RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and breastfeeding women

Pregnancy lead: Prof Marian Knight

With support of UK Teratology Information Service (Dr Ken Hodson, Medical Director)

	RECOVERY trial protocol	**Adaption for pregnancy**
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. Confirmed SARS-CoV-2 iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Same eligibility
Interventions	**First randomisation part E** • High-dose corticosteroids **First randomisation part F** • Empagliflozin **First randomisation part J** • Sotrovimab **First randomisation part K** • Molnupiravir **First randomisation part l** • Paxlovid	Interventions for pregnant women • Substitution of corticosteroid (part E) iv hydrocortisone/iv methylprednisolone/ oral prednisolone (in place of dexamethasone) • Sotrovimab • Paxlovid (**2nd/3rd trimester only**) *Not recommended in pregnancy* • *Empagliflozin* • *Molnupiravir*
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ Vital status (alive/ dead, with date and presumed cause of death, if appropriate) ➢ Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) ➢ Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) ➢ Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same follow-up and outcomes, with **addition of UKOSS case number** (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		Dexamethasone may be considered, otherwise the same interventions as in pregnancy should be used. UKOSS case number added if available.

Frequently asked questions

1. **Are the drugs safe in pregnancy?** The pregnancy leads for the trial have reviewed the safety literature (Annex A), and experience around using these drugs for other conditions, and consider that participation in the trial is reasonable for pregnant and breastfeeding women. The regulators (MHRA and HRA) have agreed to the inclusion of pregnant women for each of the agreed treatments above.
2. **Where can I find information specifically written for pregnant women about the drugs?**
   The links below are provided with permission from the bumps (best use of medicines in pregnancy) website, who have developed information leaflets for each of the drugs used in the RECOVERY trial. The bumps website and information are provided by the UK Teratology Information Service (UKTIS), a not-for-profit organisation funded by the UK Health Security Agency.
   - Medications for covid-19: https://www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-IN-PREGNANCY/
   - https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MOLNUPIRAVIR-IN-PREGNANCY/
3. **Who has endorsed the trial?** The trial itself has been endorsed by the **Chief Medical Officer and NHS England Medical Director.** Inclusion of pregnant and postpartum women has been endorsed by NHS England, the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Royal College of Physicians, Tommy's Charity, British Maternal and Fetal Medicine Society, Macdonald Obstetric Medicine Society, the Neonatal Society, the Reproductive Health and Childbirth Specialty Group Lead (NIHR Clinical Research Network).
4. **Who should take consent for inclusion in the trial?** Any healthcare professional with appropriate training and knowledge of the trial can take consent. Obstetricians, obstetric physicians and midwives can make their colleagues aware that pregnant and postpartum women are eligible for the trial and should be approached for participation. ***Consent discussions concerning medications not routinely used in pregnancy should involve an obstetrician or obstetric physician and should be clearly documented in medical records for audit purposes.***
5. **Can I offer the trial to a woman who is in hospital for another reason?**
   If you are looking after a symptomatic woman with a positive covid-19 swab result who was initially admitted for another reason, ask whether you are uncertain about the benefits of treatment or not for this woman, either for treatment or to prevent deterioration. If you are uncertain, then it is reasonable to provide the information to the woman, offer the trial and make a shared decision. We do not know the optimal time to offer treatment.
6. **Who collects the outcome data?** The outcome data will be collected as usual for the trial, with the exception of pregnancy-specific data, which will be collected by research nurses or research midwives as part of the ongoing **UKOSS COVID-19 study in pregnancy**, using the **UKOSS COVID-19 Data Collection Form.** All pregnant women should be reported within the UKOSS study (although this does not need to be started before consent to RECOVERY), and the UKOSS number should be included in the outcome data.
7. **Can we give women corticosteroids for fetal lung maturity?** Yes, if indicated, as in usual clinical obstetric practice (see **RCOG guidance in COVID-19 pandemic**)
8. **Can we take part?** Any hospital that has R&D approval for RECOVERY can take part. There are no special approvals needed for including pregnant and breastfeeding women. A 'pregnancy lead' healthcare professional has been identified in 160 sites, to work alongside the site Principal Investigator.

Annex A: Trial drugs in pregnancy and during lactation

All trial drugs in this platform are scoped for safety in pregnancy, with information taken from a number of sources including where drugs have been used in pregnant women with pre-existing medical disorders The existing data related to each drug is summarized below.

Prednisolone/Hydrocortisone/Methylprednisolone
Currently in routine use in pregnant women.

Empagliflozin
There are minimal data on empagliflozin in pregnancy and breastfeeding, and they are not sufficient to recommend use within the RECOVERY trial. It is therefore not being included for pregnant or breastfeeding women in the RECOVERY trial.

Sotrovimab
Sotrovimab is an IgG1 monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Preclinical animal studies have not evaluated the risk of reproductive toxicity. However, the manufacturer reports no off-target binding in a cross-reactive binding assay that used a protein array enriched for human embryofetal proteins. As the binding target for sotrovimab is unique to COVID-19 viral proteins, it is not expected that the administration of sotrovimab in pregnancy will affect fetal development. Therefore, it is reasonable to offer sotrovimab to pregnant women with COVID-19 in a clinical trial setting as there are no perceived fetal risks to treatment, but potential for significant maternal and fetal benefit.

Molnupiravir
Although COVID-19 in pregnancy presents a significant risk to both the woman and her baby, both the mechanism of action of molnupiravir and the preclinical animal data warrant a cautious approach towards its use in pregnancy. Molnupiravir is not currently routinely recommended in pregnancy until further studies have established its effectiveness and safety.

Paxlovid (for women in their second or third trimester only)
Paxlovid (nirmatrelvir/ritonavir) is licensed for the treatment of COVID-19 in adults who do not require supplemental oxygen, but who are at increased risk of developing severe illness.
Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease which prevents viral replication. Ritonavir is included in the formulation as a pharmacokinetic enhancer, to inhibit CYP3A mediated metabolism of nirmatrelvir, and does not possess pharmacodynamic activity against SARS-CoV-2 3CL protease. Preclinical animal reproductive toxicity studies have not identified adverse effects on fetal morphology or embryo-fetal viability in rat or rabbit models with doses of nirmatrelvir up to 12 times the human dose.The offspring of pregnant rabbits administered 24 times the equivalent human dose, lower fetal body weights were observed but evidence of maternal toxicity was described (impact on weight gain/food consumption), which may explain the effect on fetal weight.
There is a large amount of published evidence relating to the safety of ritonavir in human pregnancy, collected from antiretroviral and HIV/AIDS pregnancy registries.
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.