TGHN Workshop Report – COVID-19 Hub

REMAP-CAP and Why We Need Platform Trials in a Pandemic

Introduction

On 13th May, The Global Health Network (TGHN) supported the virtual open workshop 'REMAP-CAP and Why We Need Platform Trials in a Pandemic'. This workshop contributed to the workshop series on the COVID-19 response from various regions across the globe, organized by TGHN at the University of Oxford, UK in partnership with the REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia**)** team.

The workshop featured a panel of three experts involved in the REMAP-CAP study. The workshop's key aims were:

- *To establish the concept of adaptive platform trials*
- *To introduce REMAP-CAP to new countries and study groups*
- *To seek input into what the barriers might be and whether any adaptations might be required for different settings around the world*
- *To increase engagement in the REMAP-CAP study from sites across the globe.*

A total of almost 300 people registered for the open workshop in advance, and 119 attended via Zoom on the day of the session. The workshop was also streamed live on TGHN's Facebook page. The attendees spanned 31 different countries.

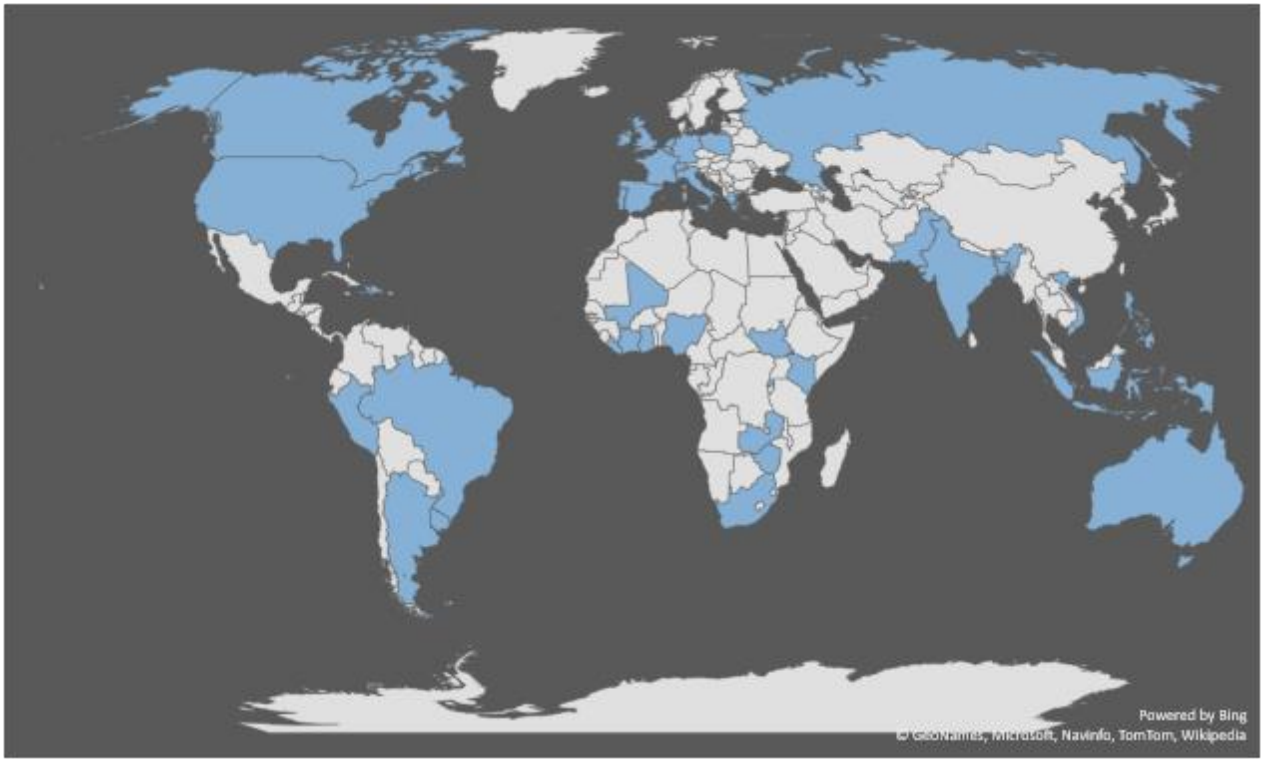

Figure 1 - Location of attendees. 119 participants attended the workshop from the 31 countries shaded in dark blue.

Summary of Individual Presentations

Prof. Srinivas Murphy

Associate Professor of Infectious Diseases and Critical Care, University of British Columbia, Canada
REMAP-CAP International Trial Steering Committee

Over 1000 COVID-19-centered clinical trials are now in operation across the globe, the bulk of which are located in Europe, East Asia and North America. Ongoing trials can be viewed using the Cytel clinical trial tracker. However, there are two major concerns with the range of trials that have been conducted to date, the first of which is that many of the trials are very small (50% of them have less than 100 participants). In addition, there is little variety between trials, with a small pool of treatments being investigated across a large majority of trials. As an example, Chloroquine/hydroxychloroquine (HCQ) feature as treatments in 118 separate trials, all of which have very similar aims and objectives.

Currently, clinical research response lags behind preclinical research response and public health response. However, the epicurve can be pushed downwards through high quality research.

Adaptive platform trials serve as a vastly improved method of rapid knowledge generation in a pandemic. The table below explains how platform trials differ from traditional trials:

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

One of the most important aspects of platform trials is that they use response *adaptive randomization*. This is when there are multiple interventions which are tested, and randomized and assigned as both individual treatments and in combination. As outcomes accrue and more data is collected, the randomization allocation changes as treatment arms that prove the most beneficial will preferentially be randomized, and the patients will preferentially receive the most beneficial interventions. This means the interventions that are found to be less beneficial will get filtered out and removed from the randomization scheme. Therefore, the response adaptive randomization functions as a learning system which allows patients to receive an optimal standard of care.

The ways in ***which response adaptive randomization can help alleviate challenges*** when conducting research studies in a pandemic are outlined below:

- Ethical challenges: Responsive adaptive randomization allows randomized patients to move from control arms to the better performing arm without effecting the statistical power of the study.

- Time: Time required to set up trial, including multi-site and multi-nation coordination, is reduced thanks to the use of pre-established networks.
- Human resources: Research staff are available to help the consent and randomization process. They are already embedded within the healthcare setting, making footprints at sites as minimally as possible, and making the trial infrastructure as operationally easy as possible.
- Data: Allows aggregation of databases with larger population across countries and continents
- Implementation: Easy to implement at site level with region-specific models, sponsored locally, and ability to implement regionally relevant questions.

Prof. John Marshall:

Professor of Surgery and Critical Care Medicine at the University of Toronto

REMAP-CAP is a sleeping trial that was implemented in 2009 after the swine flu pandemic. Pneumonia studies are necessary because it is the phenotype of many pandemics, and COVID-19 fits this well. Until January 2020, REMAP-CAP was unfolding in 4 different continents, studying 3 different domains. These domains are the Antibiotic domain, Macrolide Duration Domain, and the Corticosteroid Domain.

Since the outbreak of COVID-19, the ***Pandemic Appendix to Core protocol was activated***, resulting in 2 specific changes to the trial. These changes are that the primary focus is now on patients with COVID-19 infection who have organ dysfunction, and the primary outcome has shifted to organ support-free days over 21 days – in the hope that the response to adaptive randomization occurs in a nimble fashion.

REMAP-CAP has also expanded in scope, with multiple domains being added on top of the ones mentioned previously. These domains are:

- Antivirals: Lopinavir/ Ritonavir, HCQ
- Immune Modulation: Interferon- β1a and Anakinra Tocilizumab
- Immunoglobulins: Convalescent plasma
- Anticoagulation: Heparin
- Vitamin C: High dose Vitamin C
- Ventilation: Pending

REMAP-CAP is currently recruiting in 173 different sites in the following regions: UK, Europe, Saudi Arabia, North America, Australia, and New Zealand with active efforts to move it further into Latin America and hopefully Africa and South-East Asia. There are currently 926 patients randomized in the trial, with 431 of them having suspected COVID-19 infection.

One of the important questions is how to transfer ***REMAP-CAP to Low-Middle Income Countries*** (create a REMAP-LMIC). The domains needed for this to happen are: Basic Support, strategies to avoid intubation, steroids, Heparin, Vitamin C, and Oxygen. The data collection must be simple and pragmatic, with the dominant funding sources being the Wellcome Trust and BMGF.

COVID-19 has not only drastically changed many aspects of our lives, but also the way we are thinking about research. ***These main changes are*** trial design – master protocols and platform trials have come to the foreground, new models of collaboration, new models of oversight and reporting – for example the 118 trials of hydroxychlorine should share their data, and accelerated results in order to inform patient care.

Prof. Fernando Zampieri:

Research Coordinator at HCor-Hospital de Coração, São Paulo
Associate Professor, University of Southern Denmark

There are several ***challenges surrounding how to get trials running in Low-Middle Income Countries*** (LMICs). Brazil is used as an example of what challenges exist – first and foremost due to the large regional inequality within the country. REMAP-CAP is the most correct, ethical way to run a clinical trial in the context of a pandemic, but there are always going to be people with issues surrounding a new design. It is important to explain the trial clearly to persuade governments and trials centers that it is an optimal clinical trial framework during a pandemic.

The challenges with getting a large clinical trial were summarized into the 5 following groups:

- Ethics and Regulatory Agencies:
  - Lack of experience with external collaborations – for example *who holds the data and has access to the data?*
  - Lack of experience with adaptive trials – Ethics Communities and Regulatory Agencies are used to fixed trials with fixed dates.
  - Some regulatory agencies still ties with "$p<0.05$" or nothing approach.
- Funding:
  - Funding is always problematic as there are very few funding lines.
  - Problematic 'funding share' which is required, especially when most funding comes from public sources.
  - Persuading governments to fund a global trial when they often want localized trials. The return in terms of money spent can be much greater with the global adaptive platform trials.
- Consent forms:
  - Illiteracy is still an issue in many LMICs. In these circumstances, families are usually called in but this can be tricky during a pandemic.
  - How do we obtain consent from patients when contact precautions/lockdowns are in place? In Brazil, this was all done via papers, which increases the risk of the transfer of the virus.
  - Email or verbal consent forms are not possible as not everyone has an email address.
- Logistics:
  - In most ICUs there are no dedicated research personnel. Therefore a burden is imposed on a healthcare worker, not a researcher. This could be solved through funding, which could be used to hire someone to collect the data etc.
  - *How do you make the drugs arrive at sites to make the trial run*? Mobility issues are especially pertinent in geographically large LMICs. The best resolution is to start small and slow, and gradually increase the scale of the trial.

REMAP-CAP is a great opportunity to provide new answers and avoid excessive burdens to already overstressed healthcare systems. This is a very good chance to engage people in doing research that provides answers for clinicians in LMICs.

Summary of Q&A, Open Discussion and Comments

The workshop was recorded, and comments and questions captured. The following chart shows the themes that emerged.

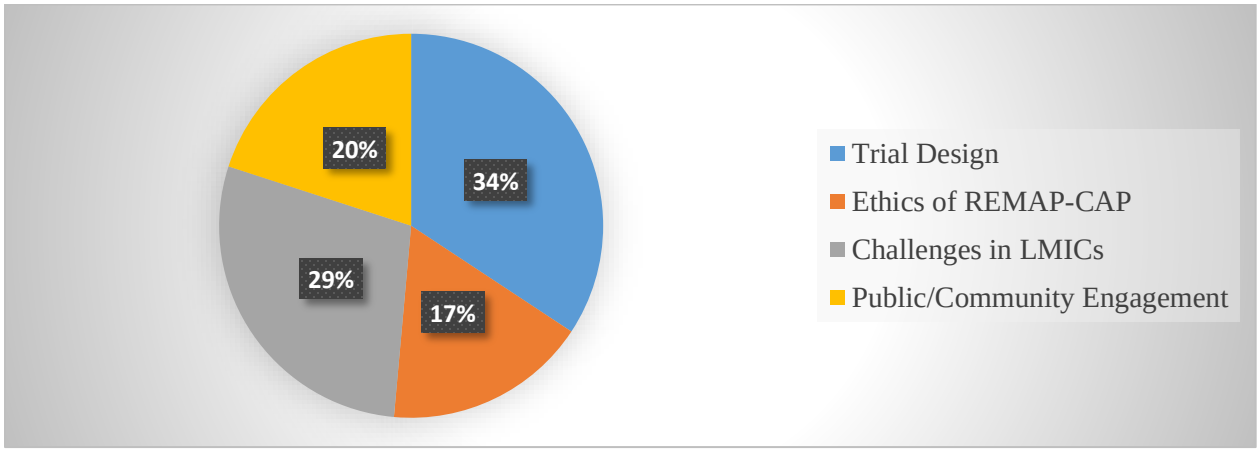

Fig. 2: Main themes that emerged from the REMAP-CAP workshop.

Within these four themes, it was then possible to categorise the questions, comments and discussions into sub-themes.

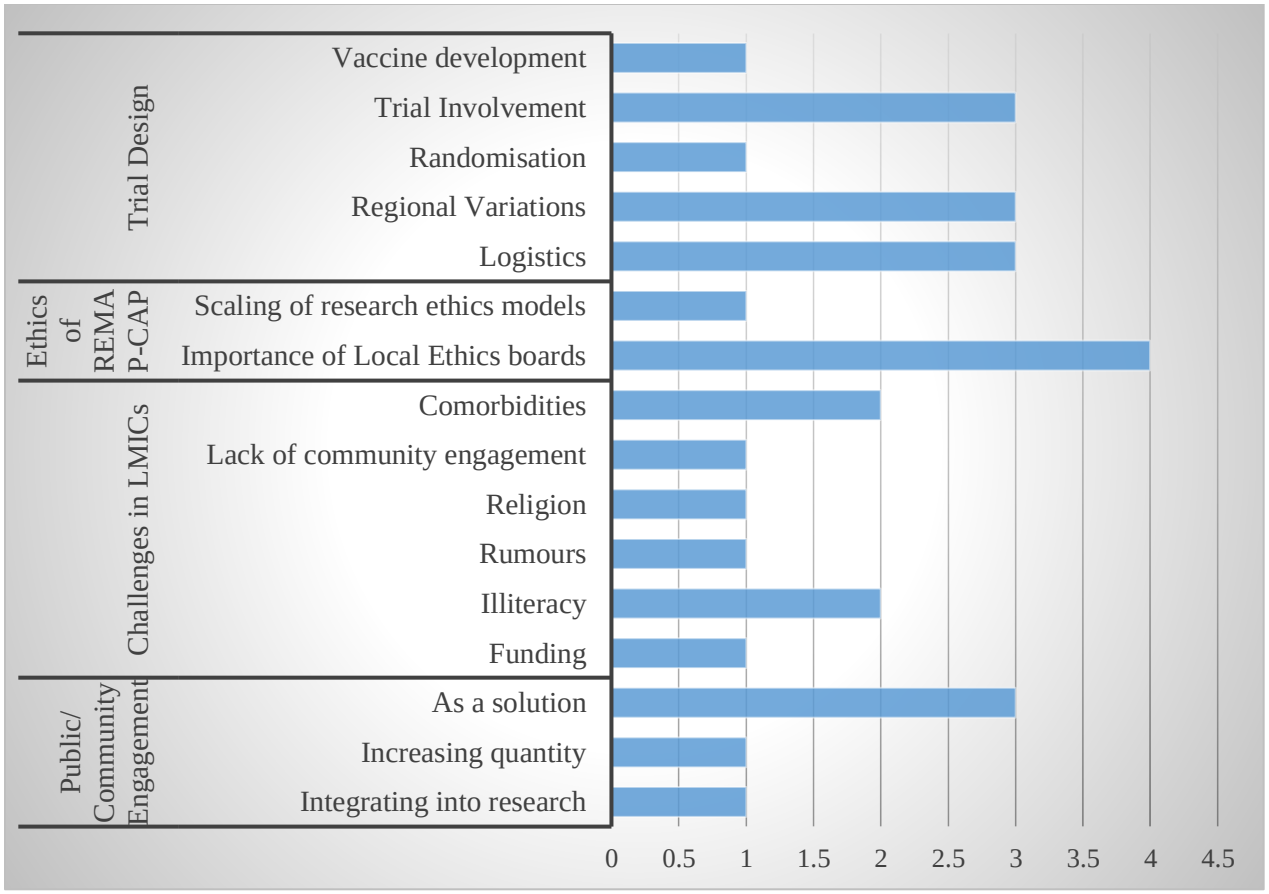

Fig. 3 Categorisation of questions, comments and discussions to sub-specific area

Trial Design:

Trial design was touched upon several times by the panellists and participants. The length of the trial was discussed in terms of short-term and long-term outcomes, as well as variation in the standard of care between regions and hospitals. Randomisation is essential as it balances these variations out in the end. Furthermore, REMAP-CAP allows multiple covariates to be analysed and has the ability to assess the covariates that mediate the outcomes the most and least.

Ethics and local committees:

The panellists mentioned the importance of local ethics committees and research boards on multiple occasions. The importance of the trial being overviewed by local research ethic committees was explicitly mentioned by Prof Murphy. Prof Marshal also urged to rethink research ethics models not only at the individual level but also at the national level.

Challenges in Low-and-Middle Income Countries (LMICs):

There are several challenges with implementing REMAP-CAP in LMICs. The panellist from Brazil mentined some of them and this was then reinforced by attendees who also mentioned the *"lack of well-equipped structure for clinical trials, poor access to funding of clinical trials", "illiteracy, and how to cope with concipary*", a lack of community engagement.

The problem of comorbidities and how to address these in the trial design was also a recurring theme, especially from attendees based in the tropics where many diseases follow seasonal profiles. One attendee from Kenya made the point that whislt good quality trials can be carried out in Kenya, ther is a struggle with Malaria, and that *'these problems need to be addressed not just in terms of disease characterisation, but also treatments and vaccines.'* Dr Zampiery agreed that agreed in Brazil this challenge is an issue too, specially during summer with Yellow fever, Dengue, ZIKA etc. Prof. Murphy explained that one of the covariates that REMAP CAP embeds is the ability to assess which covariates mediate outcomes as much as possible.

Community Engagement:

Public and community engagement was agreed to be an absolutely essential consideration, and a unique opportunity. One panellist asked *'my concern is considering different public perception and opinions during a Pandemic; how does this affect the success of a platform trial and how should a researcher manage such especially in participant selection for the trials in LMICs?*' Panellists agreed that Public engagement is crucial, and explained that they have had to do a lot of public education about the importance of clinical research. Every region will be different, and must emphasise the importance of patient and community engagement. For example, *"in Africa, religion has a great underlying effect on how public perceive any interventions or trial. So, there is need to include both religious leaders or network them as stakeholders in public engagement'.*

Summary

Consolidating feedback from the panellists and the questions and comments in the webinar, we can conclude that this workshop particularly emphasised that:

- Adaptive Platform trials such as REMAP-CAP are a good way to respond to pandemics.
- Public engagement is critical and should be considered when implementing any kind of platform trial, and education is the best method with which to introduce people to platform trials.
- There is an international Data Monitoring Survey Board (DSMB) for REMAP-CAP, and through the WHO there is an ongoing project bringing together DSMBs of multiple similar trials.
- There is huge variance in the 'Standard of Care' for COVID-19 not just on a national level but also between hospitals – REMAP-CAP deals with this through the randomization process meaning it all ends up being balanced.
- It is essential to consider how to transfer the REMAP-CAP trial design to LMIC's, especially with the plethora of challenges that LMIC's face.

Call to Action and Next Steps

If you are involved in research on COVID-19, please get in touch and share any relevant protocols, experiences or advice.

Over the next few days please send in your comments and feedback on this workshop. For those who want to get involved in the REMAP-CAP trial, or if you have further questions, you can find contact details for the REMAP-CAP teams **here**.

Further virtual workshops are planned, which will be topic-specific and based on demand. If you would like us to conduct a workshop related to a specific area of COVID-19 research, please let us know what topics would be most helpful.

You can get in touch here: info@theglobalhealthnetwork.org