Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

1st June 2020

Agenda

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1. Introductions
2. Update on progress
   - Main recruitment
   - Second randomisation and convalescent plasma
3. Remdesivir
4. Hydroxychloroquine
5. Future plans
6. Q&A

Introductions

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- One of the central study team will talk to the agenda
- If you have questions please enter them into the “Q&A” on the right side of your screen.
- Questions may be answered directly or to the whole group

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PROGRESS UPDATE

Current trial design

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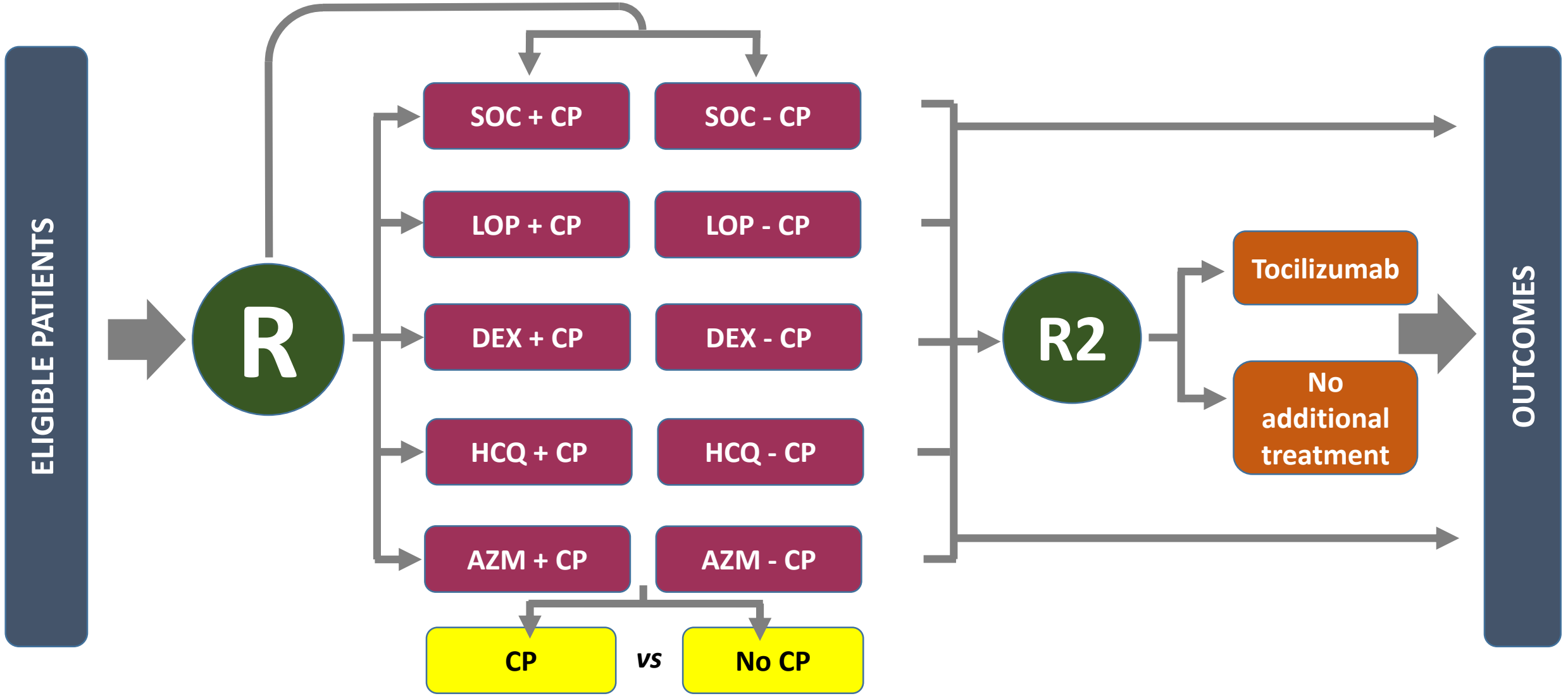

Recruitment by site

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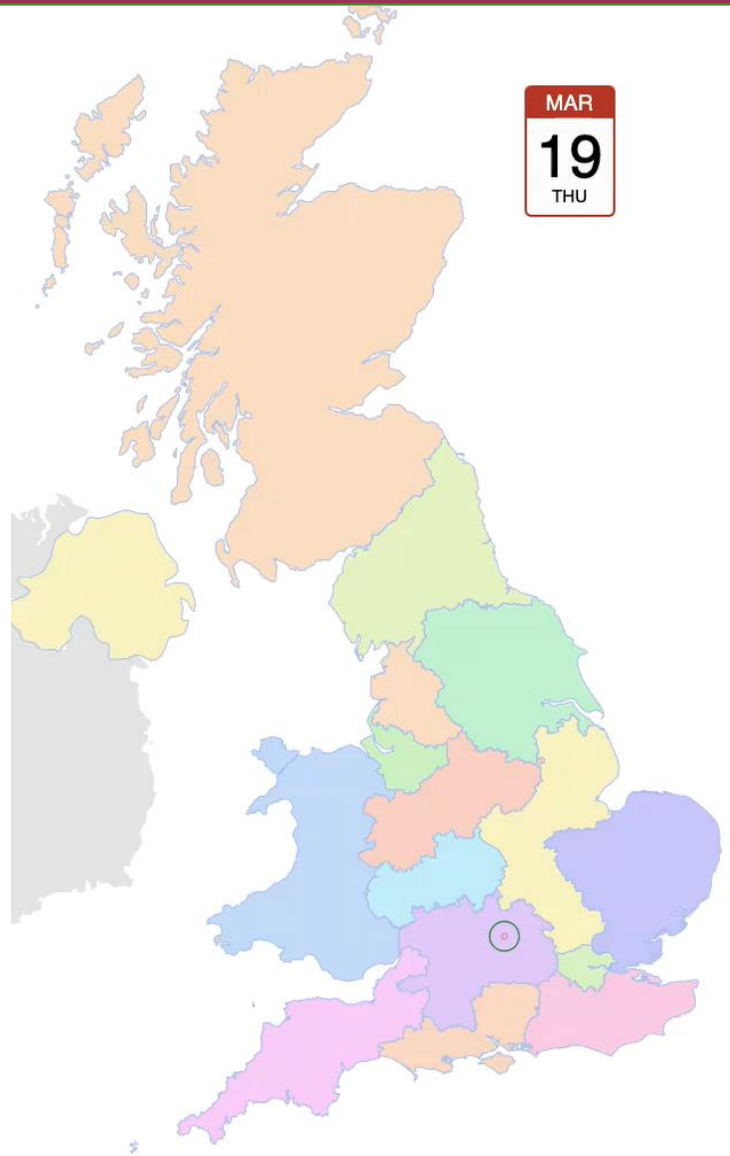

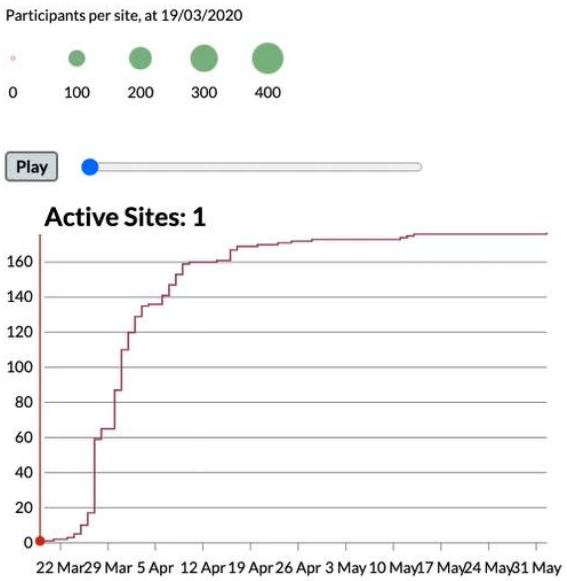

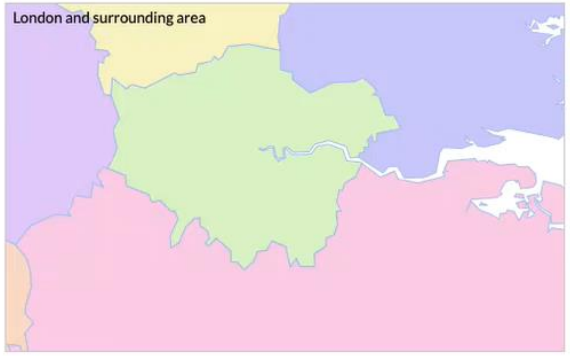

Recruitment progress

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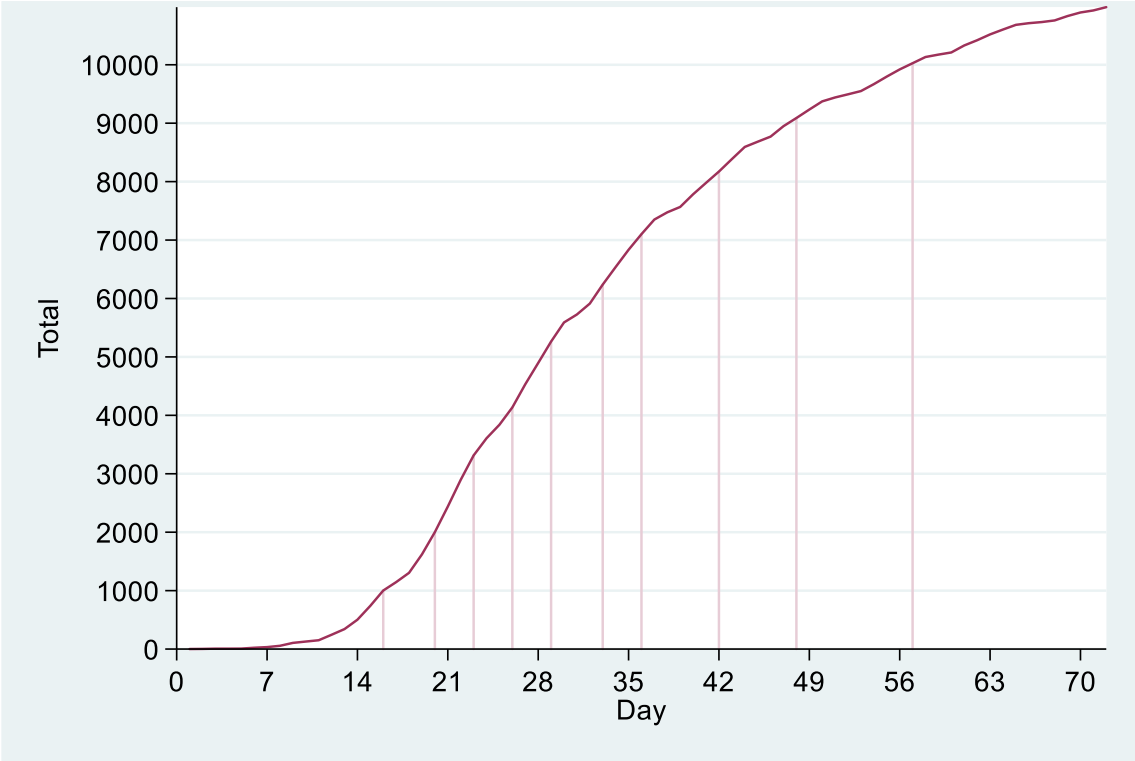
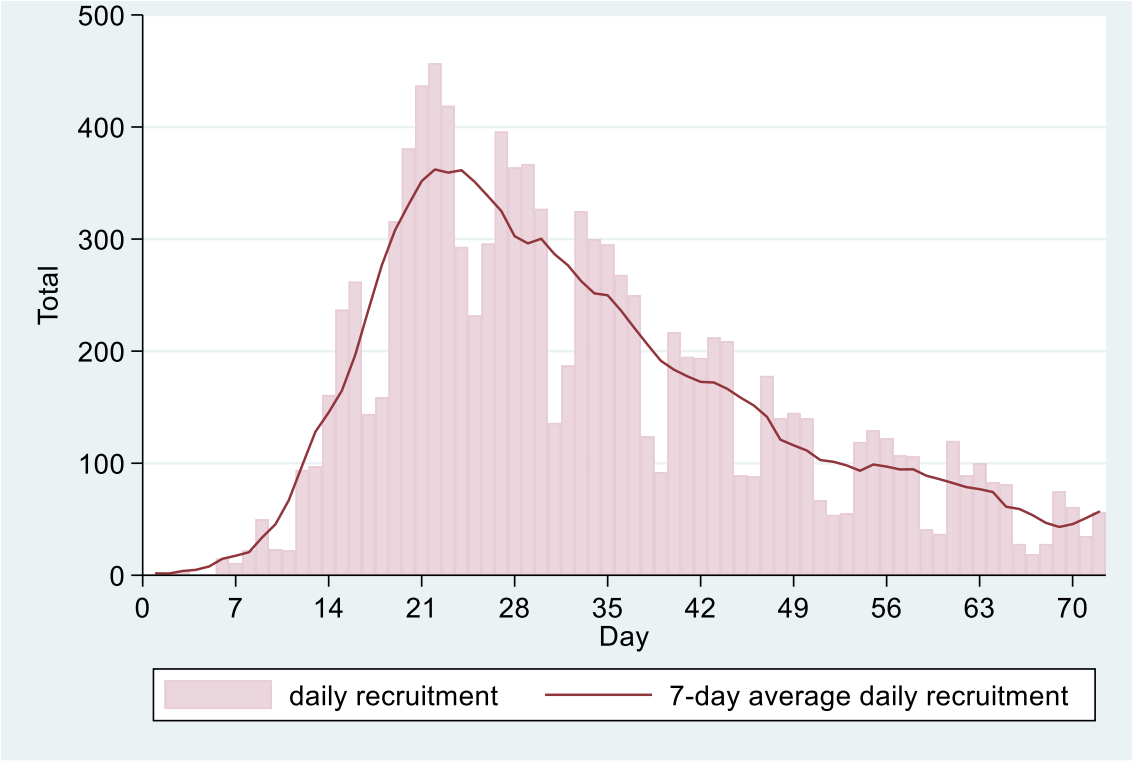
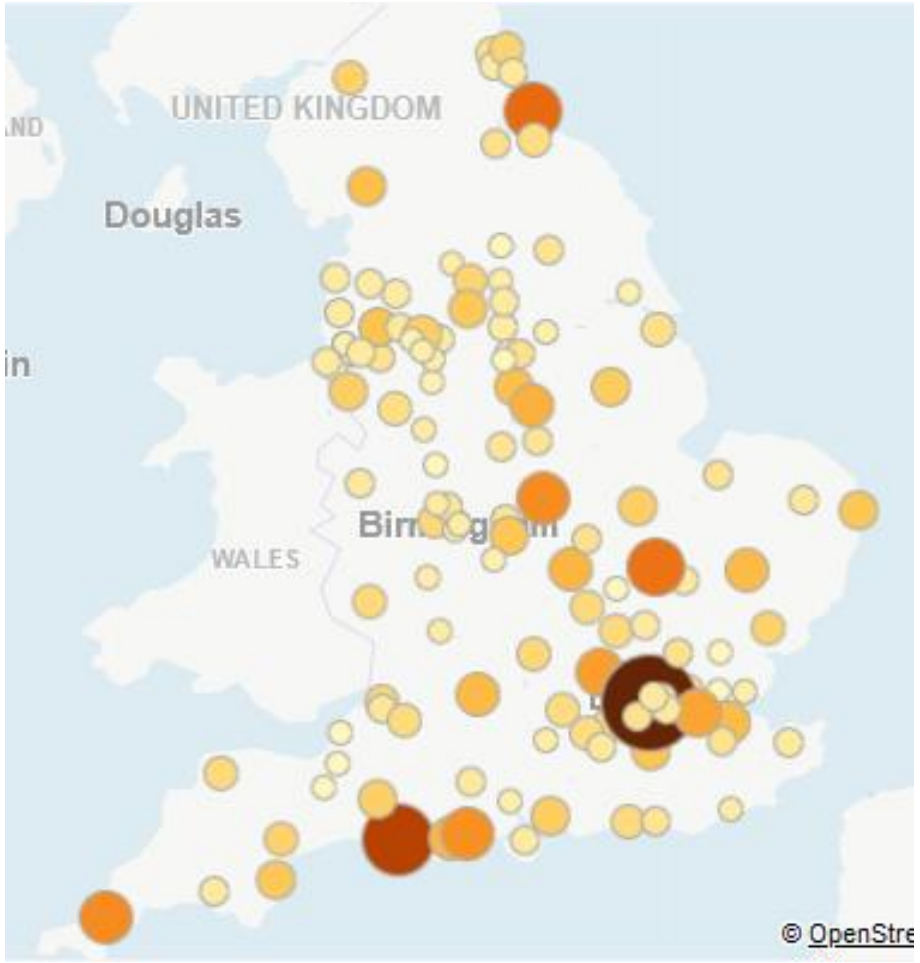
Total recruitment



Daily recruitment



Recruitment “efficiency”



- England-only data available from www.odp.nihr.ac.uk
- Larger darker circles indicate higher recruitment rate per 1000 admissions
- Varies from 1.5% to 64% (over 40 fold!)
- Average 101 per 1000

Characteristics at main randomisation (n=10,755)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		6786 (63%)
Age		66 (16)
Days since symptom onset		9 (5-13)
Days since hospitalisation		2 (1-5)
Severity of disease	No oxygen required	2622 (24%)
	Supplemental oxygen only	6633 (62%)
	Ventilation/ECMO	1502 (14%)
Prior disease	Diabetes	2896 (27%)
	Cardiovascular disease	2903 (27%)
	Chronic lung disease	2359 (22%)

What can we see in data?

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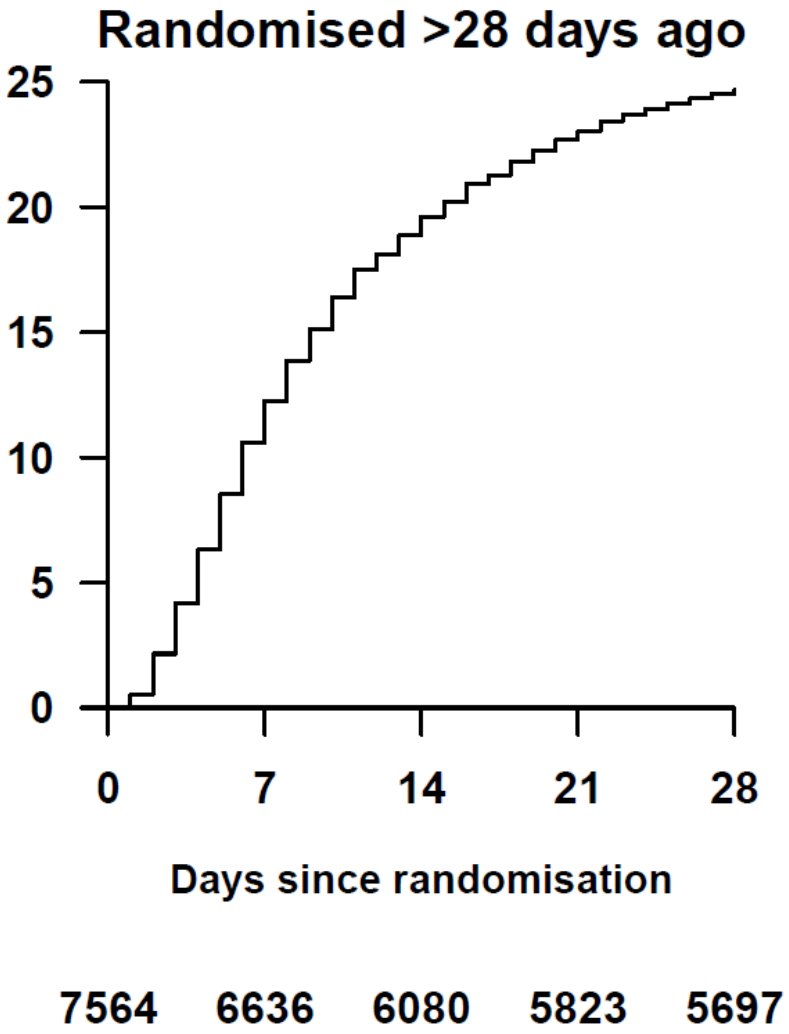

Characteristic		% dead at 28d
Age (years)		
	<50	7.7
	50-59	13.6
	60-69	23.6
	70-79	32.7
	80+	40.2
Sex		
	Female	19.1
	Male	25.7
Severity of disease		
	No oxygen	14.8
	Oxygen only	22.1
	Ventilation	35.0
Comorbidity		
	Diabetes	26.7
	Heart disease	33.1
	Chronic lung disease	31.1

When will we get some answers?

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- Although over 11,000 recruited now we still need 28 day follow-up
  - Please keep on top of the Follow-up forms!
- Due to design of trial, there are fewer than 2000 people on any one treatment (except standard of care)
  - Please keep recruiting!
- DMC review the data every two weeks (last review 28th May)

Second randomisation

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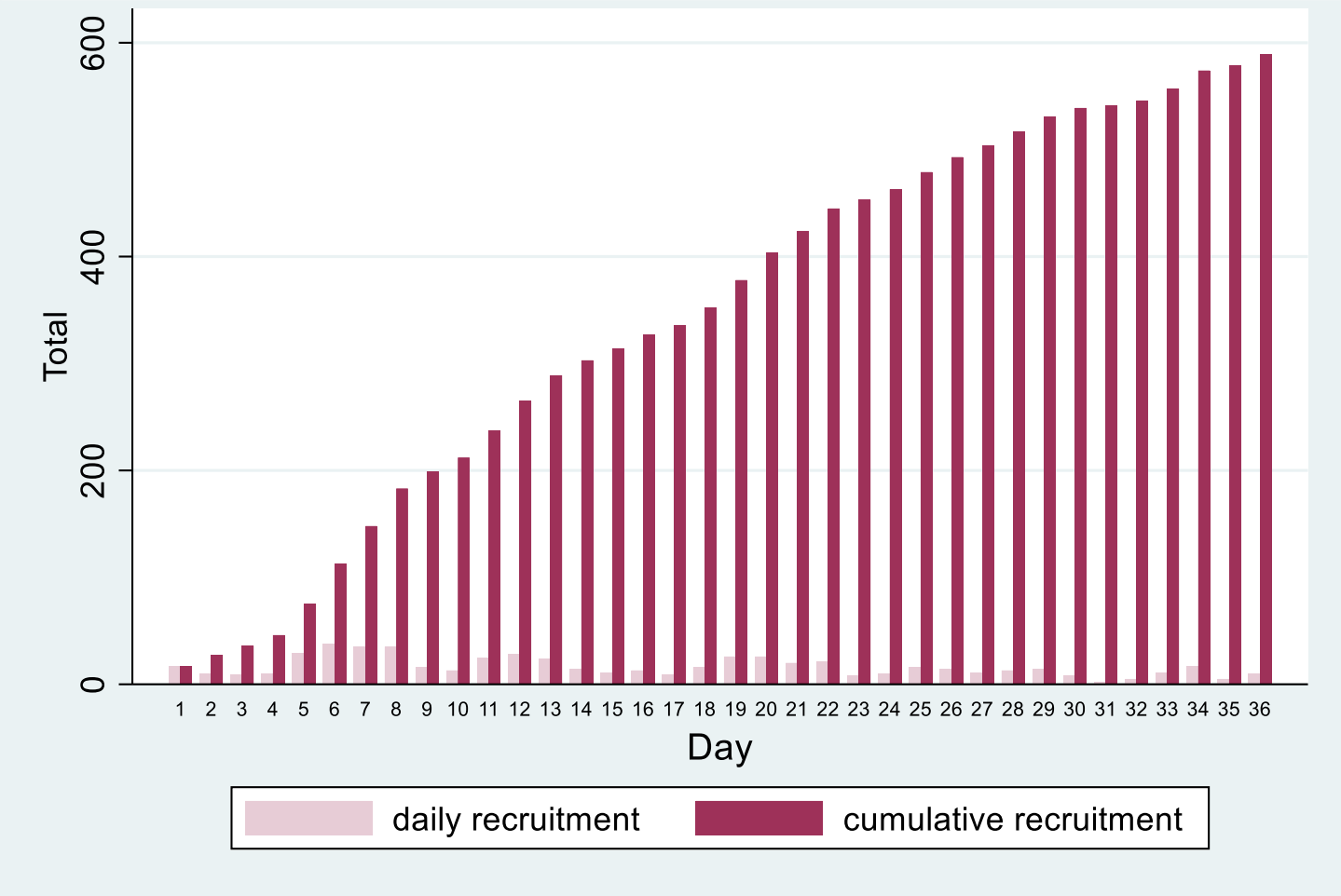

Convalescent plasma

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- First sites opened last week
- NHSBT are busy training transfusion laboratory staff and collecting plasma
- Aim is to open as many sites as possible, but rate will be determined by supply of convalescent plasma

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REMDESIVIR

ACTT-1 data

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- 1063 participants with laboratory proven COVID-19 and hypoxia
- Randomised between remdesivir (10 days) or placebo
- Primary outcome: time to recovery
  - Recovery = discharge alive or no longer requiring oxygen or medical care
- DMC stopped trial after 482 participants had recovered

ACTT-1 data (n=1063)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		684 (64%)
Age		58.9 (15)
Days since symptom onset		9 (6-12)
Severity of disease	No oxygen required	127 (12%)
	Supplemental oxygen only	618 (58%)
	Ventilation/ECMO	272 (26%)
	Missing	46 (4%)
Prior disease	Diabetes	275 (26%)
	Cardiovascular disease	2903 (27%)
	Chronic lung disease	2359 (22%)

ACTT-1 results

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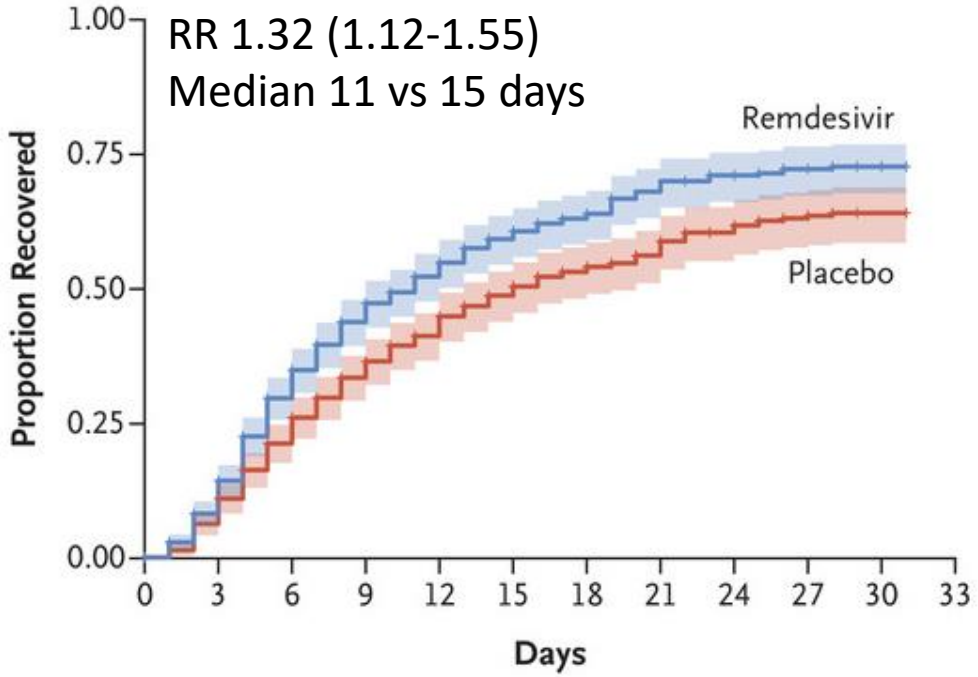
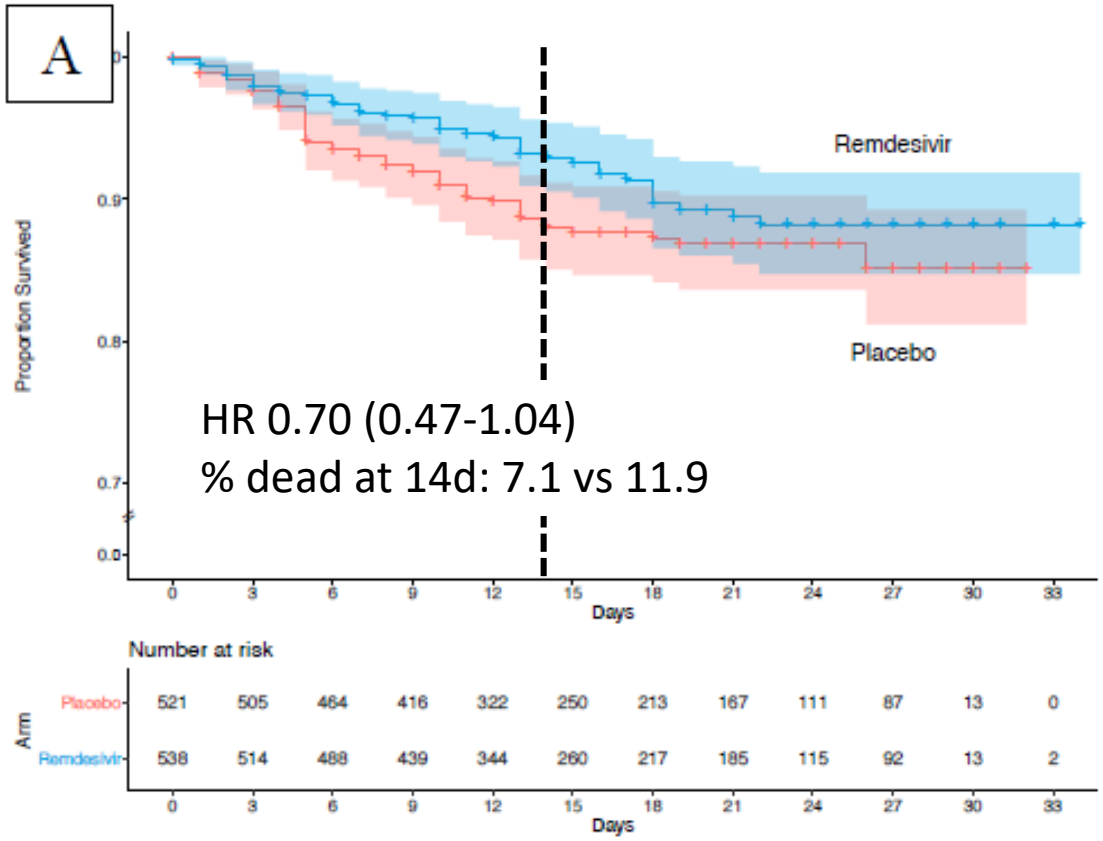
Recovery



No. at Risk

Remdesivir	538	481	363	274	183	142	121	98	78	65	3	0
Placebo	521	481	392	307	224	180	149	115	91	78	2	0

Survival



Remdesivir in RECOVERY

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- Remdesivir will be made available through Early Access to Medicines Scheme (EAMS) for selected patients with COVID-19

- **Patients on remdesivir can still be recruited into RECOVERY**

- **RECOVERY participants can be treated with remdesivir**

- Information on remdesivir use will be collected on Randomisation and Follow-up forms

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HYDROXYCHLOROQUINE

Hydroxychloroquine

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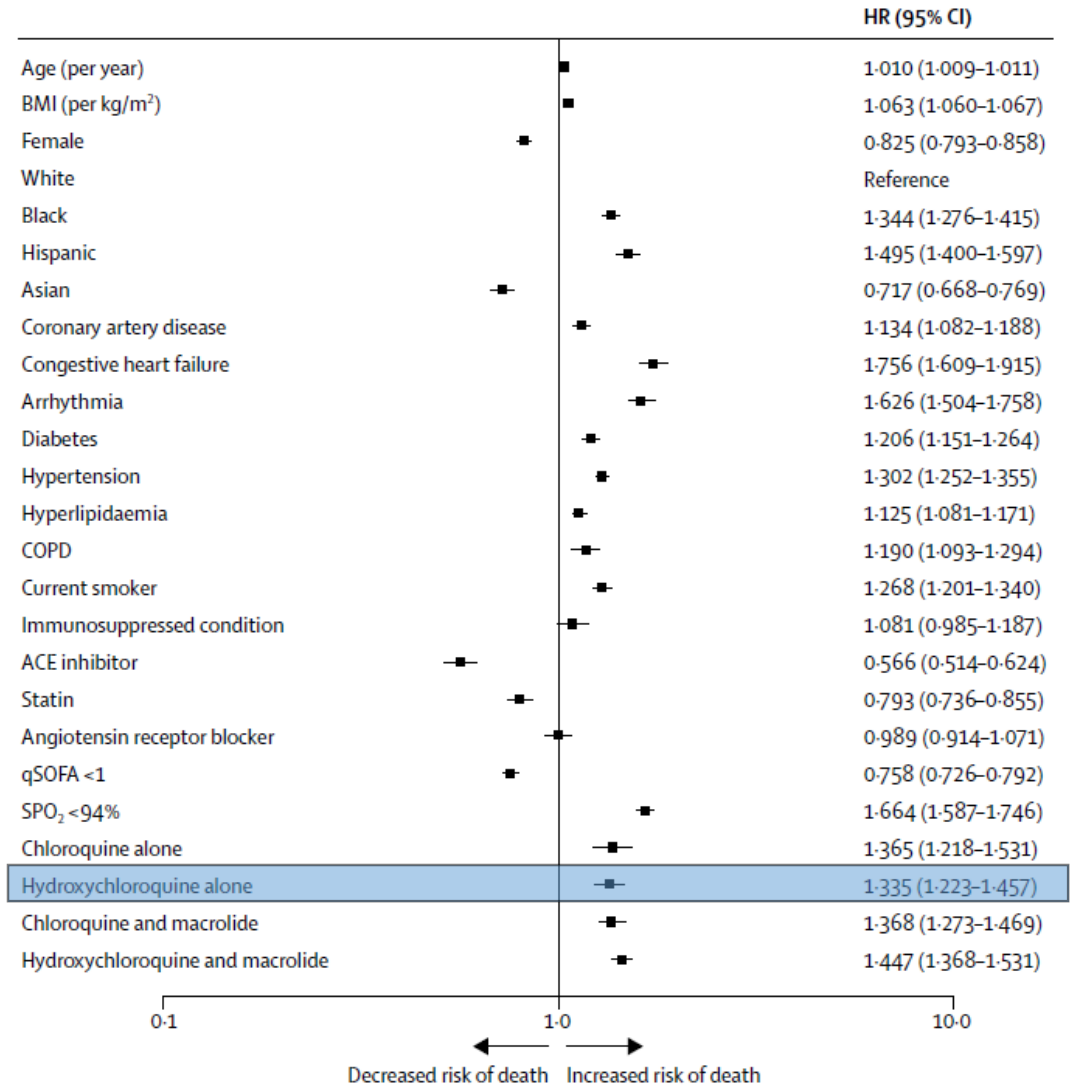

- **Non-randomised** analysis of factors associated with death
- Patients given HCQ will be different to those not given HCQ
- Non-randomised analyses cannot fully account for these differences so will be biased
- Authors acknowledged need for RCTs to test HCQ reliably

Discussions with MHRA

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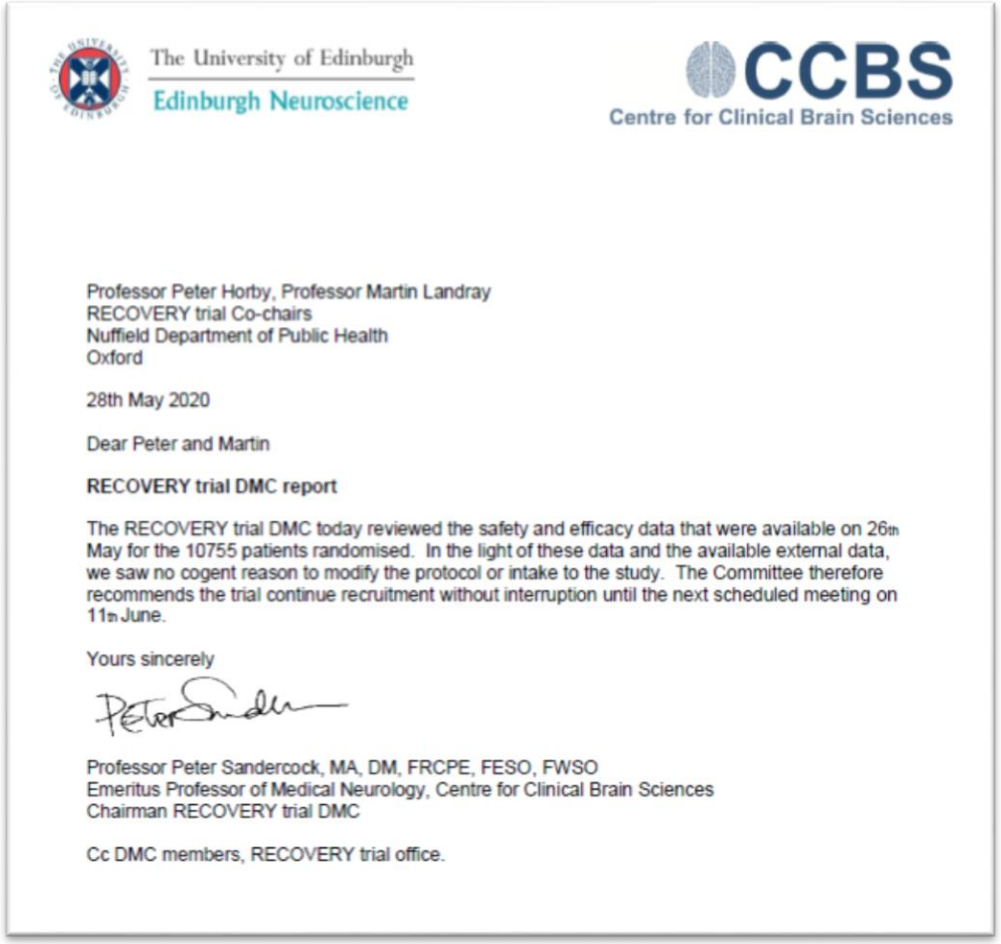
- MHRA wrote to all trials testing HCQ and requested the stop recruitment to HCQ arms on Friday 22nd May

- Updated data provided to RECOVERY DMC who met on 23rd May and concluded that no change to RECOVERY protocol was required

- RECOVERY Principal Investigators spoke to MHRA on 23rd May (before DMC meeting) and 24th May. MHRA agreed to allow RECOVERY to continue pending planned DMC review on 28th May

RECOVERY DMC



The University of Edinburgh
Edinburgh Neuroscience

CCBS
Centre for Clinical Brain Sciences

Professor Peter Horby, Professor Martin Landray
RECOVERY trial Co-chairs
Nuffield Department of Public Health
Oxford

28th May 2020

Dear Peter and Martin

RECOVERY trial DMC report

The RECOVERY trial DMC today reviewed the safety and efficacy data that were available on 26th May for the 10755 patients randomised. In the light of these data and the available external data, we saw no cogent reason to modify the protocol or intake to the study. The Committee therefore recommends the trial continue recruitment without interruption until the next scheduled meeting on 11th June.

Yours sincerely

Professor Peter Sandercock, MA, DM, FRCPE, FESO, FWSO
Emeritus Professor of Medical Neurology, Centre for Clinical Brain Sciences
Chairman RECOVERY trial DMC

Cc DMC members, RECOVERY trial office.

28th May

"…we saw no cogent reason to modify the protocol or intake to the study. The committee therefore recommends the trial continue recruitment without interruption until the next scheduled meeting on 11th June."

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FOLLOW-UP

Completeness is key

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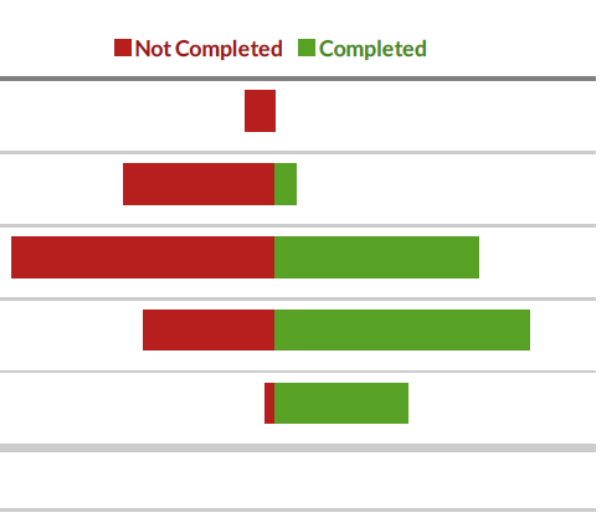
- Weekly reminders will be sent out by trial team to PI and staff with responsibility for completing Follow-up forms, highlighting participants randomised >28 days ago without complete form

- Please do complete these as soon as possible

Follow-up form completion summary

Days Since Rand.	FU Not Completed	FU Completed	Total Rands.
7 ≤ 14	3 (100.0%)	0 (0.0%)	3
14 ≤ 21	15 (88.2%)	2 (11.8%)	17
21 ≤ 28	26 (56.5%)	20 (43.5%)	46
28 ≤ 35	13 (34.2%)	25 (65.8%)	38
> 35	1 (7.1%)	13 (92.9%)	14
Total	**58 (49.2%)**	**60 (50.8%)**	**118**



SAE reporting

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- Please remember that adverse events only need to be reported if they are **both**:
  - SERIOUS (e.g. prolong admission, require significant intervention to avoid life-threatening situation)

  AND
  - RELATED with reasonable probability to study treatment

- Please contact coordinating centre if such an event occurs.
- Please do not use “yellow card” system

Withdrawal of consent

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- Participants are free to withdraw consent for study procedures at any time

- It is **not** an "all or nothing" process. Withdrawal may be for:
  - Taking study treatment (e.g. they want to stop because of perceived side-effects)
  - Having hospital records reviewed for Follow-up form completion
  - Having linkage with NHS registries for long-term follow-up

- If participant wishes to withdraw, please find out which aspects they wish to withdraw from and inform coordinating centre

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FUTURE PLANS

Pharmaco-kinetic/-genomic substudy

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- Pharmacokinetics of hydroxychloroquine incompletely understood in COVID-19 population
- Predictors of QT prolongation (and other electrocardiographic changes) with HCQ (and AZM) unknown
- Plan to recruit patients allocated HCQ, AZM or control and measure:
  - ECG changes
  - HCQ concentrations at various time points
  - DNA sampling and other baseline characteristics
- Please contact coordinating centre if you are interested in participation

Carry on recruiting!

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- No additional arms currently being planned
- Need to continue recruitment and collection of follow-up information to provide DMC with information about efficacy and safety of study treatments
- As admission rates fall, please focus efforts on recruiting as many admitted patients as possible
- Thank you!

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

1st June 2020

RECOVERY for pregnant women

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1. Update on adaptions
2. Follow-up
3. Update on progress
4. Future plans
5. Q&A

RECOVERY for pregnant women

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HOME FOR PATIENTS FOR SITE STAFF NEWS Search

For Site Staff / site teams

Site teams

This page contains additional information for RECOVERY site team members. Follow these links for guidance on randomisation and how to collect follow-up data.

INTERVENTION INFORMATION

RECOVERY intervention sheet - lopinavir-ritonavir

RECOVERY intervention sheet - hydroxychloroquine

RECOVERY intervention sheet - dexamethasone

RECOVERY intervention sheet - azithromycin

RECOVERY intervention sheet - tocilizumab

GUIDES FOR SPECIFIC PATIENT GROUPS

RECOVERY for pregnant and postpartum women

RECOVERY for patients with chronic kidney disease

RECOVERY Privacy Notice for Trial Staff

COLLABORATORS' MEETING

Slides presented at the collaborators' meeting on 20 & 21 April 2020

Slides presented at the collaborators' meetings on 6 & 7 April 2020

RECOVERY for pregnant women

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RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and postpartum women

Pregnancy leads: Prof Lucy Chappell, Prof Catherine Williamson, Prof Marian Knight

	RECOVERY trial protocol	Adaption for pregnancy
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. SARS-CoV-2 infection iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial	Same eligibility
Interventions	• Arm 1: No additional treatment • Arm 2: Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) • Arm 3: Corticosteroid in the form of dexamethasone by oral or intravenous preparation 6 mg • Arm 4: Hydroxychloroquine • Arm 5: Azithromycin	Same option of 5 arms, but substitution of corticosteroid (arm 3): iv hydrocortisone 80mg bd/ oral prednisolone 40mg od (in place of iv dexamethasone)
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 should be used as for pregnant women. UKOSS COVID-19 case number added if available.

Eligibility = same

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2.1 Eligibility

Patients are eligible for the study if all of the following are true:

(i) Hospitalised
(ii) SARS-CoV-2 infection (clinically suspected[1] or laboratory confirmed)
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

- No criterion for ‘requiring oxygen’

Notes on eligibility

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- What about women with a positive covid-19 swab result but initially admitted for another reason…?
- Are you uncertain about the benefits of treatment or not for this woman, and whether it might 'treat' or prevent deterioration?
- If you are uncertain, then reasonable to provide the information to the woman, offer the trial and make a shared decision.

- **For any woman reportable to UKOSS, ask yourself whether you can offer her participation in RECOVERY**

Interventions = almost the same

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Trial design

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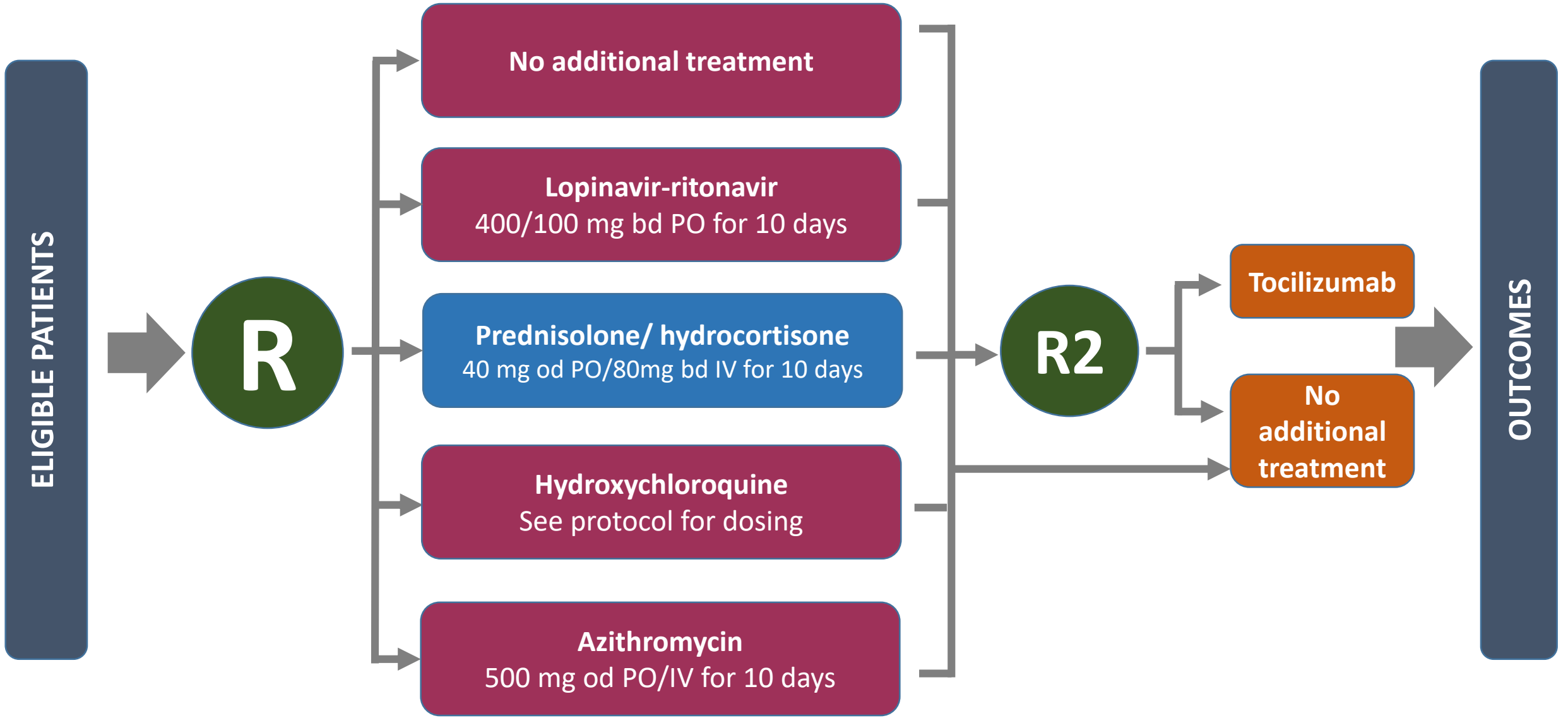

Use of drugs in pregnancy

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Annex A: Trial drugs in pregnancy and during lactation

All trial drugs 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 existing data related to each drug is summarized below.

Annex A: Trial drugs in pregnancy and during lactation
All trial drugs 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 existing data related to each drug is summarized below.

Lopinavir-Ritonavir
Lopinavir-ritonavir (400/100mg) treatment is used throughout pregnancy to treat HIV, with treatment reducing viral load and vertical transmission.[1] Elevated liver transaminases and impaired glucose tolerance should be screened for, but are not commonly seen in pregnancy. Some studies reported increased rates of late preterm birth in lopinavir-ritonavir-treated women compared to other protease inhibitors .[2] However, a systematic review that included nine studies (2,675 lopinavir/ritonavir-treated pregnant women with HIV) and considered preterm birth, low birth weight and stillbirth did not suggest any safety concerns.[3] Ergometrine should be avoided in women receiving lopinavir-ritonavir. Lopinavir and ritonavir are detected in breast milk, but the levels are considerably lower than maternal blood levels, and most studies have reported very low infant blood concentrations,[4] as reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501550/).

Hydrocortisone/ prednisolone
Prednisolone 40 mg PO od or, in women unable to take oral medicine, hydrocortisone 80mg IV BD are recommended instead of dexamethasone treatment in light of accumulating evidence that repeated doses of dexamethasone have deleterious effects on long-term neurodevelopment of the fetus.[5-7] While 90% dexamethasone is transferred transplacentally to the fetus, both hydrocortisone and prednisolone are converted by 11β-hydroxysteroid dehydrogenase to inactive glucocorticoids and considerably less drug is transferred to the fetus. Glucocorticoids can worsen maternal glycaemic control, so blood glucose should be checked and managed appropriately. Otherwise there is no convincing evidence that prednisolone use is associated with increased rates of adverse pregnancy outcomes when taken in the first trimester or later pregnancy.[8] Very low concentrations of prednisolone enter breastmilk. There is a paucity of data about pharmacological use of hydrocortisone, but it is likely that this is also safe when breastfeeding,[8] as also reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501076/). Prednisolone (or hydrocortisone) should be used in breastfeeding women, in preference to dexamethasone.

Hydroxychloroquine
Several studies have provided reassuring safety data for the use of hydroxychloroquine (HCQ) in the first trimester, later pregnancy and when breastfeeding.[8, 9] The doses used in the RECOVERY trial are higher, but acceptable given the good safety profile of HCQ. Reports of retinopathy, nephrotoxicity, myopathy and cardiomyopathy have all been reported after long-term (more than 6 months) treatment, rather than the short course proposed here.

Azithromycin
Azithromycin is used in pregnancy to treat genital Chlamydia trachomatis infection, with a Cochrane systematic review and meta-analysis reporting fewer gastrointestinal side-effects compared to erythromycin, and inconsistent results on risk of preterm birth, preterm rupture of membranes, perinatal mortality and low birthweight, confounded by the indication for treatment.[10] A recent systematic review and meta-analysis of all macrolide antibiotics acknowledges potential bias in child outcome reports due to treatment indication.[11] The UK Teratology Information Service monograph concludes that there is no definitive evidence linking azithromycin with increased risk of miscarriage or congenital malformations (https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MACROLIDES-IN-PREGNANCY/). Azithromycin is detected in only low levels in breastmilk and is not expected to cause adverse events in breastfed infants (reviewed in Lactmed database: www.ncbi.nlm.nih.gov/books/NBK501200/) .Azithromycin has also been used in several trials in preterm infants as a prophylactic treatment to prevent bronchopulmonary dysplasia.[12]

Second randomisation intervention: Tocilizumab
Two pharmaceutical global safety registry database studies have reported on tocilizumab use in pregnancy, including outcomes from 288 pregnancies [13] and 61 pregnancies,[14] typically for rheumatoid or other arthritides, and with the majority having received the drug in the first trimester. These data suggest that the rates of congenital abnormality, spontaneous pregnancy loss and other adverse outcomes were not higher than in the general population.[14] Small studies have shown that tocilizumab is transferred to the fetus with serum concentrations approximately 7-fold lower than those observed in maternal serum at the time of birth.[15] Very low concentrations of tocilizumab are identified in

New information for women

RECOVERY
Randomised Evaluation of COVID-19 Therapy

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and breastfeeding women

Pregnancy leads: Prof Lucy Chappell, Prof Catherine Williamson, Prof Marian Knight

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.
   - Lopinavir-ritonavir: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Lopinavir-and-ritonavir/
   - Prednisolone: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Prednisolone/
   - Hydroxychloroquine: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Hydroxychloroquine/
   - Azithromycin: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Azithromycin/
   - Tocilizumab: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Tocilizumab/

Convalescent plasma

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Additional randomisation intervention: Convalescent plasma (prepared with Dr Sue Pavord, Consultant Haematologist)
Convalescent plasma is plasma from people who had confirmed COVID-19 (SARS-Cov-2) infection, and have now recovered and been free of the infection for 28 days. The plasma contains antibodies that their immune systems have produced in fighting the virus. It is hoped that giving this plasma will help speed up recovery of a patient with active infection and improve their chances of survival. Plasma is already used as a treatment in pregnant patients who are bleeding,[18] or have particular blood conditions.[19, 20] The plasma being used in this trial is from a selected donor and hopefully contains anti-SARS-Cov-2 antibodies, but is otherwise no different. Plasma infusions can occasionally cause side effects. Mostly this is a rise in temperature, itching or a rash, and in very extreme cases, anaphylaxis. Other potential complications include breathlessness and changes in blood pressure. Monitoring of pulse and blood pressure takes place before and after the infusion. There is no risk of miscarriage or fetal loss, preterm birth, preterm rupture of membranes, perinatal mortality or low birthweight, from plasma transfusions and there are no concerns with breast feeding.

Follow-up = the same, + linkage

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NPEU

Nuffield Department of
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Search (e.g. Randomisation)

You are here: UKOSS / Current Surveillance / COVID-19 in Pregnancy

COVID-19 in Pregnancy

UKOSS
UK Obstetric Surveillance System

Key points

- Covid-19 is an infectious disease caused by a new strain of coronavirus.
- Covid-19 had not been detected in humans before the outbreak in December 2019.
- As the virus is new, little is known about its effect on certain groups of people, including pregnant women.

Surveillance period

1st March 2020 – 31st March 2021

Background

On this page

Update on progress

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- 159 pregnancy leads identified, supported by research midwives
- Midwife champions on board
- 14 women recruited

Moving forward

If reporting to UKOSS, check whether you could be offering the trial…

Lessons learned from recruiting sites:

- Engaged PI
- Proactive research midwives and nurses
- Good liaison with main site PI (e.g. sharing information)
- Avoidance of ‘gatekeeping’
- Understanding fetal safety data (see UKTIS)
- Embedding into usual clinical care (aim of RECOVERY trial)

UKOSS form adaptations

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4.4 Was the woman admitted to hospital? Yes ☐ No ☐

If Yes, please give date of admission D D / M M / Y Y

If Yes, what was her oxygen saturation on admission ☐☐☐ **%** or tick if not measured? ☐

What was the primary reason for admission? *(please tick one)*

COVID-19 disease or symptoms ☐ Delivery ☐ Other ☐

If Other, please specify _____

UKOSS form adaptations

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4.10 Was this woman recruited to the RECOVERY trial? Yes ☐ No ☐

4.14 Did the women require respiratory support for COVID-19 disease? Yes ☐ No ☐

If Yes, what was the maximal level of support required *(please tick one)*

O_2 via nasal prongs ☐ O_2 via mask ☐ O_2 via non-rebreathe mask ☐

CPAP ☐ Invasive ventilation ☐ ECMO ☐

Q&A

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