

Justification for RECOVERY Protocol V23.0

(including response to MHRA notice of non-acceptance to protocol V22.0)

This document is a detailed justification for the changes to the RECOVERY protocol in version 23.0, some of which have been made in response to the notice of non-acceptance from MHRA to protocol V22.0. The MHRA's comment is shown in *italics* below followed by the trial team's response.

1. *Due to the limited data available regarding Paxlovid use in pregnancy it is not currently possible to make an informed decision regarding the drug-associated risk of adverse developmental outcomes. Therefore, the SmPC states that Paxlovid is not recommended during pregnancy. Taking into consideration the fact that there are treatment options suitable for pregnant women it is not deemed appropriate to administer Paxlovid to pregnant women in the RECOVERY trial.*

Response: Pregnant women are continuing to be admitted to hospitals in the UK in high numbers (Figure 1) on the basis of the UK Obstetric Surveillance System (UKOSS) study of hospitalisation with covid-19 in pregnancy. Approximately half of women admitted are symptomatic,¹ and most recent data indicate that of those that are admitted who are symptomatic, around a third require respiratory support, 16% receive intensive care and 1% die.² The current maternal mortality rate is approximately 50% higher than the usual background rate, entirely due to an excess of COVID-19 deaths in unvaccinated pregnant women (confidential data from MBRRACE-UK presented to the JCVI on December 2nd 2021).³ Vaccine hesitancy remains high in pregnancy, with the best recent estimates suggesting that around 50% remain unvaccinated.^{4,5} As a consequence of these data pregnant women were moved into an 'at risk' group for priority vaccination by the JCVI.³

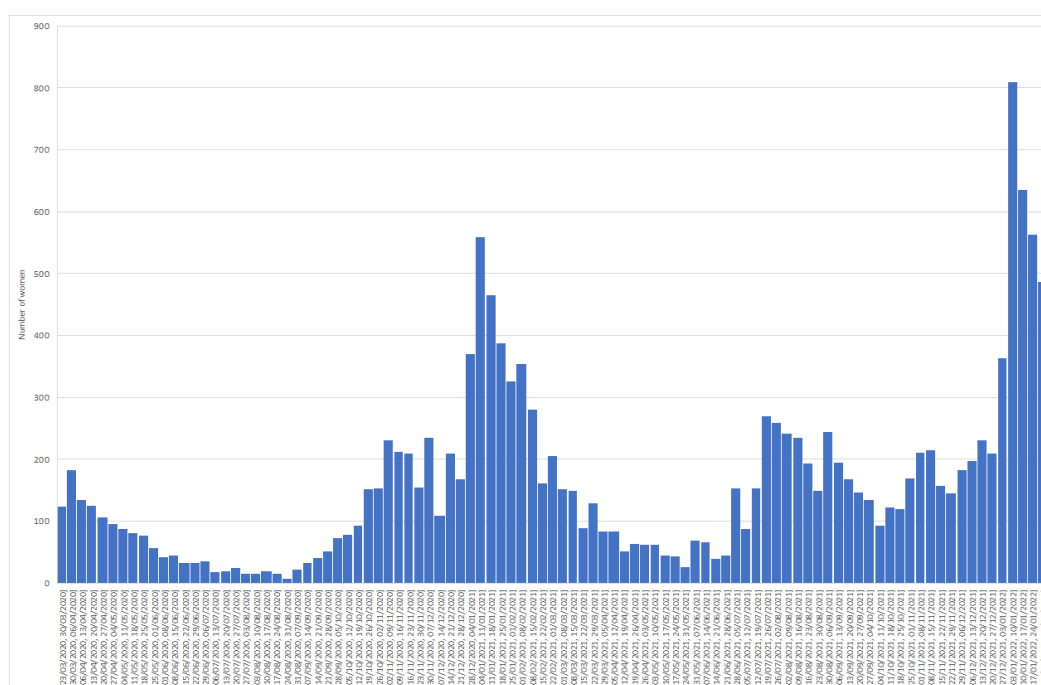


Figure 1: Notified admissions of pregnant women to hospital with a positive SARS-CoV-2 test within the previous 7 days, UK Obstetric Surveillance System (UKOSS) unpublished data 02/02/2022

A specific analysis of the UKOSS data (unpublished) to inform DHSC occupational health guidance showed that 75% of women admitted with symptomatic COVID-19 in pregnancy are 28 weeks or greater gestation, 90% are 22 weeks or greater gestation. 96% of these women admitted are unvaccinated. 75% of women admitted to intensive care with COVID-19 are 26 weeks or greater gestation, 90% are 23 weeks or greater gestation. 98% of these women admitted are unvaccinated. The vast majority of severe disease therefore occurs in the second half of pregnancy when organogenesis is complete and the risk of teratogenesis is very low.

An independent assessment by the UK Teratology Information Service⁶ considers that *“Despite the lack of human pregnancy safety data for [Paxlovid], there may be specific circumstances where the benefits of use during pregnancy could outweigh the risks. Such circumstances may include the use in women at high risk of developing severe disease (due to non-vaccination status or clinical vulnerabilities), or in women experiencing severe symptoms of COVID-19 where other more established treatments have failed.”* The assessment notes that no concerns about the use of Paxlovid have been identified on the basis of animal reproductive toxicity studies using high doses of the drug.⁶ On the basis of the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group guidance ethical principles which state that *“Justice requires that pregnant women have fair access to research that offers the prospect of direct benefit”*,⁷ pregnant women will be included in the Paxlovid arm of the RECOVERY trial. On the basis of the UKTIS assessment, women included will be those experiencing severe symptoms of covid and in later pregnancy (second or third trimester) as this is the population where the potential benefits most clearly outweigh any theoretical risks.

All pregnant women receiving Paxlovid as part of the RECOVERY trial will be followed up through UKOSS until hospital discharge to ascertain maternal and infant outcomes. All pregnant women and infants will be further followed up through the statutory processes of the UK Teratology Information Service to identify pregnancy outcomes (if women had not given birth at hospital discharge), congenital anomalies and neonatal complications through structured telephone interviews and/or mailed questionnaires sent to the mothers or their healthcare providers and/or linked data sources.

As Paxlovid is not yet available in the UK, RCOG guidance on coronavirus in pregnancy does not include current reference to its use. Previous guidance has been updated in line with NHS and UKTIS advice and an updating process is currently underway. We do not have final update wording. The current guidance states that *“Other therapies are being investigated for the management of COVID-19, and pregnant women should be offered the opportunity to enrol in clinical trials (such as the RECOVERY trial) for which they are eligible.”*

There is equipoise over whether Paxlovid is efficacious in the treatment of acute, symptomatic covid-19 in pregnancy. Phase 2/3 studies have demonstrated considerable improvements in hospitalisation and mortality in an at-risk non-pregnant population. Although the non-pregnant population are not directly comparable, pregnant women admitted with symptomatic COVID-19 are at significant risk of disease progression. The risks to the baby are uncertain because Paxlovid is new, however, there are no safety concerns from animal data nor from its mechanism of action, since it targets viral proteases only. Data from RECOVERY will define the benefit of Paxlovid in acutely unwell pregnant women and provide novel safety data that is highly beneficial and is likely to inform national treatment guidelines for COVID-19 in pregnancy. Pregnant women should not be denied the

opportunity to be able to participate since there are potential benefits to themselves and the pregnant population as a whole. The trial protocol has therefore been revised:

- To exclude women in first trimester (ie, first 12 weeks) of pregnancy.
 - Follow-up of the mothers and their babies is now described (using the UK Obstetric Surveillance System).
2. *The document entitled 'Justification of substantial amendment for RECOVERY protocol V22.0' states the following: "It will therefore be possible to assess each antiviral when given as monotherapy or in combination with other antivirals". The use of drug combinations is not acceptable based on the current protocol version because the protocol does not pre-specify which combinations will be used, which are the criteria for assigning a participant to a specific combination rather than to a monotherapy, which are the potential risks associated with each pre-specified combination and how they will be mitigated via eligibility criteria, safety monitoring, etc. In addition, the investigation of combinations requires the addition of specific statistical considerations to the statistical analysis section of the trial documentation (and subsequent regulatory approval).*

Combination therapies have in effect been part of the RECOVERY protocol since tocilizumab was added to the protocol in May 2020. The factorial nature of the randomisations allows the each treatment to be assessed in the presence or absence of other randomised treatments (e.g. tocilizumab in the presence or absence of dexamethasone, or aspirin in the presence or absence of colchicine). For the avoidance of doubt, the trial has not randomised participants between, for example, a combination of drug A and drug B versus control, but rather has randomised eligible participants between drug A and control and, separately, drug B and control which naturally creates some participants who have both drug A and drug B (and some who have neither and some who have just one or the other). The availability of multiple antiviral therapies now allows a similar approach with them which is very important for two reasons. First, combination therapy *may* be more effective than monotherapy and possibly more effective than expected from knowledge of the efficacy of each drug alone (i.e. there may be synergy between the drugs). Second, combination therapy *may* reduce the risk of antiviral resistance developing (as has been demonstrated in other viral diseases such as HIV) and of treatment failure due to prior or treatment-emergent resistance to one agent. Both of these important questions can only be answered by testing combinations (as well as monotherapies). Combination therapy is a standard pillar of routine antimicrobial therapeutics approaches. The DHSC New and Emerging Respiratory Viruses Threats Advisory Group has stated "*Combination anti-viral therapy is, in theory, preferable to monotherapy in terms of a reduced risk of resistance and, possibly, improved clinical efficacy. There is, therefore, a pressing need to assess the safety, efficacy, and resistance potential of combinations of DAAs (and other) drugs.*"⁶

The RECOVERY protocol does include assessment of resistance based on nasal swab samples collected during treatment which will be sequenced to identify genetic resistance markers.

It is not possible to reliably predict which combinations are most worthwhile (indeed results of other comparisons in RECOVERY and other trials in COVID-19 have often contradicted the prevailing opinion of experts at the time). Instead, investigators will consider the suitability of each individual patient for the available treatments and randomisation will naturally create comparable groups of participants who are receiving one or more therapies.

The potential for interactions between all IMPs in the protocol has been considered (including the potential for combinations of more than two investigational medicinal products) and no significant interactions are expected with the exception of that between Paxlovid and high-dose dexamethasone (which could potentially create excessive dexamethasone plasma concentrations). This combination is described and excluded in the protocol (and enforced by the trial IT system). The combination of Paxlovid and standard-dose dexamethasone (6mg once daily for up to 10 days) is not of concern.

The statistical analysis of combination therapy will rely on tests for interaction between the randomised treatments (e.g. as was done in the tocilizumab paper where concomitant therapy with dexamethasone was of particular interest⁹). This will be described in more detail in an update to the trial's statistical analysis plan (available at <https://www.recoverytrial.net/results>). We can provide the Data Monitoring Committee with these analyses in the data they review so they can monitor the safety and efficacy of the combinations as well as the overall effects of each treatment.

3. *The protocol needs to remove any wording relating to continuation of paxlovid course at home. Home dosing is currently not acceptable due to the lack of clinical oversight in this scenario in RECOVERY. In particular participants on half dosing cannot receive such posology at home.*

Paxlovid is licensed for the treatment of patients at home. Prescribing of Paxlovid in the hospital setting in the context of a clinical trial is likely to provide greater oversight and mitigation of potential safety issues than prescribing in the community. The median duration of admission is greater than 5 days so most participants will complete their treatment course in hospital. Please see the response to 7 below about monitoring of participants after discharge.

Participants with moderately reduced kidney function (eGFR <60 mL/min/1.73m²) should only take half the dose of nirmatrelvir. Inspection of the Paxlovid packaging has demonstrated that it is entirely feasible to remove one of the two nirmatrelvir tablets from each dose without affecting the integrity of the remaining tablet (Figure 2). Because each participant allocated Paxlovid would be provided with their own Paxlovid packet (containing their complete course), local pharmacists will be instructed to remove the unwanted tablets before providing the treatment to the participant so there would be minimal risk of overdose if the course needs to be completed at home.



Figure 2: Picture of Paxlovid packaging demonstrating separation of nirmatrelvir blisters.

4. *The list of contraindicated medication needs to be amended and must state that the list is not exhaustive, but clinical judgement is required to evaluate other drugs that are not explicitly listed. The investigators should also be referred to the Liverpool COVID-19 drug interactions website: <https://www.covid19-druginteractions.org/>*

The reference to the summary of product characteristics has been replaced with a link to the Liverpool COVID-19 drug interactions website, and includes a warning that such lists may not be exhaustive.

5. *Footnote u must be removed. The protocol must not refer the investigators to the online SmPC for the list of contraindicated medications. The investigators need to refer only to the SmPC approved by the MHRA for use in this trial. Changes to the contraindications and/or drug-drug interaction guidance in the SmPC need to be reviewed by the Sponsor and can be implemented only after approval of a substantial amendment by the MHRA.*

As described above, this footnote has been amended to refer to the Liverpool COVID-19 drug interactions website and includes a warning that such lists may not be exhaustive.

6. *It does not appear appropriate to randomise to Paxlovid arm participants who are taking contraindicated drugs on the grounds that they will be temporarily withheld. The sudden change of treatment will constitute an additional risk for the participants and therefore this wording should be removed: "It may be appropriate to temporarily withhold such drugs while receiving Paxlovid". If the Sponsor insists on keeping this wording it must be clarified that it applies only to participants who have no other treatment options and the protocol must explain who will be responsible for managing the restarting of the withheld drugs.*

Managing short-term interactions between treatments is common-place in hospital medicine (e.g. the interaction between macrolide antibiotics and statins which necessitates temporary withdrawal of the statin until the antibiotic course is complete). Hospital teams would routinely provide guidance to patients and general practitioners about when such treatments could be safely restarted and if any checks (e.g. INR check in someone on warfarin) are required beforehand. In addition, all discharge medications are routinely checked by a pharmacist.

The current wording has therefore been replaced with the following: "Managing clinicians may consider if it is appropriate to temporarily withhold such drugs while receiving Paxlovid or consider alternatives. The risks and benefits of doing so should be explained to the participant. Clear plans should be made about restarting such treatment and – if necessary – any checks that need to be made beforehand. These plans should be communicated to the participant and their general practitioner in the discharge summary."

7. *The protocol must state that participants in randomisation part L will be monitored at least until the end of Paxlovid treatment course.*

All participants in RECOVERY are flagged with national databases and NHS records in order to collect information on death, hospital admissions and other important diagnoses (e.g. cancer) for several years after discharge from hospital. This ensures that follow-up for the primary outcome is complete (>99%). Such information will be available for the pre-specified 28 day and 6-month analyses so any effect of Paxlovid (or other RECOVERY IMPs) on cause-specific hospital re-admission will be available.

It is recognised that complete information about adherence to Paxlovid will not be available in the small number of participants discharged before they complete their course (although their adherence while in hospital will be collected). As all RECOVERY analyses are “intention to treat”, this lack of information will not have any bearing on the scientific validity of the trial.

We also wish to make the following changes to the protocol. The numbering below reflects the numbering in the Amendment Tool. Changes 1 and 2 are described above.

Change 3: Collection of pregnancy outcome information

At the REC’s request we now provide information on the method of data collection, namely linkage of participants with their records collected in the UK Obstetric Surveillance System.

Change 4: Removal of tocilizumab and anakinra

We have now completed recruitment into our assessments of tocilizumab and anakinra among children with PIMS-TS so we wish to remove these from the protocol.

Change 5: Collection of swab samples at home

As some participants are discharged before day 5, those in the antiviral comparisons with COVID-19 or influenza pneumonia would not have a day 5 swab sample collected. As these samples provide important information on both the efficacy of treatment but also resistance we seek permission to request that participants take these samples at home and post them to the trial laboratory. Instructions would be provided (and are included in this submission) along with all necessary materials including freepost envelopes appropriate for such samples.

Change 6: Addition of further safety information collection

Because some of the treatments now in the RECOVERY are not so well-known we wish to expand the safety information that we collect from all participants to include seizures and liver blood test results. We believe that this, along with the ongoing collection of suspected serious adverse reactions, will provide comprehensive safety information. These data would be provided to our Data Monitoring Committee routinely.

Additional Change (not on Amendment Tool): Expansion of molnupiravir comparison

Because molnupiravir is now available in countries outside the UK, we wish to include these countries in our comparison of molnupiravir.

References

1. Vousden N, Bunch K, Morris E, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). PLoS One 2021;16:e0251123.
2. Vousden N, Bunch K, Morris E, et al. Severity of maternal infection and perinatal outcomes during periods in which Wildtype, Alpha and Delta SARS-CoV-2 variants were dominant: Data from the UK Obstetric Surveillance System national cohort. BMJ Medicine 2022;In Press.
3. Pregnant women now a priority group for COVID-19 vaccination. National Perinatal Epidemiology Unit, 2021. (Accessed 31/01/2022, 2022, at <https://www.npeu.ox.ac.uk/news/2194-pregnant-women-now-a-priority-group-for-covid-19-vaccination>.)
4. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med 2022.

5. UK Health Security Agency. COVID-19 vaccine surveillance report Week 4 27 January 2022. London: UK Health Security Agency; 2022.
6. Medications used to treat covid-19 in pregnancy. 2022. (Accessed January 18th, 2022, at <https://www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-IN-PREGNANCY/>.)
7. The PREVENT Working Group. Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response. . Baltimore, MD: Johns Hopkins Berman Institute of Bioethics; 2018.
8. <https://www.gov.uk/government/publications/nervtag-antiviral-drug-resistance-and-the-use-of-directly-acting-antiviral-drugs-daas-for-covid-19-8-december-2021>
9. RECOVERY Collaborative Group. Lancet 2021; 397: 1637-1645