CLINICAL INVESTIGATION

The adaptive trial opportunity for biotechs and smaller pharmaceutical companies

"Using an adaptive trial design in combination with modeling allows the amount and type of data collected to be optimized."

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Tom Parke
Tessella Ltd, 26 The Quadrant, Abingdon Science Park, Abingdon, Oxfordshire, OX14 5EE
tom.parke@tessella.com

Using an adaptive design [1] for a drug's Phase II trial allows a drug developer to get better value from their asset and have a cost profile more attractive to their investors [2]. Large pharmaceuticals are slowly coming round to realizing this [3], but conservative decision making, the need to align many departments and the cost of retooling clinical operations are still obstacles to adoption [4]. Biotechs and small pharmaceuticals should be able to adopt adaptive designs much more quickly because they have smaller, better interconnected decision groups and the freedom to select the most appropriate outsourcing partners to implement the trial.

Not only *can* smaller companies be quicker to adopt adaptive designs, they *should*. Why? Because, as I hope to show below, adaptive designs have much to offer to Phase II trials and for small companies looking to license a compound on the basis of the Phase II trial results, the execution of Phase II is critical. A larger company can to an extent 'leave risk' to Phase III in order to get there quicker or more cheaply, but when in-licensing a compound large pharma will strongly prefer opportunities where risk of late stage or market failure have been minimized.

One way of looking at drug development is that it is all about reducing uncertainty. Not simply 'is it effective and safe?' but how best to use it (dose, treatment regime) and who best to treat (population, disease) [5]. Failure to address these uncertainties in early development increases the risks of: failure in Phase III, low valuation of the treatment by payers, reductions in dosing (and hence payment) after registration and even forced withdrawal from the market.

A company looking to out-license a treatment after Phase II will have more suitors and command a higher price, the better it has de-risked the asset by reducing these uncertainties. For instance, having a good estimate of the dose response makes it more likely that the dose selected for Phase III maximizes the treatment effect without unnecessary risk of safety or tolerability problems. Identifying a significant subpopulation where the treatment effect is particularly marked, allows a smaller, safer Phase III to be run in that subpopulation, getting to market quicker and with a strong cost justification for payers. Larger Phase III trials in the whole population or a larger subpopulation can be run in parallel or subsequently.

But Phase II requires time and money from investors to back an as yet unproven asset. How can these uncertainties be addressed without costing more, taking longer and being less attractive to investors? The answer is a combination of modeling in the trial analysis and adaptation in the trial design [6].

The power of modeling

Analyzing data using a model usually increases interpretability, parsimony and the validity of predicting results beyond the range of the data [7]. Such models are typically based on the biological model of the drug effect or on the structure of the data, thus the estimated parameters of the model have natural interpretations (such as the ED50, the proportion of patients who are 'responders,' etc.). Analysis using models has

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greater power by using fewer parameters or allowing data to be combined. For instance, using a dose-response model typically gives better estimates of the dose response than studying doses independently and gives better estimates when more doses are studied, whereas pairwise comparisons require disproportionately larger trials if more doses are studied. An example of data combination would be the use of a Bayesian hierarchical model to borrow information between patient subgroups – dynamically pooling the data in the subgroups that appear to be responders, in a flexible way that reduces the borrowing the more the results diverge.

Using an adaptive trial design in combination with modeling allows the amount and type of data collected to be optimized. The trial can be optimized at two levels – the amount of investment in the trial and where that investment is spent within the trial.

How adaptive trials deliver value

The most fundamental type of adaptation in a trial is whether to stop it or not, allowing the overall size of the trial (and hence its time and cost) to be adjusted. This type of adaptation is available in many forms – group sequential designs and sample size reassessments for confirmatory trials, and as early stopping rules within Bayesian adaptive designs. For small biotech and pharmaceutical companies, the use of early stopping rules allows the investment in their Phase II trial to be flexible. Rather than a fixed sum, investors can agree their maximum investment in the trial with preagreed stage payments at interims; payable as long as the trial has some probability of eventual success (i.e., does not meet the early futility criteria). Investors may value the flexibility of having certain interims where they can cap their further investment based on external factors – in particular any perceived changes in the future market for the treatment. The trial design may also include the option of stopping early if the data are particularly favorable, as long as there is sufficient data to attract a licensee. This provides investors with a very attractive possibility of quicker and cheaper success, if the data allow, without having to depend on it.

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The second level of optimization is considering how the investment is spent within the trial. There are many ways to do this – for example, adaptive designs typically try to reduce the testing of doses or subjects where the interim data indicate they are unlikely to form part of our plans for a future Phase III trial. Thus we might dial back the proportion of subjects allocated to a low dose that has results that are no different from the control, or to a high dose when there is a substantial treatment effect on a lower dose. Similarly, we might stop recruitment into a subgroup where the treatment effect is poor, or in an adaptive biomarker study stop recruiting subjects with a biomarker score well below the estimate of the optimal cutoff value for the biomarker for identifying responders.

Both early stopping and adjustment of allocation during a trial are not done in *ad hoc* ways, but using predefined rules. That these rules are prudent and aligned with the sponsor's goals is ensured by building models of the trial and running simulations, a practice that has significant benefits over and above being able to optimize the trial design.

A key feature of these designs is that they include multiple interims rather than just one, and decision rules that take the amount of data available at the interim into account. Including multiple interims means the trials use an automated analysis at the interims, enabling them to take less than a day in total. Running one or two very early interims before any adaptation will be recommended allows the systems and processes to be exercised in the production environment. Expert checks and backup rules are put in place so that in the event of any problem the worst that can happen is that the trial runs as though it were a fixed trial.

Taking the plunge

Sponsors considering an adaptive design for Phase II will often need a little courage to cope with a sense of 'unease with the unfamiliar.' It is likely that for some of the groups that will work on the trial that this will be their first adaptive trial (though this is slowly becoming less common). One of the developing ways to provide concrete justification for the use of the adaptive trial is to simulate not just the Phase II trial but the subsequent development process as well and assess the likely probability of success, time to registration and expected Net Present Value of the alternative designs for Phase II [8,9]. These assessments can reveal whether there are advantages in the use of adaptive design in a compelling and quantified way.

Running these trials requires clinical research organizations that can collect data swiftly and reliably and make it available for frequent interim analysis, a preprogrammed adaptive analysis program that accepts the data and calculates the required adaptation, and a screening and randomization system that can be easily and reliably updated to implement the adaptation [10–12]. Together with trial designers Berry Consultants and many different CROs, we have helped run many of these types of trials over the past 10 years and we know that, with careful planning and preparation, they run successfully and

smoothly. We have never seen a sponsor that regretted an adaptation, though some, with hindsight, have regretted that they had not adapted sooner.

Financial & competing interests disclosure

T Parke works for a company that, among the many services it provides science based industries, supports Pharmaceutical and Biotech companies execute adaptive trials. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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