Lex Parsimoniae Applied to CNS Trial Design

Introduction
Ockham’s Razor was developed by William of Ockham and codifies a preference for simplicity in problem solving. In the presence of competing hypotheses, with all things being equal, preference should be given to the simplest alternative. Weight is to be given to theories with the fewest assumptions. Is it time that the industry has a discussion of how Ockham’s Razor can be applied to CNS clinical design? Rising costs are a major limiting factor in CNS drug development. Compared to other therapeutic areas, CNS drug candidates have a lower probability of success (8.2 per cent vs 15 per cent) and a longer development path (by two years). Even in Phase III, the probability for success is significantly lower than with other therapeutic areas. Some of the largest pharmaceutical companies in the world do not consider CNS a core therapeutic area for research and development spend.

Trial Complexity
There are many factors that have led to this current state of increasingly complex trials. Nevertheless, there is now data to support a re-examination of the complexity of the clinical trials in CNS indications. Getz has reviewed some of the recent data that inform the impact of protocol complexity on trial success. Protocol development, formerly the remit of clinical scientists, is now influenced by a large number of stakeholders. These additional stakeholders have been added over time and generally in response to perceived risks. Risk mitigation likely applies an upward pressure on the number of protocol procedures and protocol amendments. Sometimes the number of procedures increases to facilitate potential secondary endpoints that can be used to get the most out of the results and possibly inform future study designs. The costs of adding any one procedure or visit are usually small. However, in the aggregate they can add substantially to cost. The data around this are compelling. In the period ending in 2012, the number of procedures per Phase III protocol was 170, up from 106 in 2002. Similarly, a study in 2012 had on average 11 visits and had an average duration of 230 days compared to nine visits and 187 days ten years earlier. The industry is building in substantial extra costs by adding more and more procedures and visits.

Importantly, this added protocol complexity may not be adding value in terms of increasing probability of study success. Rutherford et al. have demonstrated that in geriatric depression studies, each added study visit increased the average placebo response by 2.5 per cent without a corresponding increase in medication response. Similarly, in a meta-analysis of 111 studies of antidepressant medications, the authors found that while increasing the number of visits did not improve treatment
response, it did increase study dropouts\(^5\). These data are meta-analyses and not conclusive, but they do suggest that added procedures and added visits – all of which drive higher costs – are not improving the probability of study success and may be doing the opposite.

**Site Perspective on Protocol Complexity**

It is also important to consider the effect of trial complexity on investigator adoption of CNS trials. Lamberti\(^6\) performed a global survey of investigators to get a better handle on the factors that affect a site’s decision to take on a study. The survey was conducted across therapeutic areas and CNS was the primary focus for 13.3 per cent of the sites who responded to the survey. Approximately 40 per cent of the investigators were from North America, but all regions were strongly represented. Eighty-eight per cent of respondents indicated that Availability of Patients to Meet Inclusion/Exclusion Criteria had a significant influence over their decision to participate in a clinical trial. It is perhaps not a surprising result since that is a category that can incorporate many factors, but is driven by the overall complexity of the trial, specifically the number of inclusion/exclusion criteria. Other notable factors in this survey were that 88.5 per cent of investigators reported that Protocol Complexity was a significant influence or had some influence over their decision to participate in a trial. Similarly, 81.2 per cent of investigators listed Patient Visit Schedule as a significant influence or had some influence over their decision to participate in a trial. Investigators were also asked questions about the factors that affected their ability to conduct protocols successfully. 24.3 per cent indicated that the administrative burden of sponsor processes, and 23.9 per cent reported that protocol amendments, were significant factors impacting their ability to be successful with a protocol. These observations represent useful and systematic feedback from investigators and give insights into the evaluation process that investigators use in selecting trials in a competitive environment.

**Conclusions:**

As sponsors and contract research organisations (CROs) plan and design studies and programmes, it is increasingly important to assess the number of procedures and visits. As programmes are executed, these data call for added cost as well as time and training for investigators and their staff. Data suggest that efforts here may be rewarded with not only cost savings and greater investigator engagement, but also perhaps studies more likely to detect drug effects.

**References**

1. Kaitin KI, Milne CP. A Dearth OF New Meds: Drugs to treat neuropsychiatric disorders has become too risky for Big Pharma. Scientific American. 2011; 305:16.

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