

# Smart Designs

## Tom Parke at Tessella plc highlights the advantage of designing trials that use techniques such as modelling and adaptation

Successfully developing new drug therapies continues to get more difficult, partly because the industry is a victim of its own success. The 'easier' therapeutic needs having been, to varying degrees, met, the industry has to target the more difficult diseases or improve on the treatments it has already created. It is a victim of its failures too, which have led to regulators demanding increased burdens of proof that new treatments are safe and efficacious.

Drug discovery and pre-clinical departments are tackling this difficulty on a number of fronts: the development of drugs for use specifically in combination with other compounds, the targeting of drugs to particular patient sub-populations or disease sub-types, and the development of disease models. There is considerable excitement and activity around the related topics of personalised medicine, translational medicine and biomarkers.

The emerging challenge is to bridge the divide between R&D and development, and a corresponding drive to innovate drug development also seems to be lacking. Drug development is, of course, a much more conservative, risk-averse undertaking. Whereas discovery comprises many small projects, development includes a few much larger projects. Development has to work under the conflicting pressures of regulatory scrutiny and patent expiry time pressure. Avoiding patient harm, maintaining the validity of the data, avoiding unnecessary unblinding and meeting management deadlines can leave little time or appetite for innovation.

However, it seems that many of the innovations in discovery and preclinical link up nicely with the idea of smarter trial designs. Some make adaptive trials possible

in circumstances where they would otherwise be impracticable, and others require simulation and modelling of clinical designs in order to realise their potential fully.

### DRUG COMBINATIONS

In many areas, particularly oncology, new treatments have to be used in combination with existing ones, and the efficacy and the toxicity of the combined treatments can be hard to predict. Testing combinations of different strengths of two drugs is likely to give rise to more treatment arms to test than conventional trial designs can cope with economically.

Conventional designs have a problem with 'multiplicity': they not only require more subjects because they need to allocate them to the additional treatment arms, but the higher the number of treatment arms being tested, the greater the chances of one randomly doing well. The only solution to this, in a conventional design, is to recruit more subjects on every arm, to reduce the chances of random fluctuation. New trial designs, however, allow us to test more treatment arms without increasing the overall number of subjects required. They achieve this in two ways. The first is through adapting the randomisation as the trial runs. Over time, fewer subjects are allocated to the arms that are doing poorly and more on the arms that look the best candidates for subsequent development. The second is by analysing the trial data using a statistical model, resulting in a smoother estimate of the response across the treatment arms than if they are considered in isolation as in a conventional pairwise comparison. This smoothing 'irons out' the random fluctuations in the observed response, reducing the risks introduced by multiplicity. In effect, we are exploiting an assumption that responses on related treatment arms will be similar to each

other. For example, if the responses on the 200mg, 400mg and 600mg doses are only modest, we would be suspicious of a particularly good response from subjects on the 300mg dose.

Dealing with multiplicity in dose combination trials is more complex than dealing simply with more doses of the same drug, but the problem is not so complex that it should not be attempted; without overcoming it, developing dose combinations therapies will be very expensive, or will have to rely on a lot of luck.

### PERSONALISED MEDICINE

Personalised medicine looks at differences in response between different patient subgroups, often based on differences in genetic markers in the subjects or in the disease. Here, there is a different type of multiplicity problem, but with similar consequences (more subjects are required in conventional trials, for example). Adaptive trials can help here too, by dropping subgroups that are not responding well while the trial is running, or restricting recruitment to the one subgroup where it is working best. However, using smoothing is likely to be less appropriate in this case. A particularly exciting approach to developing personalised medicines is the ISPY 2 trial (1).

### BIOMARKERS

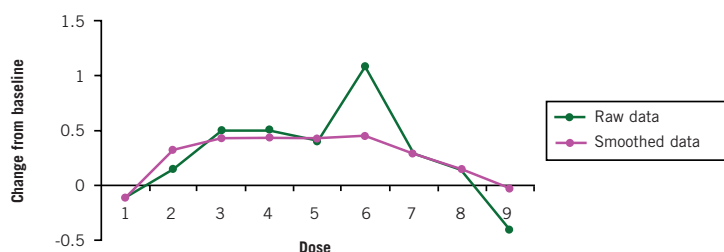
A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (2). They are being developed for many roles in drug development. The taxonomy of biomarker types still seems to be a work in progress, but the following currently appear to be the main areas of interest: markers of disease susceptibility, disease diagnosis, predictive of response,

**Figure 1:** A simulated clinical trial, data simulated from the 'null case', showing how smoothing reduces the risk of a false positive claim, by reducing the estimate where there is a random 'spike' in the data

Data simulated from the 'null case' shows how smoothing reduces the risk of a false positive claim by reducing the estimate where there is a random 'spike' in the data.

Each subject's pain is measured on the standard 10-point pain scale, taken daily and averaged over a week. The subject's final score is the improvement in their weekly average pain score in the final week compared to the baseline week.

The 'raw data' shows the actual mean scores of improvement for the subjects on each dose/treatment arm for each group in this simulation and the 'smoothed data' shows the estimated true underlying mean for each group after fitting a smoothing curve to the data (a normal dynamic linear model was used).



disease prognosis, drug monitoring and early warning of safety issues.

These clearly have a potential application in clinical trials. A marker of susceptibility could allow us to restrict enrolment in a trial to those most likely to suffer the event (such as heart attack or stroke) that we are trying to prevent. A marker of disease diagnosis could allow us to restrict enrolment to those with the disease of the right sub-type or at the right stage for treatment, or it could be used to detect whether a treatment has delayed disease progression. Markers of disease prognosis allow us to forecast disease outcome, and can be used as an early endpoint to guide trial adaptation. Predictive markers can be used to identify patient sub-populations to monitor for different responses to treatment. Drug monitoring markers can be used for proof of concept trials, guides for trial adaptation and dosing. Markers for safety issues can be used as guides for trial adaptation.

One of the clear benefits of a number of biomarkers is that they can help us to adapt trials as they run. Examples include: dropping patient sub-populations, treating sub-populations differently, closing recruitment when the expected number of events in the trial will be sufficient, dropping treatment arms where efficacy is unlikely or safety issues are too likely, or biasing the randomisation towards treatments with the best efficacy or safety profile.

All biomarker models begin as theories and can require considerable amounts of data to

establish and calibrate them properly. However, in adaptive trials, a lack of a fully validated model need not be a barrier to employing the biomarker model as part of the design. If the design is produced carefully, it is possible to include a model for the biomarker in the analysis with no presumption of the usefulness of the biomarker. As the trial runs, the model is fitted and applied to the data as it accumulates, but in such a way that takes into account the current accuracy of the fit. To take a simple example: say we have a prognostic biomarker that we can measure early during a subject's treatment and a final endpoint measure that can be taken early enough that some subjects' endpoint data are available before recruitment is complete. We could then fit a simple linear regression model for each treatment arm to the biomarker results and the final endpoints. This model can then be used during the trial to predict final outcome results for subjects for which final endpoint data is not yet available. It is clearly important for the predicted data to be included in fitting the overall response model in a way that reflects the relative uncertainty in this data compared to measured final responses. Thus, in the same trial, we can both develop and exploit a biomarker model.

### CONCLUSION

Designing trials using modelling, simulation and possibly adaptation, allows the trial designer to answer a broader range of problems than have been tackled before and to exploit current advances in drug discovery and preclinical research. These questions can be scientific (in which patient population

does my drug work best?), commercial (when can we start the production of compounds for the next phase of development?) or operational (when can we stop recruiting subjects?). To get the most out of trials, the design should be carried out in the context of a whole programme of drug development in an indication and exploit all that is known about the drug behaviour and the disease. We have a new freedom to work out which are the most pressing questions that need to be answered, which of those can be answered for the least cost and in the least time, and to design trials that give us these answers.

### References

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2. Atkinson AJ *et al*, Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework, *Clinical Pharmacology & Therapeutics* 69(3): pp89-95

### About the author



Tom Parke has been working at Tessella plc for over 10 years. For a large part of that time he has been working on adaptive

clinical trial projects. Tom has helped to implement numerous adaptive Phase II dose finding trials that are now complete, for a range of pharmaceutical companies across a range of indications. He is currently working on his 12th adaptive dose finding trial, and consulting with a number of companies to help them define the software systems they require to move adaptive clinical trials into their mainstream activities. Before working at Tessella, Tom worked at Praxis (part of Deloitte & Touche), most notably managing projects for part of the air traffic control system at Heathrow Airport and control software for imaging systems for GE Medical Systems and Varian Oncology.

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