Smarter trials speed up patients’ access to effective treatments

27 September 2018

Adaptive clinical trials are transforming the efficiency of drug development and the MRC has played a crucial role in implementing this innovative method into the UK clinical trials landscape. This trial methodology helps to deliver the right treatment to the right patient faster than ever before. As treatments increasingly become more personalised, accommodating a complex approach within a clinical trial setting requires a new type of clinical trial with a flexible design.

A carefully implemented randomised clinical trial (RCT) design has been considered the gold standard for testing new health interventions since the MRC pioneered the first such trial in 1947 testing streptomycin to treat pulmonary tuberculosis. RCTs are valued for their ability to avoid bias, and for their statistical robustness. However, RCTs have become increasingly expensive and take much longer to complete, in a time of increased demand for resources and time.

**What is an adaptive trial?**

In contrast to a traditional RCT, in an adaptive trial the patient responses are observed and analysed at pre-defined interim points, and pre-determined modifications to study design can be implemented based on these observations. It allows an adaptive trial to be flexible and efficient without undermining the validity and scientific integrity of the study. Where appropriate, adaptive trials have the potential to vastly improve the way clinical trials are put into practice.

The lack of flexibility with a traditional RCT has several disadvantages when compared with an adaptive trial design. For example, a promising experimental drug identified in the laboratory can take nearly a decade to successfully pass through all three phases of clinical trials. Sometimes if patients on an experimental arm of a RCT fare vastly better than patients on the control arm of the study, there would be an ethical necessity to abort the RCT prematurely rather than withhold the effective treatment from the control group. Or, since patient responses are not evaluated until a RCT is complete, an ineffective treatment is only identified at the end of the study.

In contrast, adaptive trials have a degree of flexibility and efficiency that traditional RCTs cannot accommodate. Adaptive trials can seamlessly allow the addition of promising new drugs to existing studies, or halt the investigation of ineffective treatments sooner rather than later, saving both time and money while accelerating the delivery of life-saving and life-extending drugs to patients. An adaptive trial could anticipate the possibility of an experimental arm outperforming the control arm and ensure that the trial continues while making sure that all patients on the trial have access to effective treatments.

**The MRC’s support for adaptive trials**

The MRC has a rich history of supporting clinical trials, and has been instrumental in leading the
implementation of adaptive trials into the UK clinical trials landscape. The first unit to undertake clinical trials within the MRC was the Tuberculosis Research Unit which was set up in 1948, following the introduction of the first drugs to treat tuberculosis. Numerous clinical trials followed, and in 1998 the Tuberculosis Research Unit evolved into the MRC Clinical Trials Unit, to bring together research programmes in HIV and cancer. Additionally, the Clinical Trials Service Unit at the University of Oxford established in 1975 is a world leader in the conduct of large-scale RCTs and combined analyses of detailed data from randomised trials, which provide reliable evidence about the safety and efficacy of treatments.

In 2008 the MRC and the National Institute for Health Research (NIHR) set up the Methodology Research Programme to fund high-quality methodology research in areas including but not limited to clinical trials. The MRC Hubs for Trials Methodology Research Network (MRC HTMR), established in 2009, has an Adaptive Designs Working Group that collaborates closely with the academic community while also linking with key stakeholders such as regulatory bodies and industry. The Working Group also fund the position of an Outreach Officer whose principal task is to popularise adaptive designs among medical researchers and statisticians by visiting clinical trials units across the UK to promote the benefits of these flexible designs. Within three years, the Outreach Officer visited eight clinical trials units across the UK, and supported the design of five clinical trials.

The MRC HTMR Network has also supported the development of MoDEst, a software package for Model-based Dose Escalation Trials. The MoDEst source code has been available since June 2017, and downloads of this source code has steadily increased since (as seen from the graph below), preceding the formal website launch in May 2018.

These efforts have led to the development of ground-breaking adaptive trials capable of efficiently testing several promising compounds precisely targeted at specific sub-populations of patients.

From bench to bedside in two years

The benefits of an adaptive trial design capable of seamlessly allowing the addition of a promising new drug to an existing study was brought into sharp focus in 2017 with an experimental drug called AZD1775. The drug was made available for bowel cancer patients enrolled in the multi-arm adaptive trial, FOCUS4, co-ordinated by the MRC Clinical Trials Unit at University College London.

In 2015, Professor Tim Humphrey and his team at the CRUK/MRC Oxford Institute for Radiation Oncology showed that cancer cells with a mutated gene called SETD2 were killed by the experimental drug AZD1775 being developed by Astra Zeneca. This research exploits a concept called 'synthetic lethality'; in the presence of a mutation (such as SETD2) or drug (such as AZD1775), a cell can still function, but a combination of both specifically kills cancer cells. This approach has the potential to be less toxic and more effective than existing treatments by focusing lethality on cancer cells; traditional chemotherapy drugs kill all rapidly dividing cells, even normal healthy cells. As an adaptive trial progresses, new discoveries from the laboratory can be incorporated into the trial by adding new treatment arms to the existing trial even after the trial has begun, rather than setting up a brand-new trial which would take much more time. About one in 10 bowel cancer patients have SETD2 mutations and the translational potential of this targeted treatment for treating those patients is accelerated towards the clinic in less than two years thanks to the flexible design of the existing FOCUS4 trial.

Identifying ineffective treatments early

In May 2018, the STAMPEDE trial received the ‘2017 David Sackett Trial of the Year Award’ from the Society for Clinical Trials, as recognition that adaptive trials such as STAMPEDE provide methodological excellence and substantial beneficial change towards improving human health.

Launched in 2005, STAMPEDE is an ambitious clinical trial for finding the best treatment for people with advanced prostate cancer. It is funded by the MRC Clinical Trials Unit, Cancer Research UK, and
several pharmaceutical companies. STAMPEDE aims to prevent prostate cancer re-growth by adding other treatments to hormone therapy, and is the largest ever prostate cancer treatment trial, having already recruited over 10,000 men.

STAMPEDE has pioneered the multi-arm, multi-stage platform randomised trial design; it currently has eight different treatment arms and one common control arm, making it much faster for evaluating a diversity of potentially effective treatments than a traditional RCT would be. In 2015, results from STAMPEDE showed that men having docetaxel as well as standard treatment lived on average 10 months longer than men who had standard treatment alone. At the same time, results showed that men who had the drug zoledronic acid as well as standard treatment didn't live any longer than men who had standard treatment alone. Thanks to its adaptive design, the STAMPEDE team could halt recruitment for the ineffective treatment arms while continuing to investigate other promising arms of the trial.

Provided by Medical Research Council

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