Platform clinical trials: An innovative approach

The strategy improves outcomes, besides cutting short assessment timelines

The search for an effective treatment for COVID-19 continues to be a major focus for the world's clinical research community. The majority of clinical trials planned are conventional randomized controlled trials (RCT), in which one COVID-19 treatment will be compared to usual care in just one population – hospitalised COVID-19 patients. In contrast, Oxford University's Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial was designed as an innovative platform trial, in which multiple treatments were compared to standard care in a large number of hospitalised COVID-19 patients.

The RECOVERY trial, funded by UK's Medical Research Council and National Institute for Health Research, allowed a reliable assessment of various randomised treatments – lopinavir/ritonavir, dexamethasone, hydroxychloroquine, azithromycin and convalescent plasma —- on major outcomes in hospitalised COVID-19 patients in comparison to usual care. Launched on Mar 20, RECOVERY had randomised over 11,000 participants at 176 sites by Jul 20. In June, the data monitoring committee and steering committees decided to halt the dexamethasone arm because of compelling evidence of efficacy and stop the hydroxychloroquine arm because of lack of efficacy. In contrast, the results of the RCTs of single treatments — remdesivir or tocilizumab in a smaller number of patients — did not show benefits on major outcomes.

The purpose of the platform trial is to find the best treatment for a disease by simultaneously investigating multiple treatments and utilising specialised statistical tools for randomised allocation of patients and analysis of data. Response adaptive randomisation designs used in such trials allow prespecified modifications in key trial characteristics during the conduct of the trial in response to data accumulating during the trial. Emerging outcome data, e.g. death, discharge and the need for ventilation, are used to adjust randomisation probabilities to preferentially assign better performing treatment regimens, e.g. dexamethasone, to future patients. This strategy improves the outcomes for trial participants, increases the available data on efficacy and safety for the most effective treatments, and reduces the assessment time for the best therapies.

Successful implementation of platform trials rests on innovations in infrastructure and trial design. Infrastructure includes: 1) a common screening platform 2) centralised and unified governance - a steering committee, an adjudication committee and a data monitoring committee 3) wide trial networks/ large numbers of sites and 4) common processes for protocol design, randomisation, data capture, data management and quality-control oversight. Innovative design incorporates 1) adaptive randomisation 2) longitudinal modelling to decide probabilities of success or failure and 3) a common control group.

The efficient conduct of a platform trial requires high levels of planning and implementation. The cost of time and resources to establish the required infrastructure, inclusion of many trial sites and increased efforts for advance planning and coordination to make multiple parties agree on a common trial design and conduct processes and centralised unified governance are much more demanding than the execution of a stand-alone RCT.

In a pandemic setting, platform trials fulfil an urgent medical need for conducting large randomised trials with a control group rather than many small and inconclusive studies. Let's hope the lessons of RECOVERY will create an innovative platform for clinical research on non-pandemic health priorities!

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