Justification for RECOVERY Protocol V19.0

The trial steering committee wishes to extend the RECOVERY platform to investigate treatments for people admitted with influenza. The rationale is described in detail here.

Each year in the UK many thousands of people are admitted to hospital with influenza, of whom between 5-20,000 die depending on the circulating strain. There are no approved treatments that have been shown in randomised trials to improve survival in patients hospitalised with influenza. It is anticipated that the number of cases of influenza in the coming winter (2021/22) will be particularly high because social measures taken to restrict the transmission of SARS-CoV-2 also limited transmission of other respiratory viruses, so levels of immunity in the community are low. There is therefore a possibility that a large number of patients will be admitted with (and die from) influenza in the coming winter with some estimates more than double the number of deaths.[1] It is also likely that a significant number of patients will be coinfected with both SARS-CoV-2 and influenza and data from Public Health England suggest that this result in a particularly high risk of bad outcomes,[2] a concern recently discussed by SAGE.[3]

The RECOVERY platform is ideally positioned to address this important public health issue alongside its ongoing assessments of therapies for COVID-19. While developing this protocol amendment we have considered the guidance on the conduct of complex trials produced EMA Clinical Trial Facilitation Group in February 2020[4] and the commitments embodied in the G7 Clinical Trials and Vaccines Charter[5] and the Pandemic Preparedness Roadmap[6] which were informed by the experience of the COVID-19 pandemic and published in June 2021.

The RECOVERY trial was initiated at speed (draft protocol to first patient enrolled in 9 days) in order to ensure that the study could be established across the NHS in advance of the peak of the first wave of the pandemic in Spring 2020. By moving rapidly and focussing initially on the immediate needs of the public health crisis (i.e. COVID-19) it was possible to demonstrate both the benefits of dexamethasone and the futility of hydroxychloroquine in this patient group. (If trial initiation and roll-out had been delayed by about 2 weeks it is quite likely that those results would have taken a further 6 months to emerge given the low level of cases during Summer 2020.)

Not only is RECOVERY trial the largest trial (>44,000 participants) of potential treatments conducted in this or any previous pandemic, it is the first to produce results that are both compelling and sufficiently timely to change international treatment guidelines during the course of such a public health crisis. For example, the clear results of the dexamethasone comparison (which at the time some experts advised should not be conducted due to potential safety issues) have been estimated to have saved over 1 million lives.[7] RECOVERY has now identified 3 treatments that improve survival (dexamethasone, tocilizumab, casirivimab/imdevimab) for these patients. Just as importantly, it has identified 6 others that have no meaningful effect (including hydroxychloroquine, which at the time many experts advised should not be studied as they believed that withholding it would be denying patients a beneficial treatment).

Our proposal to expand RECOVERY to include seasonal influenza is consistent with and contributes to the UK's delivery of the recommendations of the G7 Roadmap for Pandemic Preparedness, endorsed by the leaders of the G7 and the EU in June 2021.[6] That report highlights the need for large, adaptive, randomised platform trials. It emphasises that these should not be 'protocols on shelves' but should be 'ever active' addressing relevant public health questions and ready to the tackle the needs of pandemics when they occur.

Our proposal is also consistent with the terms of the award letter for RECOVERY which states that, as Chief Investigators, we are expected to "*Help develop a legacy that puts UK clinical trials at the heart of a forward-looking 'post-COVID' life sciences agenda for economic growth and better health*." We have discussed our plans to expand the population group in RECOVERY with the Department of Health and Social Care, who are fully supportive.

We believe there is strong public health, scientific, quality assurance, safety and operational value in amending the protocol to include influenza at this stage. Conversely, there are significant downsides in all these areas from independent protocols.

We hope the MHRA, HRA and REC will carefully consider our position, cognisant of the unusual circumstances of RECOVERY initiation and the ongoing healthcare emergency in the UK. Mindful of the CTFG guidance (Feb 2020), we have provided further details and justification below:

1. Study design:

Although the original protocol focussed on COVID-19, the key design features described in the protocol are equally applicable to influenza pneumonia or indeed any other viral pneumonia (including future pandemics). Namely:

- large-scale enrolment of patients hospitalised with viral pneumonia
- randomisation to one or more potential treatments in addition to usual standard of care vs. usual standard of care alone
- evaluation (using intention-to-treat analyses) of the effects on mortality, duration of hospital admission, and the composite of invasive mechanical ventilation or death
- integration of the trial processes within NHS hospital practice and incorporation of information held in routine healthcare datasets (e.g. those held by NHS Digital)

We note that the CTFG guidance is not written with a view to emergency clinical studies developed at times of great uncertainty. Discussions with DHSC and our funders (UKRI and NIHR) about potential expansion to influenza and other viral infections commenced in Summer 2020 but the protocol has not been modified in this respect since the COVID-19 pandemic continued and case numbers of influenza remained very low. The situation is quite different now, with large numbers of hospitalisations for influenza anticipated and co-infections highly likely (with severe consequences and no proven treatments).[1]

Our proposal is to broaden the eligibility criteria to include patients with confirmed influenza infection (either alone or, importantly, in combination with SARS-CoV-2), but otherwise the design remains the same. The proposed design allows robust assessment of the effects of potential treatments for SARS-CoV-2 and influenza, both separately and in combination, in a way that would not be possible if there were two separate trials. Therefore, we consider this to be an extension of the study population rather than a change in the overall hypothesis or study design. We do not believe a new master-protocol is necessary or feasible.

2. Scientific integrity:

The original protocol was focussed on COVID-19 because it was the only viral pneumonia in circulation at the time of the submission. Elements of the protocol (including the original dexamethasone comparison) were adapted from existing protocols for pandemic influenza (ASAP trial, EudraCT 2013-001051-12).

The scientific integrity (the ability to generate a clear, reliable and interpretable result) with respect to COVID-19 mono-infection is unaffected by this amendment. The scientific integrity

with respect to studying influenza mono-infection is unaffected by inclusion in a single protocol with COVID-19. The scientific integrity with respect to co-infection is much stronger in a combined protocol.

3. Trial conduct and feasibility:

The CTFG guidance is concerned with the clinical feasibility of complex trials. It is clear in this case that a single protocol (which is actually straightforward in terms of care pathways, inclusion and randomisation) has substantially greater clinical feasibility than independent protocols.

Patients will receive information about the trial and can be guided by their clinicians about which sections are relevant according to which infection(s) they have. The overlap is substantial so the burden on patients (e.g. in terms of the amount of information to read and consider) which be much less. Similarly, research teams will simply need to confirm which infection(s) the patient has and the IT system will then seek information on the availability and suitability of relevant treatments. It will be no more complex recruiting patients with a combined protocol.

By contrast, creating a new master protocol or initiating a second trial focussed purely on influenza would add substantial burden for NHS hospitals and clinicians, local investigators and the trial coordination team. The duplication of effort (including, *inter alia,* contracts, training, monitoring, data management, linkage to routine NHS data sources, clinical oversight, safety reporting) would add delay, cost, and potential for errors (with negative impact on both the quality of the results and the safety of the participants).

For example, running two parallel trials would have significant disadvantages because coinfected patients would have to be asked to join two trials (with separate consent forms) at a time of significant illness. RECOVERY has worked hard to be integrated into clinical care pathways to facilitate recruitment, and introducing a second protocol would double the work required by hospital staff who are already under significant pressure. This may reduce recruitment into either trial, to the detriment of both.

Given the enormous pressures that remain on NHS and NIHR staff as a direct and indirect result of the pandemic, it is highly unlikely that a separate trial of influenza could be implemented this winter (2021/22). Such a delay would extend the period during which clinicians are forced to make treatment decisions in the absence of reliable evidence. The consequence would be continued under-use of treatments that later turn out to be effective (as was the case with dexamethasone) or the over-use of treatments that later turn out to be of no benefit (as was the case with hydroxychloroquine and azithromycin) or are even harmful.

4. Participant safety and risk-benefit balance:

Broadening RECOVERY to include influenza will facilitate participant safety because hospital staff will not need to be familiar with two protocols or sets of trial procedures. In addition, the current trial IT systems can be readily modified to ensure that coinfected participants are not recruited to incompatible comparisons (e.g., participants with COVID-19 and influenza coinfection could not be allocated to usual care in the assessment of dexamethasone in the influenza protocol (since dexamethasone is indicated for COVID).

The highly-experienced RECOVERY independent Data Monitoring Committee, which includes clinicians experienced in the management of viral pneumonia and statisticians experienced in

the analysis of multi-factorial trials) would oversee all participants with a particular focus on coinfected individuals. This would be far more challenging with separate protocols, and also potentially separate DMCs. The DMC already meet at least monthly and would advise the chief investigators and steering committee if in their opinion the protocol required modification (including stopping a comparison) for either patient safety or efficacy.

If any additional arms beyond those described here were added to the protocol (for either COVID-19, influenza or other viruses), the risk-benefit analysis would be described in a justification document and the trial's overall risk-assessment updated.

5. Data integrity:

As described above, the required data are the same for COVID-19 and influenza. The addition of influenza to the RECOVERY protocol therefore does not pose any threat to data integrity. It would require duplicate feeds of data from routine sources (e.g. NHS Digital) increasing the potential for issues relating to information governance, data transfer, and data processing and analysis. This creates a risk of either missing data or discrepant data which would require significant resources to monitor and mitigate.

6. Companion diagnostics:

The trial already uses diagnostic assays in routine clinical use and validated for this use. The diagnostic tests for influenza and SARS-CoV-2 are already mature, in widespread use in the NHS, and subject to laboratory quality assurance programmes. Such testing is already required because of the availability for therapies proven to be effective in COVID-19 (e.g. dexamethasone, tocilizumab and casirivimab+imdevimab). The proposed protocol amendment introduces no additional issues with respect to companion diagnositics.

7. Data transparency:

The RECOVERY trial has completed recruitment for 11 IMPs in COVID-19 (and the related PIMS-TS syndrome). Follow-up and analysis is completed for 9 of these and they have been published in major medical journals (or a pre-print is available while the manuscript is under peer review; the protocol includes a table pointing to these open access publications). Data analysis is ongoing for the 2 IMPs for which recruitment was completed most recently, and these will be made available in a similar way.

Investigational Medicinal Products

The treatments that have been proposed to be assessed are:

1. Low-dose dexamethasone: RECOVERY and other randomised trials have now demonstrated the benefit of corticosteroids in hypoxic COVID-19 patients.[8,9] However, the potential role of corticosteroids in severe influenza remains uncertain, with differing practices and controversy. Whilst observational studies report higher mortality associated with the use of corticosteroids in severe influenza, these studies are prone to biases, with a major concern being confounding by indication (the propensity to use corticosteroids only in the more severe patients as a rescue therapy).[10] In practice, use of corticosteroids in severe influenza is variable and widespread.[11] This therapeutic dilemma will only be resolved through an adequately powered randomised trial.

   Children and pregnant women: Steroids are widely used in all ages for many indications and RECOVERY assessed steroids in all ages for COVID-19. They were also tested in pregnant women, although alternative corticosteroids (rather than dexamethasone) were used, as guided by topic experts. We therefore wish to assess dexamethasone (or equivalent doses of other corticosteroids as required) in all ages and in pregnant women.

2. Oseltamivir: The neuraminidase inhibitors (oseltamivir and zanamivir) are influenza specific antivirals that have been shown in randomised controlled trials to improve outcomes in uncomplicated influenza and to be effective as post-exposure prophylaxis. They have not, however, been shown to be effective in patients hospitalised with severe influenza. Although observational studies have reported clinical benefit in patients hospitalised with severe influenza, there are no randomised controlled trial data. Consequently, the use of neuraminidase inhibitors in this patient population is variable. A randomised controlled trial of neuraminidase inhibitors in patients hospitalised with severe influenza has been recommended by an expert group convened by the Academy of Medical Sciences and the Wellcome Trust, and most clincians would welcome such a trial.[12,13] The dose being tested is that used in routine clinical practice already ie, 75 mg twice daily in adults.

   The protocol is designed such that clinicians who wish to treat a patient with oseltamivir may do so, but still enter the patient (if willing) into other comparisons within the influenza part of RECOVERY. This will provide valuable information on the effects of the other treatments in the presence or absence of neuraminidase inhibitors.

   Children and pregnant women: Oseltamivir is widely used in all ages in routine practice and there are observational data on the use of oseltamivir in pregnant women including >1000 women exposed during the first trimester. These studies found no evidence of adverse embryo-fetal effects. Oseltamivir is currently used in pregnant women. Its use may also be considered in breastfeeding women: it is excreted in breast milk but at low concentrations that would be subtherapeutic dose to the infant. We therefore wish to assess oseltamivir in all ages and in pregnant women.

3. Baloxavir: Baloxavir marboxil is a cap-dependent endonuclease (CEN) inhibitor. CEN is an influenza virus-specific enzyme in the polymerase acidic subunit of the viral RNA polymerase complex. Through its action on CEN, baloxavir inhibits the transcription of influenza virus genomes resulting in inhibition of influenza A and B virus replication. It is approved in the USA, Japan, Australia, Europe, and the United Kingdom for the treatment of uncomplicated influenza and for post-exposure prophylaxis in individuals

aged 12 years and older. Baloxavir is given in 2 oral doses and is well tolerated, with allergic reactions being the only reported adverse reactions.

Baloxavir is not approved for the treatment of complicated influenza. A phase III placebo-controlled trial of baloxavir in adults hospitalised with severe influenza (Flagstone NCT03684044) did not find a significant reduction in the primary endpoint of time to clinical improvement (personal communication, Roche). However, time to clinical improvement, time to clinical response, influenza related complications, mortality, and time to cessation of viral shedding were all in favour of baloxavir. Fewer adverse events were observed in the baloxavir arm than in the standard of care arm. The Flagstone trial was small, comparing 214 subjects who received baloxavir with 125 who received usual care alone, and a larger study is need to determine whether baloxavir has modest but clinically relevant benefit in patients hospitliased with influenza. RECOVERY will test the same dose used in the Flagstone trial which showed good antiviral effects.

Children and pregnant women: Baloxavir is licensed for children aged at least 12 years old so we wish to assess it in this population. Approval to extend this age range will be sought if information becomes available in the future to support this.

We have sought specific advice from the National Teratology Service as there are no data from the use of baloxavir marboxil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Baloxavir treatment may be of particular benefit to pregnant women with influenza, as they are at increased risk of developing severe disease. Preclinical animal models of exposure in pregnancy do not provide evidence of adverse embryo-fetal effects at doses up to five and seven times the human therapeutic dose respectively. The risk of harm from baloxavir in pregnancy is likely to be low given the animal model data, together with the therapeutic target for baloxavir being a virus specific enzyme. It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk, and baloxivir may be considered.

Other protocol modifications

Other modifications to the protocol include a change to the primary outcome for patients with influenza. The case fatality rate is much lower than COVID-19 (typically about 3%) so we will add a co-primary outcome of time to discharge alive from hospital. The details of how these analyses will be conducted will be specified in the trial's Statistical Analysis Plan including additional details of Holm's method to control for type 1 error within the co-primary outcome.

It is possible that patients will present with both COVID-19 *and* influenza. The table below clarifies which arms they would be eligible for. This would all be controlled by the trial IT system to ensure that patients were not allocated a treatment that was not suitable for them due to their co-infection.

Condition	Randomised comparisons, each vs. usual care alone	UK	India	Other countries
COVID-19	Dimethyl fumarate[a]	✓ (age ≥18 years)[b]	×	×
	Baricitinib	✓ (age ≥2 years)[b,c]	✓ (age ≥18 years)[b]	×
	High-dose corticosteroids	×	×	✓ (age ≥18 years with hypoxia)[b]
	Empagliflozin	✓ (age ≥18 years)	×	✓ (age ≥18 years)
PIMS-TS	Tocilizumab or anakinra	✓ (age ≥1 <18 years)	×	×
Influenza	Baloxavir	✓ (age ≥12 years)	×	×
	Oseltamivir	✓ (any age)	×	×
	Low-dose corticosteroids	✓[d] (any age with hypoxia)[d]	×	×

[a] an Early Phase Assessment collecting additional information on efficacy and safety; [b] without suspected or confirmed influenza infection; [c] children with COVID pneumonia; [d] without SARS-CoV-2 infection.

References

1. Academy of Medical Sciences. COVID-19: Preparing for the future2021.
2. Stowe J, Tessier E, Zhao H, et al. Interactions between SARS-CoV-2 and Influenza and the impact of coinfection on disease severity: A test negative design. Int J Epidemiol 2021;50:1124-33.
3. SAGE 96 minutes: Coronavirus (COVID-19) response. 2021. (Accessed 23 October 2021, at https://www.gov.uk/government/publications/sage-96-minutes-coronavirus-covid-19-response-14-october-2021/sage-96-minutes-coronavirus-covid-19-response-14-october-2021.)
4. Recommendation paper on the initiation and conduct of complex clinical trials. 2020. at https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf.)
5. G7 Therapeutics and Vaccines Clinical Trials Charter. 2021. at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/991582/G7-clinical-trials-charter.pdf.)
6. 100 days mission to respond to future pandemic threats. 2021. at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/992762/100_Days_Mission_to_respond_to_future_pandemic_threats__3_.pdf.)
7. COVID treatment developed in the NHS saves a million lives. 2021. at https://www.england.nhs.uk/2021/03/covid-treatment-developed-in-the-nhs-saves-a-million-lives/.)
8. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704.
9. W. H. O. Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA 2020;324:1330-41.

10. Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Shen Lim W. Corticosteroids as Adjunctive Therapy in the Treatment of Influenza: An Updated Cochrane Systematic Review and Meta-analysis. Crit Care Med 2020;48:e98-e106.
11. Hui DS, Lee N, Chan PK, Beigel JH. The role of adjuvant immunomodulatory agents for treatment of severe influenza. Antiviral Res 2018;150:202-16.
12. Bradbury N, Nguyen-Van-Tam J, Lim WS. Clinicians' attitude towards a placebo-controlled randomised clinical trial investigating the effect of neuraminidase inhibitors in adults hospitalised with influenza. BMC Health Services Research 2018;18:311.
13. Academy of Medical Sciences, Wellcome Trust. Use of Neuraminidase Inhibitors in Influenza. 2015.