RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and breastfeeding women

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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. SARS-CoV-2 infection (clinically suspected or lab confirmed) 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 A** • Dimethyl fumarate (in some sites) **First randomisation part B** • Synthetic neutralising antibodies (REGN-COV2) **First randomisation part D** • Baricitinib	Interventions for pregnant women • Synthetic neutralising antibodies *Not recommended in pregnancy* • *Dimethyl fumarate* • *Baricitinib*
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 COVID-19 case number** (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		The same interventions as in pregnancy should be used. UKOSS COVID-19 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 Public Health England on behalf of the UK Health Departments.
   - Aspirin: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Aspirin/
   - Medications for covid-19: https://www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-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 does not need to be taken specifically by an obstetrician, obstetric physician or research midwife.
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 COVID-19 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 recommended for pregnant women (except REGN-COV2 monoclonal antibodies) have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The data for colchicine is outlined below. The existing data related to each drug is summarized below.

Dimethyl fumarate

Although there are small registry case series of dimethyl fumarate suggesting no adverse safety signal in pregnancy,[2] there are also reports of toxicity in animal studies, and the BNF advises against its use in pregnancy: https://bnf.nice.org.uk/drug/dimethyl-fumarate.html#pregnancy. As dimethyl fumarate is being evaluated in a nested phase 2 study only, we are not recommending that pregnant women its inclusion for pregnant or breastfeeding women at this point.

REGN-COV2 Monoclonal antibodies

Monoclonal antibodies have been used as therapeutic agents in pregnancy over recent years, for a variety of conditions. Human monoclonal antibodies in use in pregnancy include anti-TNF agents, such as adalimumab, indicated for a variety of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Data have recently accumulated from a variety of cohort and registry studies indicating that such exposure in pregnancy was not associated with an increased risk for adverse pregnancy outcomes, when compared to unexposed pregnancies with the same underlying medical diseases.[3] This is supported by a consensus report on immunosuppressives and biologics during pregnancy and lactation, confirming no evidence of elevated adverse pregnancy outcomes or malformation risks.[4] Some monoclonal antibodies are transported across the placenta (and may also enter breast milk) but as REGN10933 and REGN10987 do not have any human targets such exposure should not be associated with risk of harm. Pregnant women, just like other patients with COVID-19, are at significant risk from the infection itself (particularly those in the third trimester.[5, 6] All pregnant women in RECOVERY are entered into the UK Obstetric Surveillance System which follows all pregnancies to their conclusion.[6] Given the early safety experience with

REGN10933+REGN10987 it would appear appropriate not to exclude pregnant women from this aspect of the trial (as such exclusion would inhibit the development of treatments for this population).[7]

A previous version (V12.1) of the RECOVERY protocol stated: *Pregnant women that are administered REGN10933 and REGN10987 must be advised that live vaccines should be avoided in children with in utero exposure to biologics for at least the first 6 months of life.* This sentence has now been deleted, following review of the biological rationale. The synthetic monoclonal antibodies (REGN10933+REGN10987) bind to the SARS-CoV-2 spike protein on the surface of cells, blocking the interaction between the spike protein and its canonical receptor angiotensin-converting enzyme 2. There are no human protein targets of the Regeneron monoclonal antibodies. This is in contrast to infliximab, a biologic drug implicated in a single case report of a 4 month old infant in London who died of probable disseminated TB following maternal infliximab use in pregnancy and infant BCG vaccination at 3 months of age.[8] Infliximab targets human TNF-alpha, such that if used in later pregnancy, the immune system of the neonate may be compromised, leading to potential systemic disease following administration of live vaccines. Regeneron monoclonal antibodies are similar in type to other immunoglobulins that are commonly given in pregnancy such as anti-D, varicella zoster immunoglobulin etc., for which an advisory warning against live vaccine administration in the infant is not required. Therefore, women do not need to be advised that live vaccines should be avoided in their infant following administration of these synthetic monoclonal antibodies.

Baricitinib

There are minimal data on baricitinib 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.

References

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