

LESSONS FROM THE RECOVERY TRIAL

SUMMARY REPORT
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List of Abbreviations

| | |
|------------|---|
| ADP | Access and Delivery Partnership |
| COVID-19 | Coronavirus disease |
| CRF | Case report form |
| CTAP | COVID-19 Therapeutics Advisory Panel |
| FDA | Food and Drug Administration |
| HITAP | Health Intervention and Technology Assessment Program |
| HSRI | Health Systems Research Institute |
| LMIC | Low- and middle-income country |
| MOH | Ministry of Health, Singapore |
| MRC | Medical Research Council |
| NCID | National Centre for Infectious Diseases |
| NHF | National Health Foundation |
| NHS | National Health Service |
| NIHR | National Institute of Health Research |
| NUH | National University Hospital |
| RCT | Randomised controlled trial |
| RECOVERY | Randomised Evaluation of COVID-19 Therapy |
| SSHSPH NUS | Saw Swee Hock School of Public Health, National University of Singapore |
| UKRI | UK Research and Innovation |

Acknowledgements

This report summarises the discussion during a meeting held on 30th June 2022 to discuss lessons learned from the RECOVERY Trial and areas of potential collaboration to conduct clinical research in Thailand. This meeting was supported by the National Health Foundation (NHF), the Access and Delivery Partnership (ADP) the Saw Swee Hock School of Public Health National University of Singapore (SSHSPH NUS), and the Health Intervention and Technology Assessment Program. The report was prepared by Madison Silzle with inputs from Sauadamini Dabak, Yvonne Teo Hwee Ling, and Assoc. Prof. Hsu Li Yang. The meeting was organized by Assoc. Prof. Hsu Li Yang and Yvonne Teo Hwee Ling from SSHSPH NUS along with colleagues from HITAP, Madison Silzle, Dimple Butani, and Evan Huang Ku. The findings, interpretations and conclusions expressed in this report do not necessarily reflect the views of the funding or participating agencies.

Background

The COVID-19 pandemic has challenged the research community to respond and provide clinical solutions for COVID-19. A range of options have been considered for treating the disease and early during the pandemic, the UK Research and Innovation (UKRI)'s Medical Research Council (MRC) and the National Institute of Health Research (NIHR) jointly funded the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial that is being led by University of Oxford.

The RECOVERY Trial was established by Professor (Sir) Peter Horby (Oxford Nuffield Department of Medicine) and Professor Martin Landray (Oxford Population Health) in March 2020 to address the clinical uncertainties in the treatment of COVID-19 – a novel disease for which no proven therapeutic options were available

It was clear that RECOVERY required a mechanism for conducting randomized controlled trials (RCT's) at a large scale in order to provide robust clinical evidence, recruiting patients in their thousands. This was achieved by means of a disruptive pragmatic trial design which focused on collecting small amounts of data on large numbers of subjects, while also making use of the National Health Service's (NHS's) electronic healthcare data collection system which already gathered data as part of routine care.

Within 2 weeks of the grant being awarded, the first patient was recruited on March 19th 2020. Within the first hundred days, it had delivered key results on hydroxychloroquine (no clinical benefit), lopinavir/ritonavir (no clinical benefit) and dexamethasone (effective in reducing mortality in hospitalized patients), findings that has been used to save lives globally.

At present, more than 47,000 subjects across 198 trial sites in UK have been recruited, with definitive results delivered for 10 therapeutic agents. The platform trial is still going strong, with RECOVERY International having been launched which includes sites in Ghana, South Africa, India, Nepal, Indonesia and Vietnam established for the recruitment of COVID-19 subjects.

In Asia, there is a growing interest in conducting clinical research which has taken on increased importance in light of the COVID-19 pandemic. There is potential to learn from the experience of the RECOVERY trial and apply it going forward in Asia. To this end, the Saw Swee Hock School of Public Health, National University of Singapore (SSHSPH NUS), is organising a meeting with the Co-Chief Investigator of the RECOVERY trial, Prof. Peter Horby, in collaboration with the Thai National Health Foundation (NHF) and the Health Intervention and Technology Assessment Program (HITAP).

Lessons from the RECOVERY Trial

Assoc. Prof. Hsu Li Yang opened the meeting with a discussion with Prof. Peter Horby about the launch of the RECOVERY Trial in the UK and the preconditions that allowed for rapid scaling of the trial. Both the speed with which RECOVERY was set up, as well as the sustainable model of the platform trial have contributed to the success of the RECOVERY Trial.

The RECOVERY Trial started in the UK, where both the National Health Service (NHS) and the National Institute for Health and Care Research (NIHR) were integral for quick implementation. The NHS provides a single, central electronic data collection infrastructure that is easily employed for the purpose of clinical trial research. The NIHR funds research infrastructure within hospitals, which helps incentivize hospitals to participate in research by supplementing healthcare costs. For example, the NIHR funds a network of research nurses in hospitals around the UK, which both simplifies training of personnel for clinical trials and ensures that funding is funneled into research and not lost within the hospital system, which often results when money is given directly to a hospital. During COVID-19 the NIHR suspended funding to most clinical trials and only funded a few priority trials, which included RECOVERY. This type of prioritization was only possible because there was central control over funding. Additionally, nationally recognized ethics review within the UK significantly reduced the time it took to receive approval. Centralized approval can also be done internationally; for example, in Africa multiple national ethics committees agreed to recognize approval from a central, combined committee board.

One of the benefits of the platform trial is the flexibility that it provides. For example, the RECOVERY Trial proposal made clear it would start with a set of repurposed drugs, but would add amendments for new drugs. The protocol has now undergone 25 versions. This design has proven to be very efficient. The RECOVERY Trial costs about 500 USD per patient, and 50 USD per answer. By comparison, a typical pharmaceutical trial costs about 50,000 USD per patient.

Simplicity of the research protocol was another advantage of RECOVERY. Only essential data was collected in order to answer the central question. Consent and case report forms (CRF) were short and online, allowing for easy implementation and centralized updating. RECOVERY aimed to collect small amounts of data from a large number of patients, resulting in statistical simplicity that is easy to interpret. “Clinical trials are like Christmas trees; if you decorate them too much, they fall over,” said Prof. Peter. The more detailed and complicated the protocol, the more difficult and expensive it is to implement, and the less likely the results will be powerful. For example, in the US, none of the COVID-19 therapeutic clinical trials have showed mortality benefit because the trials are too small.

Selection criteria of drugs was overseen by a group of independent experts formed by the Medical Research Council (MRC), the COVID Therapeutics Advisory Panel (CTAP). CTAP screened drug submissions and made recommendations to RECOVERY Trial investigators, who could accept or reject these recommendations based on the expense, availability, etc. of the drug. Now, with fewer drug submissions, review and selection is done internally. Repurposed drugs were

used in the beginning due to their availability, such as dexamethasone, and investigation drugs were introduced later.

Another key area of success was the help of an experienced and comprehensive clinical trials unit (CTU). The RECOVERY Trial used an academic cardiology CTU, which had more experience running large multi-center trials than infectious disease CTUs, and could provide many services, such as a 24-hour helpline and website. The cardiovascular clinical trials being conducted by this CTU had been suspended during the pandemic, allowing for the RECOVERY Trial to leverage their knowledge and experience. In addition to offering many resources, the CTU can help respond to inspections so that the trial meets regulatory standards.

One of the challenges to the RECOVERY Trial has been the name, surprisingly. RECOVERY was set up to study COVID-19 therapeutics, as the name suggests. When proposing to include flu therapeutics as well, regulators opposed this initially, citing that a trial cannot be extended if it has different objectives. Prof. Peter said he would make the study name and objectives broader, if he could do things differently. Additionally, he would have done more intensive compliance monitoring. It was difficult to keep track of documentation, especially during COVID-19 when hospital systems were already under stress. This led to issues with consent compliance, particularly around the use of proxies and document tracking. RECOVERY has also been criticized for lack of safety monitoring by regulators.

Setting up RECOVERY during the COVID-19 pandemic presented a unique context that mitigated some obstacles to clinical research trials, while worsening others. Given the urgency of the situation, speed and feasibility was essential. RECOVERY Trial took advantage of the fact that patients would be receiving drugs regardless of a clinical trial. Randomization at the patient interface allowed these drugs to be compared under RECOVERY Trial. Other measures were taken to expedite trial set up, such as not allowing hospitals to negotiate contracts; they had one contract option they could accept or deny. The pandemic also changed how quickly data was released to the public. Investigators released results from the trial based on the perceived immediate need or benefit of this information. For example, it was clear early in the trial that dexamethasone provided a benefit to patients, and given it is available in most pharmacies, they decided to release these results before all patients had completed 28 days per protocol. However, with other drugs that showed no benefit, or perhaps were not widely available, they did not release data early.

Expanding the trial internationally has been slower, as many countries do not have the same systems in place as the UK. For example, many countries do not have data linkage already available, specifically with national death registrations, requiring more follow up at sites. Additionally, negotiation with hospital clusters was unavoidable. Monitoring of the trial was done through regional sub-contracting and regional CTUs.

Funding for platform trials is becoming more common, however it may be difficult to find sustainable funding. Another area of concern is lack of representation from LMICs, especially in leadership, of platform trials. The capacity required to run a platform trial is significant, however

can be eased by a simple trial design and minimalist dataset. Regulators from LMICs can look to the simplicity and cost effectiveness of RECOVERY Trial to guide their own platform trials. Another approach to increase representation in leadership is to set up a platform trial with different domains, in which domain leaders are different countries. This would allow for centralization, but provide experience for LMICs on running platform trials.

Although it may be unfeasible for countries to nationalize their healthcare systems in the near future, steps can be taken to pave the way for successful clinical research trial platforms. For example, centralizing ethics review or setting up a funding scheme similar to that of the NIHR has proven to be very efficient. Singapore has started to move towards a similar funding approach via Centre Grants, in which funding is provided for individual research groups in hospital clusters. These changes can be made gradually, similar to how the UK set up national research approval, starting with site level approval to regional approval, and finally to regional ethics committees with national authorization. Another approach, as suggested by Prof. Peter, would be to develop a central approval process that a network of major hospitals within the country will accept.

It was noted by both colleagues from Singapore and Thailand that convincing policymakers to make these changes may be challenging. Prof. Peter suggested that one of the best ways to convince policymakers is to demonstrate the impact of these systems. If you can start small and prove effectiveness, they are more likely to accept changes.

As a result of this meeting, the clinical consortium lead by the NHF in Thailand has taken steps to join the RECOVERY Trial, alongside several other Asian countries, including Nepal, Indonesia, and Vietnam. Additionally, another event has been tentatively planned later this year in Thailand with Prof. Peter that will be open to the public. Key stakeholders in Thailand, including the FDA, funders, and ethics committees, will be invited to discuss clinical research infrastructure in Thailand, and what changes can be made to support clinical research in response to public health emergencies.

Appendices

Appendix 1: Agenda



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Lessons from the RECOVERY Trial for Asia

The RECOVERY Trial:

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial was established by Professor (Sir) Peter Horby (Oxford Nuffield Department of Medicine) and Professor Martin Landray (Oxford Population Health) in March 2020 to address the clinical uncertainties in the treatment of COVID-19 – a novel disease for which no proven therapeutic options were available. It was jointly funded by the UK Research and Innovation (UKRI)'s Medical Research Council (MRC) and the National Institute of Health Research (NIHR).



It was clear that RECOVERY required a mechanism for conducting randomized controlled trials (RCT's) at a large scale in order to provide robust clinical evidence, recruiting patients in their thousands. This was achieved by means of a disruptive pragmatic trial design which focused on collecting small amounts of data on large numbers of subjects, while also making use of the National Health Service's (NHS's) electronic healthcare data collection system which already gathered data as part of routine care.

Within 2 weeks of the grant being awarded, the first patient was recruited on March 19th 2020. Within the first hundred days, it had delivered key results on hydroxychloroquine (no clinical benefit), lopinavir/ritonavir (no clinical benefit) and dexamethasone (effective in reducing mortality in hospitalized patients). At present, more than 47,000 subjects across 198 trial sites in UK have been recruited, with definitive results delivered for 10 therapeutic agents. The platform trial is still going strong, with RECOVERY International having been launched which includes sites in Ghana, South Africa, India, Nepal, Indonesia and Vietnam established for the recruitment of COVID-19 subjects.

Discussion with Professor (Sir) Peter Horby

We have organized a closed hybrid meeting with Prof Horby in Singapore on 30th June 2022 at 10:00 – 11:30 am Singapore time/9:00 – 10:30 am Thai time. The objectives are:

- To learn about the lessons of implementing the RECOVERY trial and potential application to Asia for creating platforms for clinical research; and,
- To identify potential areas for collaboration among participants involved in establishing research networks for clinical research.

Participants include representatives from: National University of Singapore (NUS), Singapore; National University Hospital, Singapore; Thai Ministry of Public Health; National Health Security Office (NHSO); Ramathibodi Hospital; National Health Foundation (NHF); Health Systems Research Institute (HSRI); Access and Delivery Partnership (ADP); Rockefeller Foundation; Health Intervention and Technology Assessment Program (HITAP); and partners from academic and governmental organisations in Asia.

The meeting will be conducted in English. Simultaneous translation in Thai will be provided.

Agenda:

| Time (SGT) | Particular | Description | Speaker(s) |
|-------------------|-------------------------------------|---|--|
| 10:00 – 10:15 am | Welcome and opening remarks | Introduction of participants and objective of meeting | Assoc. Prof. Hsu Li Yang |
| 10:15 – 10:45 am | Conversation with Prof. Peter Horby | <ul style="list-style-type: none"> • What are the pre-conditions for success of the RECOVERY or similar platform trial? • What are some of the lessons learned - both scientific and operational - in running the RECOVERY trial? • What is the future of such a network of sites? • What would be your advice for low-and-middle income countries or to researchers in multi-country networks in establishing such platforms, particularly drawing on the experience with Ebola? | Prof. Peter Horby and Assoc. Prof. Hsu Li Yang |
| 10:45 – 11:25 am | Open discussion with participants | <ul style="list-style-type: none"> • Q&A • Identifying potential areas for collaboration | All |
| 11:25 – 11:30 am | Closing remarks | <ul style="list-style-type: none"> • Summary of key points | Assoc. Prof. Hsu Li Yang |

The meeting will be recorded for reference purposes.

Expected outcome

Key points from the meeting will be summarised for future reference.

Speaker biography

Sir Peter Horby is Professor of Emerging Infectious Diseases and Global Health at the University of Oxford and the Director of the Pandemic Sciences Centre. The Pandemic Sciences Centre is a multidisciplinary initiative to create collaborative science-driven solutions to identify, prepare for, and counter pandemic threats. He is also Executive Director of the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC), a consortium of international, national and local research networks whose research activities span 134 countries worldwide.

He is Co-Chief Investigator of the RECOVERY trial of treatments for viral pneumonia.

He has advised the World Health Organisation, the UK Government and other agencies on epidemic preparedness, clinical research and clinical trial design for epidemic infectious diseases.

He is the former, and founding, Director of the Oxford University Clinical Research Unit in Hanoi, Vietnam. The unit was established in early 2006 and conducts research on infectious diseases which crosses the disciplines of basic science, medical science and public health.

Source: <https://www.ndm.ox.ac.uk/team/peter-horby>

Resources:

- <https://www.recoverytrial.net/>
- <https://www.ukri.org/news-and-events/tackling-the-impact-of-covid-19/vaccines-and-treatments/recovery-trial-identifies-covid-19-treatments/>
- <https://www.nejm.org/doi/full/10.1056/nejmoa2021436>

Appendix 2: Participant List

| No. | Name | Organization, Country |
|------------|--|------------------------------------|
| 1 | Assoc. Prof. Alex Cook | SSHSPH NUS, Singapore |
| 2 | Dr. Cherdchai Nopmanee-jumruslers | Siriraj Hospital, Thailand |
| 3 | Prof. David Paterson | SSHSPH NUS, Singapore |
| 4 | Dian Faradiba | HITAP, Thailand |
| 5 | Dimple Butani | HITAP, Thailand |
| 6 | Evan Huang Ku | HITAP, Thailand |
| 7 | Ella Nanda Sari | HITAP, Thailand |
| 8 | Assoc. Prof. Hsu Li Yang | SSHSPH NUS, Singapore |
| 9 | Kanchanok Sirison | HITAP, Thailand |
| 10 | Dr. Katika Akksilp | DMS MOPH, Thailand |
| 11 | Assoc. Prof. Hsu Li Yang | SSHSPH NUS, Singapore |
| 12 | Madison Silzle | HITAP, Thailand |
| 13 | Manit Sittimart | HITAP, Thailand |
| 14 | Dr. Mo Yin | NUH, Singapore |
| 15 | Dr. Nicholas Ngiam | NUH, Singapore |
| 16 | Prof. Ooi Eng Eong | Duke-NUS Medical School, Singapore |
| 17 | Oxford University Clinical Research Unit (OUCRU) | Vietnam |
| 18 | Prof. Peter Horby | Oxford University, UK |
| 19 | Prof. Pisake Lumbiganon | Khon Kaen University |
| 20 | Pitchawee Aksonchuen | HITAP, Thailand |
| 21 | Dr. Piya Hanvoravongchai | NHF, Thailand |
| 22 | Prof. Prasert Auewarakul | Mahidol University |
| 23 | Sarin KC | HITAP, Thailand |
| 24 | Saudamini Dabak | HITAP, Thailand |
| 25 | Dr. Sean Ong | NCID, Singapore |
| 26 | Dr. Silaporn Buasai | TRF, Thailand |
| 27 | Dr. Somsak Chunharas | NHF, Thailand |
| 28 | Assoc. Prof. Tai Bee Choo | SSHSPH NUS, Singapore |
| 29 | Waritta | Thailand |
| 30 | Assoc. Prof. Yeo Tsin Wen | Tan Tock Seng Hospital, Singapore |
| 31 | Dr. Yot Teerawattananon | HITAP, Thailand |
| 32 | Yvonne Teo Hwee | SSHSPH NUS, Singapore |