and have the option of discontinuing with that particular site due to quality of data. It is also worth noting that data analytics can help identify data fabrication, in addition to assessing ePRO data for accuracy.

With novel approaches and technology delivering patient engagement-focused eCOA, patients will enjoy and demand a much better experience within the study, resulting in the ultimate goal of capturing the most reliable data, achieving higher retention rates, and improving protocol compliance. With the benefit of a single mobile touchpoint that integrates study commitments into their daily life, including reminders about personalised medications, appointments, and other study-specific details, such extras increase engagement among patients. Bringing these together is an important way to guide patients through their study experiences – giving them the information they need all in one place. With more virtual studies and less 'hand holding' from sites for patients, the reliance on technology will become even more important.

It's owing to its proven successes that eCOA has emerged as the preferred method of capturing patient data

within clinical trials across a range of therapeutic areas, including CNS. Combined with ongoing and effective patient engagement, rater training, and endpoint reliability provided by an independent team of experienced CNS clinicians, eCOA becomes more than simply a technology solution.

As such, it will continue to improve the patient experience while ensuring sponsors and CROs capture reliable and trustworthy data, transforming clinical research and the development of new and essential life-changing therapies.

References

1. *Becker RE* et al*, Neuropsychiatric clinical trials: Should they accommodate real-world practices or set standards for clinical practices?* J Clin Psychopharmacol *29: pp56-64, 2009*
2. *Visit: s3-service-broker-live-19ea8b98-4d41-4cb4-be4c-d68f4963b7dd.s3.amazonaws.com/uploads/cked itor/attachments/8470/roche.pdf*
3. *Visit: www.nature.com/nature/outlook/parkinsons-disease/pdf/roche.pdf*

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Dr Alan Kott is based in **Signant Health's** Prague office and, until recently, was Senior Clinical Manager for Europe. Having led the development of the data analytics programme for Signant Health, he has overseen the design and reporting of data analytics in multiple large schizophrenia studies. For the past seven years, he has also provided training to investigators as an Expert Trainer. Alan has been responsible for the design and implementation of multiple in-study data quality programmes and served as a Product Business Owner for rater reliability statistical measures application.

Dr Gary Sachs is an internationally recognised expert clinical trialist with extensive experience in rater training and clinical trial methodologies for mood and anxiety disorder research. He has been instrumental in developing technology-based solutions for randomised controlled trials that identify correlates of high placebo response, improve signal detection, and reduce the risk of failed trials. As Principal Investigator of the National Institute of Mental Health sponsored Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Gary led the largest treatment study ever conducted for bipolar disorder.