Introduction

Randomized controlled trials (RCTs) remain the gold standard for evidence-based medicine, but RCTs can be challenging in small patient sub-populations, especially if there is also biological heterogeneity of the disease. Innovative clinical trials are becoming increasingly important to address the problems associated with conducting RCTs. A number of innovative trial designs have been developed, such as the legacy Pick a Winner approach; umbrella trials and basket/bucket trials. These trial designs have benefits for researchers, and possibly patients, but how will payers and health technology assessment (HTA) bodies view innovative trial designs?

Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have shown themselves willing and able to accept innovative clinical trial designs for product registration. However, payers and HTA bodies tend to be fairly conservative in their approach and prescriptive about the evidence that they require.

We looked at the Pick a Winner clinical trial design in more detail and investigated how HTA bodies would react to the inclusion of a clinical trial based on this design in an HTA submission. To gain some further insight into the Pick a Winner clinical trial design, we interviewed Professor Alan Burnett, who designed and implemented – through the United Kingdom Medical Research Council (UK MRC) - the Pick a Winner clinical trial design for clinical trials in acute myeloid leukaemia (AML), and Professor Georg Hess, an innovator and clinical trial expert who has practical experience with these types of designs, as well as being the co-chair of the Early Trial Network (ETN) cooperative group in Germany. We also interviewed Dr. Paul Miller, a health economist and former member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, and Professor Yvonne Boehler, Vice Dean for Science and Knowledge Transfer at TH Köln, Faculty of Applied Natural Sciences and former Scientific Officer at IQWiG, to understand how HTA bodies would view the Pick a Winner design.

What is the Pick a Winner clinical trial design?
The Pick a Winner design allows multiple treatments to be compared to a standard of care, with rapid removal of ineffective treatments during the trial. Patients are randomized between a control arm and multiple novel treatments. Interim analyses occur after 50 and then 100 patients have been recruited. Treatments that fail to reach a pre-determined level of clinical improvement
Newly submitted  

The experimental design included improvements in CR required to progress at each interim analysis (Δ1 at 50 patients and Δ2 at 100 patients).

**Design**
- **Drug X**
  - Interim analysis at 50 patients
  - STOP
- **Drug Y**
  - Interim analysis at 100 patients
  - STOP
- **Drug Z**
  - Phase III analysis at 200 patients
- **Control**

**CR** = Complete Response  
Δ1 = change seen at the first interim analysis  
Δ2 = change seen at the second interim analysis

**Drug X** fails to Δ1 improvement at first interim analysis  
**Drug Y** fails to show Δ2 improvement at second interim analysis  
**Drug Z** shows Δ1 & Δ2 improvements proceeding to final analysis

**How do HTA bodies view innovative clinical trial designs in general?**

According to Miller, HTA bodies simply want to make evidence-based decisions. The prime concern of the HTA bodies is that the evidence must characterize the treatment effect and the magnitude of difference compared with the treatment comparator. The gold standard is RCTs, which are preferred by HTA bodies. However, there are issues with RCTs in certain circumstances such as when there is a lack of definition of the standard of care or where researchers are struggling with patient numbers.

Boehler believes that HTA bodies are open to thinking about trial designs which overcome these problems without introducing uncertainties, but they tend not to take a proactive approach, making final decisions about particular clinical trial designs mainly when they receive a submission. This introduces risk for companies submitting data based on innovative clinical trial designs as there may be limited experience in the HTA body in assessing such trials, and therefore an uncertain outcome.

She suggested that there needs to be a forum for discussing innovative clinical trial designs outside of a formal submission. This could include an evidence-based medicine conference such as the Cochrane conference, an internal HTA body dialogue session, or in the context of early scientific advice from the HTA body. This separates the discussion from a formal submission and would allow wider discussion to take place.

**What would HTA bodies think about the Pick a Winner design?**

Both Miller and Boehler said that the Pick a Winner design was innovative and well thought through. Miller noted that it fits with the current policy drive to allow faster access to new medicines.

However, there were concerns about the potential for bias in the design. This was mainly focused on the control arm being used for each treatment. It is likely that different treatment arms would have different randomization criteria and this needed to be reflected in the control arm being used as the comparison. If the trial continued for several years, there was also the potential for the standard of care to change over time. If patients in the control arm were not contemporaneously recruited, the trial could be comparing patients receiving a novel treatment with an outdated standard of care.

We raised this with Professor Burnett who recognized this potential for bias and had taken this into account in the AML trial that he conducted. In this trial, the randomization of the control arm analyzed was designed to mirror the randomization criteria of the successful...
treatment arm. They also only used control patients who were contemporaneously recruited with the successful treatment arm.

Miller was dubious that manufacturers would want to take part in a Pick a Winner trial because of the associated risks and the need to cooperate with competitors. They would certainly not want their treatment to be one of the treatments eliminated in the interim analysis. He saw this type of clinical trial design being more relevant in academic research. Companies may be more interested if their treatment was the winner but are unlikely to want to take the risk.

**Conclusions**

We are seeing innovative clinical trial designs being developed and implemented, especially with increasing patient segmentation, personalized medicine, and the advent of the EMA’s adaptive pathways, along with the global push for earlier drug approval. Researchers are experimenting with clinical trial design and we can expect to see more alternatives to traditional designs in the future. Some of these designs, like Pick a Winner, will only apply to a limited number of conditions, but others may have wider application and companies need to know how they will be received by payers as well as regulators. As we have mentioned, regulators have been more open to innovative trial designs, while payers have a clear preference for well-designed randomized clinical trials.

Payers and HTA bodies need to watch these developments and consider how they would assess new clinical trial designs. NICE commissioned research to explore the assessment and appraisal of regenerative medicines and cell therapy products, raising some methodological issues, but acting as guidance to companies developing treatments in these areas. Similar research and discussions on innovative clinical trial designs would be helpful.

**Suggested Recommendations Regarding Innovative Clinical Trial Designs**

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<th>Recommendations made by</th>
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| **Payers**             | • Critically appraise the risk of bias introduced by innovative trial designs, especially with regard to the central HTA-question: Is this drug better than the appropriate comparator treatment?  
• Seek opportunities to discuss innovative trial designs with HTA bodies besides dossier submissions and be a driver of open, methodological dialogue. |
| **Authors**            | • Investigate how new trial designs could provide better clinical value substantiation and be used fluidly across indications and stages of diseases in an environment with increasing treatment alternatives.  
• Increase collaboration between academia, HTA bodies, regulators, and manufacturers to define value substantiation that meets new treatment approaches. |

*Note: These suggested recommendations represent the thoughts of the authors and those experts interviewed for this article.*

**ACKNOWLEDGEMENTS**

We would like to thank Professors Yvonne Boehler, Alan Burnett, Georg Hess, and Dr. Paul Miller for their generous input into this research.

**REFERENCES**