Ethics of adaptive trial designs

The urgency of the COVID-19 pandemic has necessitated the investigation of multiple potential therapies in a timely way. In this context, adaptive trials are taking place to investigate multiple treatments and that are intended to continue beyond the evaluation of any one treatment. These complex trials have the potential to answer more questions efficiently and improve care for research participants by dropping therapies that are shown to be ineffective, but they present challenges. How should the risks and benefits be communicated to participants, understanding that the benefit:harm ratio may change over the course of the study? What consent model is appropriate for such dynamic trials? And how can regulators and research ethics committees be supported to understand and evaluate these statistically and logistically complex trials?

The 2017 Global Forum on Bioethics in Research (GFBR) meeting focused on a range of novel trial designs, including adaptive trials. The full GFBR meeting report is available at this link. This PHEPREN and GFBR seminar will reflect on the GFBR meeting conclusions and the ethics of current COVID-19 adaptive trial, including RECOVERY, Solidarity and REMAP-CAP.

Chair: Ross Upshur, University of Toronto, Canada
Panel: Srinivas Murthy, BC Children's Hospital Research Unit, Canada
Fyezah Jehan, Aga Khan University, Pakistan
Jerome Singh, University of KwaZulu-Natal, Durban, South Africa; and Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

The following questions will form the basis of the seminar's panel discussion. Seminar attendees are invited to submit questions in advance of the seminar when they register or by email, or during the live discussion.

1. How have platform trials been employed in the COVID-19 research response, and why (e.g. RECOVERY, Solidarity, REMAP-CAP)?
Efficiency and rapid identification of effective treatments during a public health emergency; ability for usual care arm to change as better care is identified

2. What unique ethical issues have these adaptive platform trials for COVID-19 treatments faced in an LMIC setting? Have these factors constrained the use of the design?
Complex studies; community consultation; logistically demanding; unfamiliar to RECs, local regulators and healthcare providers and therefore requiring effective communication to help address any misconception that adaption decreases scientific rigor and efficiency

3. How have the benefits and risks of study participation been conceptualized in these COVID-19 studies?
The fact that arms are added and dropped make these studies complex; how does clinical equipoise apply?; and might apply to the decision to add or drop arms; benefit-harm ratio will change over the course of the study and may be better at the end of the study

4. What consent models are being used in adaptive trials for COVID-19 therapies?
Can a one-time consent model be comprehensive enough to achieve the appropriate amount of participant information? Can the adaptive randomization concept be explained in a clear and timely manner during a public health emergency?

5. Reflecting on the experience of using adaptive trials for COVID-19, what policy and/or governance mechanisms are required to support the use of these designs in future?
What training programmes or support needs to be put into place e.g. to help RECs assess the statistical claims that are make in adaptive trial protocols? What does capacity building mean in this context? What role does the public or other stakeholders have (if any)?