Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

15th June 2020

Agenda

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1. Introductions
2. Update on progress
   - Main recruitment
   - Second randomisation and convalescent plasma
3. Hydroxychloroquine
4. Dexamethasone
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

Previous trial design

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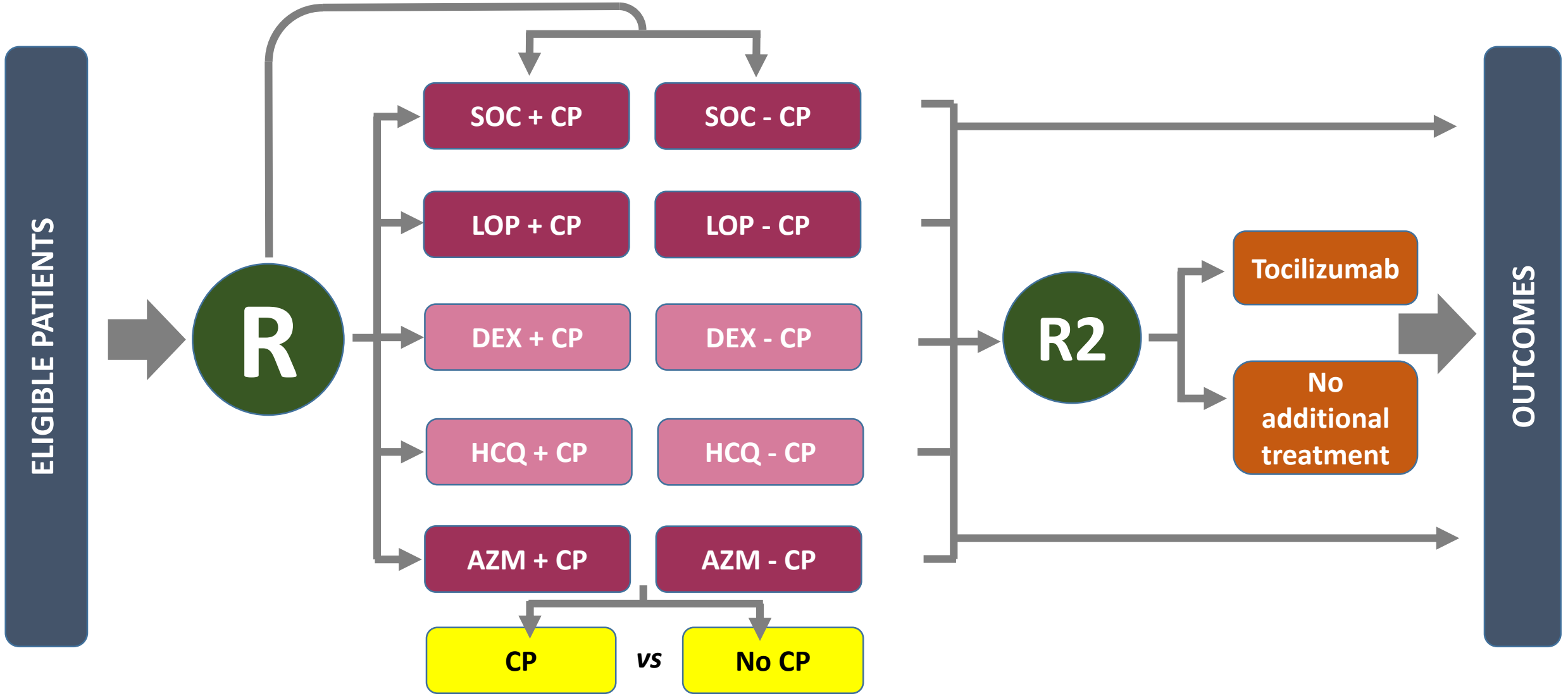

Current trial design

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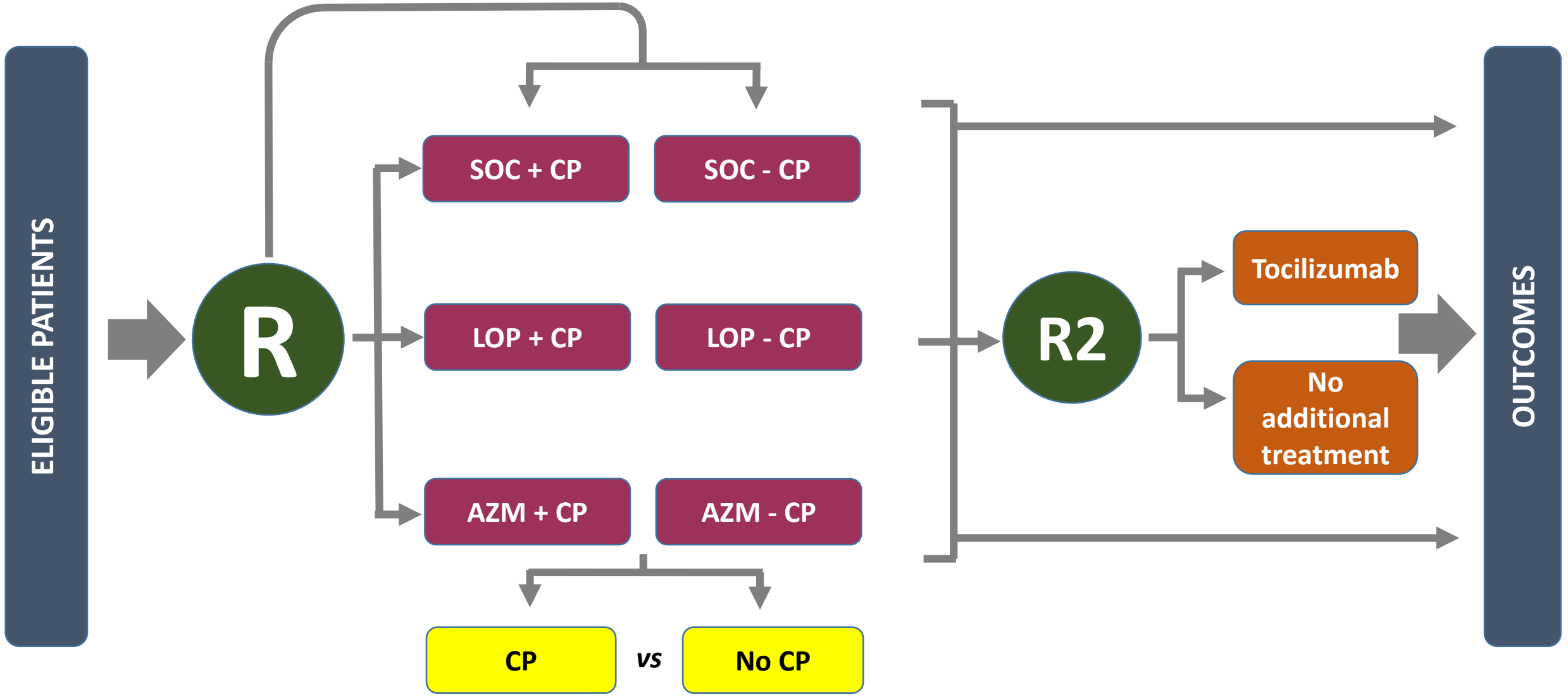

Recruitment by site and by time

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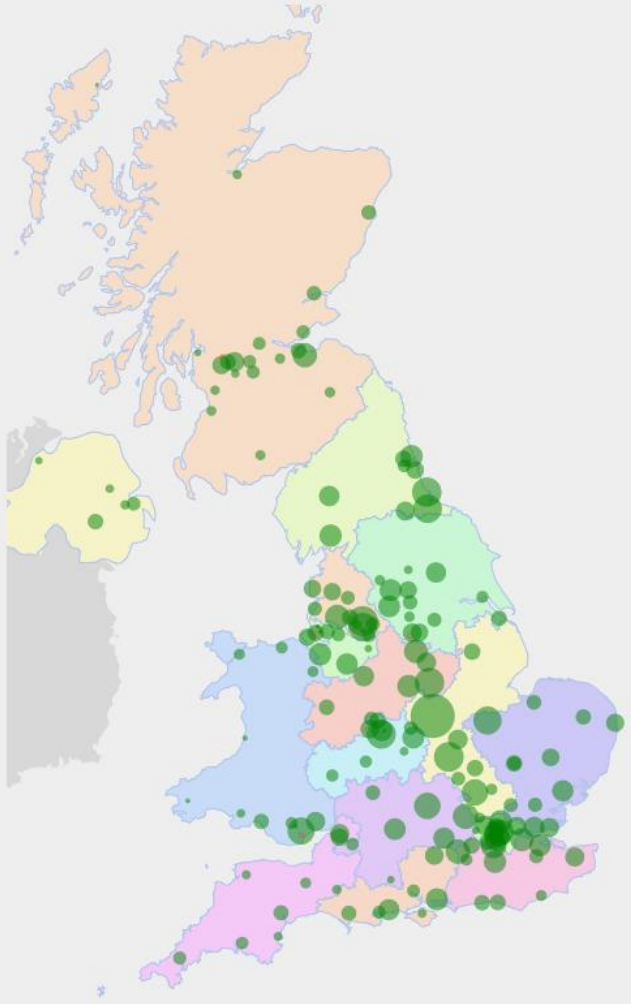
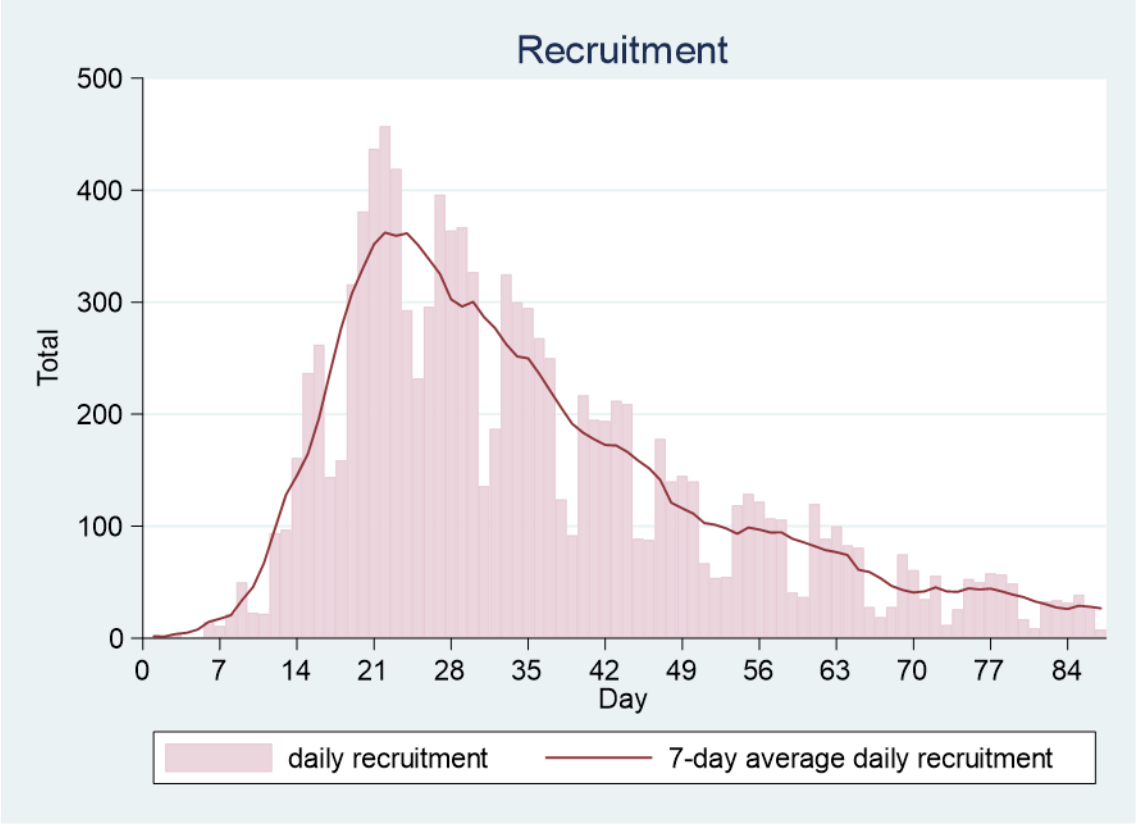
Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.
176	172	11492	693	42





Second randomisation

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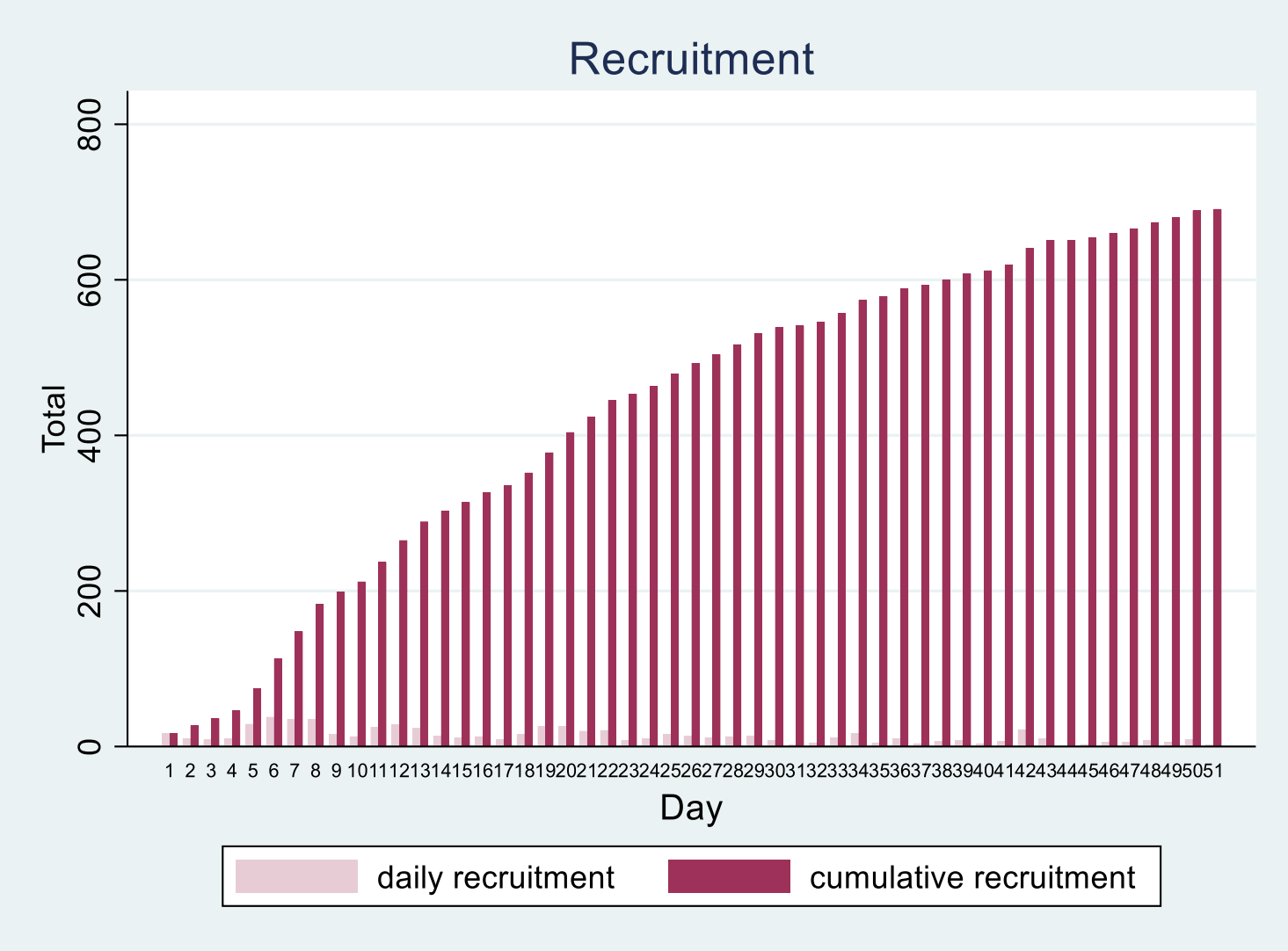

Convalescent plasma

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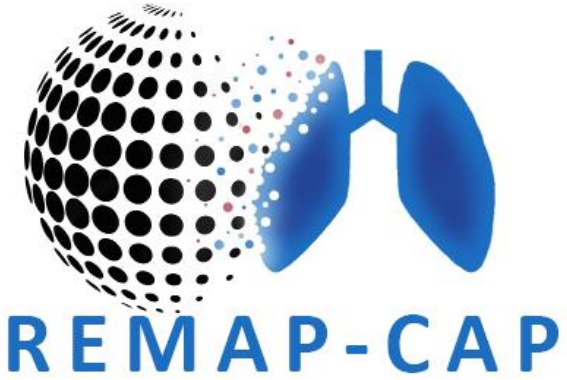
- 47 sites invited to participate, of which 17 are now open
- 42 participants recruited
- NHSBT are busy training transfusion laboratory staff and collecting plasma



When will we get some answers?

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- We have!

- DMC continue to meet each fortnight: last met on 11 June:

11th June 2020

Dear Peter and Martin

RECOVERY trial DMC report

The RECOVERY trial DMC reviewed the safety and efficacy data that were available today for the 11354 patients randomised. We recommend continuing recruitment into the trial. The next scheduled review by the DMC will be on 25th 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

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HYDROXYCHLOROQUINE

Why did we test HCQ?

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- In vitro data suggested HCQ had antiviral properties, possibly by inhibiting viral entry into cells
- Early reports of efficacy in COVID-19 (largely small, non-randomized studies)
- Widely available and cheap

Conclusions

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- Current data suggest that HCQ provides no meaningful benefit for treating patients admitted to hospital with COVID-19
- Ongoing analyses of secondary outcomes
- Should change clinical practice in countries where HCQ is currently recommended
  - USA, Brazil, India, China, S Korea, France, Italy, Netherlands

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DEXAMETHASONE

Dexamethasone

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- Recruitment stopped because sufficient participants recruited
- 2000 participants on dexamethasone *vs* 4000 controls provides very good (90%) statistical power to detect 18% reduction in risk of death
- Follow-up and analysis ongoing

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FOLLOW-UP

Completeness is key

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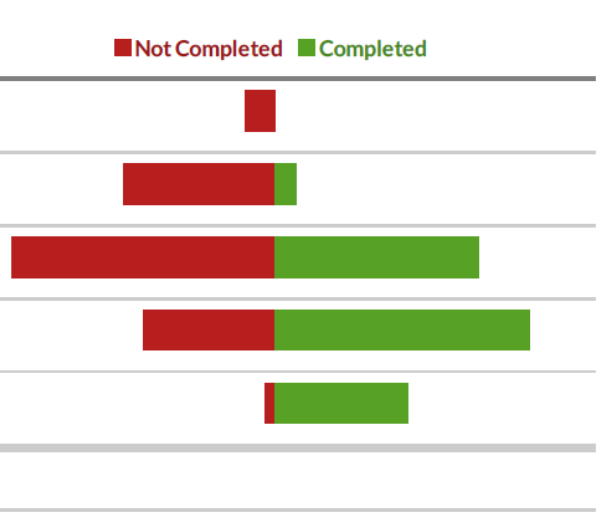
- Weekly reminders will be sent out by trial team to PI and staff with responsibility for completing Follow-up forms, highlighting participants randomised >28 days ago without complete form

- 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**



Data queries

- Trial management team (Lucy, Karen, Sarah, Richard, Wojtek and Ayten) may be in touch about “data queries”

- Please respond as quickly as possible in order to get data ready for publications

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

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FUTURE PLANS

Protocol amendment

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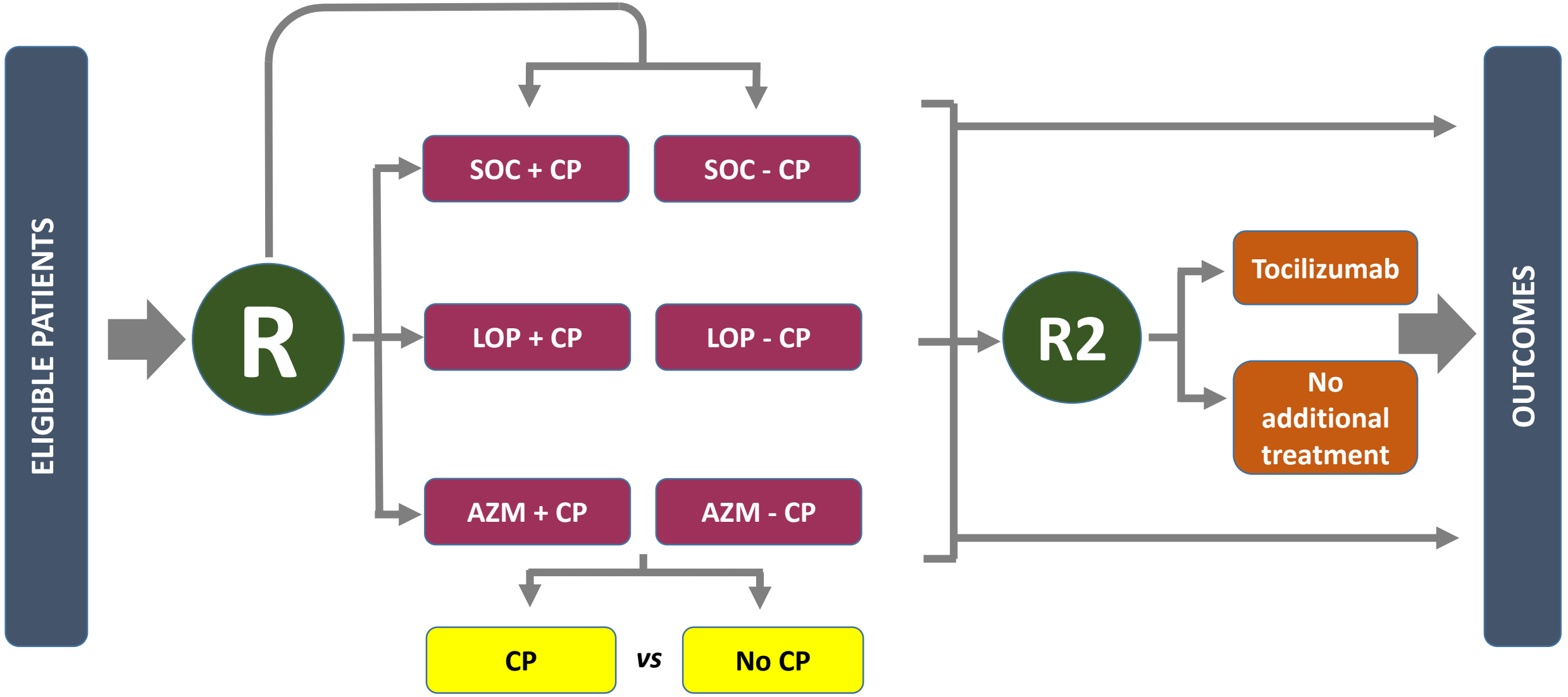

Carry on recruiting!

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- 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 for Pregnancy

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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Recent trial design

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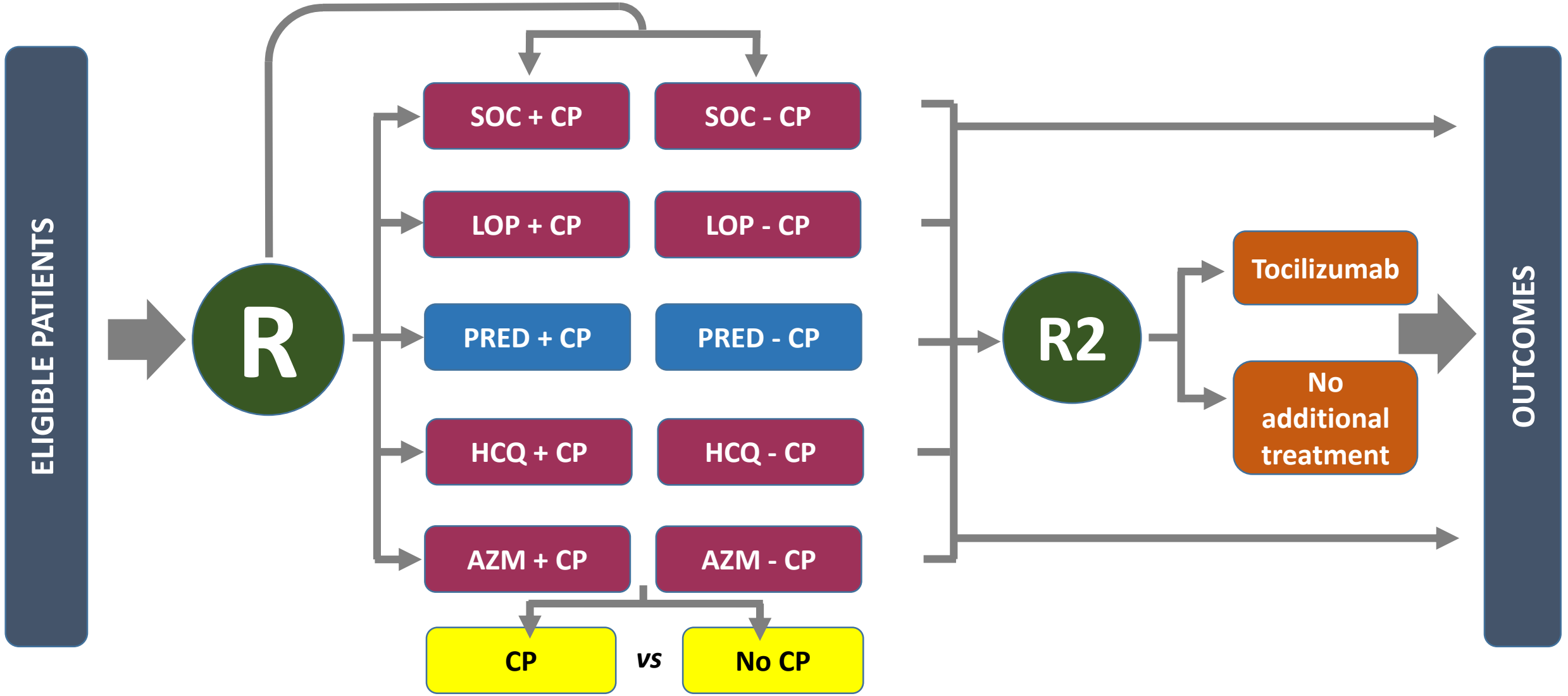

Current trial design

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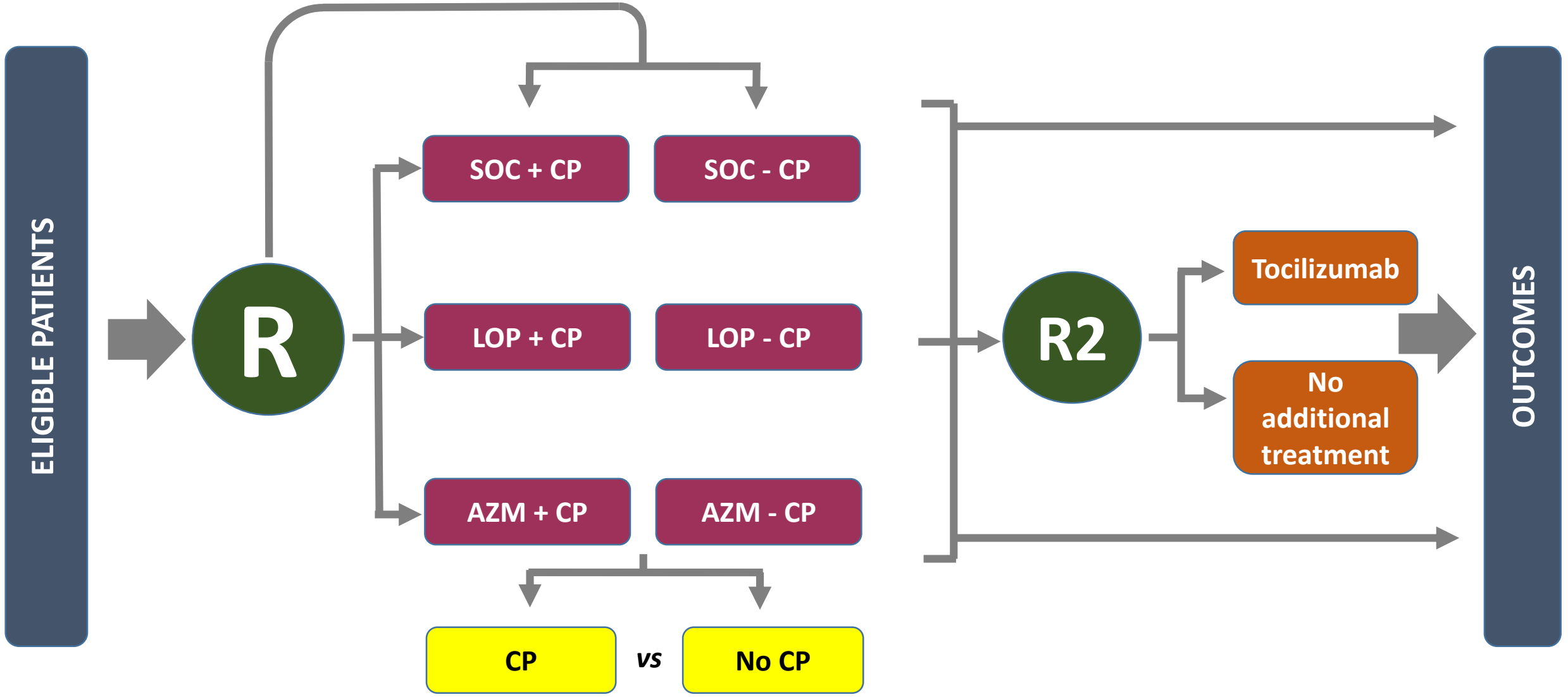

Use of drugs in pregnancy

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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

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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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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

Update from UKOSS this week

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UKOSS: SARS-CoV-2

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RESEARCH

Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study

Marian Knight,[1] Kathryn Bunch,[1] Nicola Vousden,[2] Edward Morris,[3] Nigel Simpson,[4] Chris Gale,[5] Patrick O'Brien,[6] Maria Quigley,[1] Peter Brocklehurst,[7] Jennifer J Kurinczuk,[1] On behalf of the UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group

WHAT THIS STUDY ADDS

More than half of pregnant women admitted to hospital with SARS-CoV-2 infection in pregnancy were from black or other ethnic minority groups

Most women did not have severe illness, and most were admitted in the third trimester of pregnancy

Transmission of infection to infants of infected mothers may occur but is uncommon

the bmj | *BMJ* 2020;369:m2107 | doi: 10.1136/bmj.m2107

Where are we now: positives

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- Equity of access to the trial
- Readiness for future cases
- Link with UKOSS for outcomes
- Research working across disciplines within sites
- Strong ongoing support from RH&C teams
- Blueprint for rolling out a trial in future

Where are we now: challenges

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Previous

- Site set-up, including pharmacy
- Opened after peak

Ongoing

- Lower number of cases in maternity compared to rest of hospital
- Uncertainty over different presentations/ overlap with normal obstetric presentations

Moving forward

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If reporting to UKOSS, check: can we offer 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)

Q&A

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