CortiCare
The New Wave of EEG Services

The Utility of EEG in Clinical Trials
White Paper

EEG plays an important role in inclusion/exclusion criteria for safety and efficacy evaluations and as biomarkers in clinical trials. Given the heterogeneity of understanding of the strengths and the limitations of EEG in this context, we provide a brief commentary to inform drug sponsors, contract research organizations, and academic partners on some of the questions to consider.

Pre-Clinical Screening

In drug development, fewer than 99% of compounds make it past pre-clinical testing in animals. Greater than 90% of those drop out in Phase 1, first in human trials. The entire timeline from bench to bedside takes over a decade and nearly $1billion. Central Nervous System (CNS) drugs demonstrate among the higher failure rates. Other than for multiple sclerosis, the failure rate for disease-modifying treatments in chronic neurodegenerative disorders is 100%. One impactful way of reducing time and resources from bench to bedside is subject enrichment in "first-in-human" trials. What methods can we employ to enrich our subject population in Phase 1/2 CNS drug development? There are broadly three methods. We will discuss these within the context of establishing safety and efficacy of a drug in Phase 1/2 trials, which has implications for CNS drugs but also any compound that penetrates the blood-brain barrier.

The three methods of subject enrichment include strategies to reduce variability, prognostic enrichment, and predictive enrichment. For purposes of examining these strategies, we will use the increasingly common safety EEG study that assesses the potential of a drug to produce epileptiform discharges or seizures. We can reduce the variability of a non-normal EEG outcome with clinical and EEG criteria used to exclude those who begin with clinical or EEG abnormalities.

A more detailed neurological history alone would better equip Sponsors to screen for exclusion in baseline brain dysfunction. This does not necessarily require an expert to deploy or interpret. It would be relevant to know whether the subject had a history of seizures with fever as a child, brain surgery, brain injury, concussion with loss of consciousness, brain infection, or stroke. Questions should specifically interrogate the following for greater sensitivity for undiagnosed seizures: episodic loss of time, episodic speech difficulty, repetitive behaviors, loss of consciousness, and/or motoric paroxysms resulting in social embarrassment or injury. Public understanding of seizures is often about motoric seizures only, which may miss subjects who exhibit non-motoric symptoms.

CNS diagnostic testing can help identify clinically silent abnormalities. The most readily available neurodiagnostic, given cost and portability, is EEG. EEG allows us to detect both structural and functional abnormalities. It is the diagnostic modality of choice for identifying epileptiform changes, which expose a propensity for seizures. This can be relevant in drugs with specific CNS targets (or in characterizing off-target effects of any CNS penetrating drugs) that have demonstrated epileptogenic potential in preclinical studies or exhibit theoretical risk. For this reason, drug sponsors decide and are increasingly asked by the FDA to incorporate safety EEGs in Phase 1 studies for vulnerable compounds.

Value of QEEG

Qualitative EEG can be employed to identify abnormalities of brain structure and function for inclusion/exclusion of patients for clinical trials. Quantitative EEG (QEEG) studies can be used to group analyses of specified populations. This would allow for subject enrichment and a more nuanced understanding of which individuals do and

do not exhibit a response to the compound under study. QEEG can be used for prognostic and predictive enrichment. To explore this utility of QEEG, we will discuss its role in evaluating an anti-seizure medication, where the purpose would be to quantify epileptiform discharges and seizures before and after dosing. We can enrich for patients who have many epileptiform discharges at baseline, therefore with a greater likelihood of having a seizure or worsening of seizure frequency. This would increase the absolute effect difference between groups. We can also enrich for patients more likely to respond to the drug treatment than other patients with the condition being treated to enhance the absolute and relative effect size, which would enable the use of smaller study populations. QEEG biomarkers related to the study drug mechanism could help inform the selection of patients for predictive enrichment.

Need for Qualified, Standardized Interpretation

Part of the challenge of incorporating EEG into clinical trials is a consistent understanding of what comprises 'abnormal' and intra-reader and inter-rater agreement. There are numerous 'normal variants' that are commonly overread as epileptiform abnormalities. To further compound the issue, the inter-reader reliability (in a heterogeneous sampling of inpatient and outpatient studies or in a specific diagnosis) in calling EEG reactivity, periodic discharges, and electrographic seizures, is poor. The inconsistency that may result from the inherently subjective nature of EEGs can be mitigated by requiring multiple fellowship-trained clinical neurophysiologists to converge on the interpretation of studies or with a clear process of how to navigate discordant reads with adjudication.

Once subjects have been included in a Phase 1 study following an EEG screen for normality (or at least for the absence of epileptiform abnormalities) in 'healthy normal volunteers,' safety EEGs while on drug may help to confirm that a compound does not exhibit epileptogenic properties at specific doses. A compound is considered epileptogenic if it produces what we call interictal epileptiform discharges or ictal activity (seizures). The diagnosis of seizures is electrographic, clinical, and electroclinical. They can demonstrate rhythmicity with stereotyped evolution electrographically, stereotyped behaviors clinically, and also the combination of rhythmic, evolving, and clinically apparent discharges. Video-EEG allows us to record and correlate electrographic and clinical data to determine whether a drug is epileptogenic.

In now hundreds of "healthy normal volunteers," we have observed non-epileptiform abnormalities that were of unclear clinical significance or were subclinical (i.e. abundant excess fast activity, occasional focal slowing) in up to 20% of subjects screened. Underlying abnormalities in this population suggest a possible reason for attrition in trials and highlight the importance of screening and exclusion and/or analyses based on EEG criteria.

While the FDA has provided guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs since 2005, they provide no guidance on brain monitoring in CNS drug development.

CortiCare's Clinical Trials Services

CortiCare's expertise and services are actively informing the new frontier of functional brain assessments in CNS drug development. In addition to safety EEGs, we work with Sponsors and CROs on controlled QEEG data collection to assess for drug efficacy.

Versatility of CortiCare's EEG services

More trials are moving to a decentralized design. We have the operational versatility at CortiCare to offer in-clinic, CRO site-based, and in-home EEG acquisition, with or without real-time or intermittent monitoring for data integrity and/or for purposes of subject safety and escalation for acute EEG findings. We leverage an on-call network of EEG technologists and board-certified clinical neurophysiologists to monitor and interpret studies remotely.

CortiCare's qualitative EEG services include but are not limited to consultation and execution on the following:

Planning and Design:

- Navigation of cost and operational constraints
- Protocol consultation on EEG recording and staff requirements

Execution:

- Data collection, analyses, visualization, and reporting
- Cloud storage and data accessibility
- Data management, transfer, and case report form integration

CortiCare's QEEG services include but are not limited to consultation and execution on the following:

Planning and Design:

- QEEG for subject enrichment, pharmacokinetic, pharmacodynamic and other exposure-response analyses, and exploratory endpoints
- EEG statistical analysis plan generation

Execution:

- Data collection, analyses, visualization, and reporting
- Cloud storage and data accessibility
- Data management, transfer, and case report form integration

With an emerging literature on QEEG and excitement about the promise of sophisticated computational methods of QEEG in clinical trials, we also help sponsors navigate the chasm between abundant data and scarce correlations with clinically relevant measures and outcomes.

References

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