



Smarter adaptive platform clinical trials in neurology

Something interesting is happening in the world of clinical trials that is likely to have a profound impact on how we evaluate new therapies for brain disorders. It is the advent of novel designs that often integrate adaptive clinical trial methodology and master protocols within platform trials to allow multiple treatment arms to run concurrently. While standard trial designs are ballistic creatures (once launched, they follow a predefined trajectory), adaptive trials allow for interim analyses that permit a range of decisions to be made on the subsequent course of the trial.¹ Master protocols within platform trials provide unified study protocols that cover several sub-studies,² with different interventions often being compared to a single control group, thereby reducing numbers of patients who receive only placebo or standard treatment.

Compared to some specialties, neurology has, at least until now, lagged behind in developing innovative trial methodologies that can answer questions rapidly. We have instead been wedded to conventional, large scale randomized controlled trials that take many years to complete. Most of them conclude that a drug that was promising in an animal model actually does not seem to have a significant impact on the disease in humans. Sadly, neurology is littered with an array of such 'failed' and costly trials.

Our patients—and Pharma—have understandably become frustrated at the lack of progress in some areas. Although we can point to a few great successes, for example in multiple sclerosis and epilepsy, the field that has been most challenging to crack has been that of neurodegenerative diseases. Here, many fingers have been burned and much money spent to very little avail. Some important considerations have become apparent over the course of many disappointments.

First, traditional trial designs are unwieldy, cumbersome and costly. One solution might be to deploy relatively small-scale human trials that provide investigators—and Pharma—confidence to decide whether to take a compound into expensive, larger scale randomized trials. However, for such Go/NoGo trials to succeed, they are, almost by definition, going to have to be unconventional. One possibility is to use novel outcome measures: not ones currently approved by regulatory agencies, but nevertheless having the potential to be more sensitive to changes in disease state. They might be fluid or tissue biomarkers; genomic, proteomic or metabolomic profile; brain imaging (PET or MRI) or neurophysiological signals; cognitive measures; or even indices of gait. But the key point is that, whatever the outcome measure used, it has to have far more dynamic range and sensitivity than conventional ones. In summary, the metrics simply have to be better.

Second, one of the big issues that has likely had a huge impact on the outcome of many clinical trials is patient heterogeneity. This confounding factor has probably been appreciated best in oncology where it has become clear that the molecular and genetic signature of tumours might be crucial for the effects of drugs that precisely target a particular molecular pathway. If a new drug that specifically attacks one cause of a particular cancer is used in an unselected group of patients, the likelihood of obtaining a positive outcome is very low. Just increasing the sample size is unlikely to yield any better dividend. Precision medicine can work only if patient selection is also precise.³ Better phenotyping of recruits to trials is going to be essential. Ultimately, what is needed is a therapy that is specific for an individual. If possible, it would also be important to test in that individual whether the therapy provides an effective outcome. Ideally this might be embedded within an N-of-1 design, as successfully performed in some recent trials, discussed previously in these pages.⁴


Third, a key aspect of traditional trial designs is that they often take many years to complete. Hence the need for smarter adaptive trials which allow interim analyses and thereby pre-planned changes in trial trajectories. These include a confident early termination of a compound on the basis of futility or lack of a discernible effect. But there are many other possibilities: from refining the sample size, through altering the allocation ratio of participants in each arm of a trial, to identifying patients most likely to benefit from a particular intervention or suffer from unexpected side effects.¹

Finally, the use of a master protocol within a platform trial design can facilitate concurrent testing—and elimination—of several potentially promising therapies. Oncology has reaped some important rewards with some ground-breaking studies, including the I-SPY 2 platform trial for breast cancer, which has evaluated 16 agents since 2010, with three gaining accelerated approval.⁵ This trial uses Bayesian adaptive randomization at recruitment, with enrolment in a particular arm being stopped when the Bayesian predictive probability of success reaches a prespecified outcome threshold. New treatments are added as agents being tested are either 'graduated' to the next phase or eliminated from further assessment. Interestingly, the primary end point in I-SPY 2 is considered a surrogate as it is defined as pathological complete response using serial MRI. This means end points can be assessed within 24 weeks, not years. More recently, the RECOVERY trial platform in the UK has successfully tested several different interventions concurrently for SARS-CoV-2, rapidly reporting success with some agents^{6,7} as well as the futility of others.⁸ In this trial, outcomes were evaluated even more rapidly—within 28

days—because many outcomes, such as need for ventilation, death or discharge actually occurred within a relatively short period. The issue of time to detect meaningful change is a crucial one if such trial frameworks are to be adopted into brain disorders such as neurodegenerative diseases.

One condition where disease progression can be relatively rapid is ALS and it is especially pleasing to see the remarkable developments that are occurring, at pace, in this field. The HEALEY ALS trial platform in the USA is pioneering the testing of several compounds, as well as aiming to identify novel biomarkers and trial end points.⁹ It brings an adaptive design with a master protocol to the platform, with enrolment already complete for three agents. In more slowly progressive conditions, such as Alzheimer's disease, platform trials have also been initiated, firstly in autosomal dominant Alzheimer's disease as in the DIAN-TU platform, but the challenges of running such trials have become very apparent, at least with established cognitive outcome measures.¹⁰

What might be important for future development in Alzheimer's disease is to build on all the lessons learned to date. First, the metrics have to be better. We need to consider the use of newer measures such as more sensitive indices of memory developed in cognitive neuroscience labs. Second, screening needs to use a range of tools—fluid biomarkers, genomic, proteomic or metabolomic profiling, imaging and digital cognitive measures—to phenotype individuals better and thereby reduce the heterogeneity of trial-ready cohorts. And, given the likely levels of heterogeneity (multiple pathologies often exist in patients given a clinical diagnosis of Alzheimer's disease), screening needs to be performed at scale using national platforms such as NHS Digital in the UK. Third, trials need to be adaptive to be efficient and economical. Finally, smarter trials are also likely to require a platform design, testing several interventions concurrently and developing new biomarkers or surrogates in the process. The road ahead is definitely a challenging one but the potential is huge.

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