The Mixed Randomised Controlled Trial – A New Study Design

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#1 Background
Reimbursement authorities often require pharmaceutical companies to provide them with more than just placebo-controlled data from randomised controlled trials (RCTs). They typically seek comparable effectiveness data from a wider, real-world setting, in which the focus is on comparing the new therapy with standard of care, or currently available marketed therapies.

The current tendency is to provide post-authorisation evidence from separate, often larger and less well-controlled trials. Typical examples of these are pragmatic trials (randomisation, little/no control), purely prospective observational studies (no randomisation, no control) and use of historic controls.

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#2 Problem
This approach is far from ideal as the analysis of comparative effectiveness data obtained outside a robust and controlled Phase 2/3 developmental environment can lead to biased treatment comparisons. Results from these less well-controlled trials are often met with criticism by the reimbursement authorities.

For example, it is extremely difficult to compare evidence obtained from observational trials with that from RCTs if they are conducted under wildly varying protocols, in different patient populations, countries, etc.

There is currently considerable debate and investigation into the differences in treatment comparison estimates between randomised and non-randomised data. Given all the problems with uncontrolled trials, observed treatment effect sizes obtained from them would need to be dramatic in order to obtain reimbursement approval.

A further problem is that gathering additional evidence of drug benefit after Phase 3 development inevitably leads to time delays before reimbursement approval can be granted. It is evident that shortening these delays (e.g. via a streamlining of the RCT approval process) would be advantageous.

In order to meet these challenges head on, new clinical trial designs are required. Some progress has been made in this area but many previously proposed alternative designs are still in their infancy and have yet to gain widespread acceptance by reimbursement authorities. It has been noted that there is no hard distinction between pragmatic trials and RCTs.

Our proposed study design takes advantage of these blurred lines.

#3 New study design: Mixed RCT (cont.)
In a Mixed RCT patients would be selected and randomised to one of three trial arms:

• Trial Arm #1: Randomised Controlled Trial (RCT)
• Trial Arm #2: Pragmatic Trial (PT)
• Trial Arm #3: Observational Trial (OT)

Patients randomised to the PT and OT arms of the trial could be offered extended treatment which would allow the gathering of long-term effectiveness data, which is a stumbling block in many reimbursement dossiers.

Enrolment would often be easier in the Mixed RCT as patients would be more likely to receive active treatment and would be less likely to have to undergo a battery of clinical tests. Primary efficacy and safety data from the PT and OT arms would be combined with the RCT arm data (using standard analytical methods) in order to support regulatory approval.

This would reduce the costs compared with a stand-alone RCT.

#4 Advantages
The simple act of randomising patients to each trial arm (RCT, PT or OT) would ensure a balance of baseline patient characteristics across the arms.

As a result, the efficacy and safety of the experimental treatment obtained from the RCT setting can be compared with more ‘real-world’ settings.

The Mixed RCT design allows for a ‘head-to-head’ comparison of direct evidence in a controlled setting with that in less controlled settings.

Moreover, robust comparative effectiveness data using placebo and active comparators can be more readily obtained. In essence, our approach transforms indirect evidence into quasi-direct evidence, with little increase in trial complexity.

#5 Summary
Reimbursement authorities require robust real-world evidence, whilst regulatory authorities require robust perfect-world evidence. It is inherently inefficient to gather this evidence from multiple clinical trials separated in time by months, if not years.

The differences between the two sources of data are not black and white, but rather shades of grey along a continuum. The industry requirement for reimbursement is for clinical trials to better reflect the real-world, while incorporating elements of the robustness and internal validity that RCTs have provided over the past decades.

There are potentially substantial cost reductions and time gains to be made from incorporating pragmatic and observational trial elements into a wider randomised controlled trial framework. The Mixed RCT provides a novel and formal framework for the collection and analysis of real-world data in a robust RCT setting.

References
9. Pragmatic, and Observational Clinical Trial Data. www.numerus-ltd.com

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