Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

18th May 2020

Agenda

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1. Introductions
2. Update on progress
   - Main recruitment
   - Second randomisation
3. Convalescent plasma arm
4. Follow-up
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

Recruitment by site

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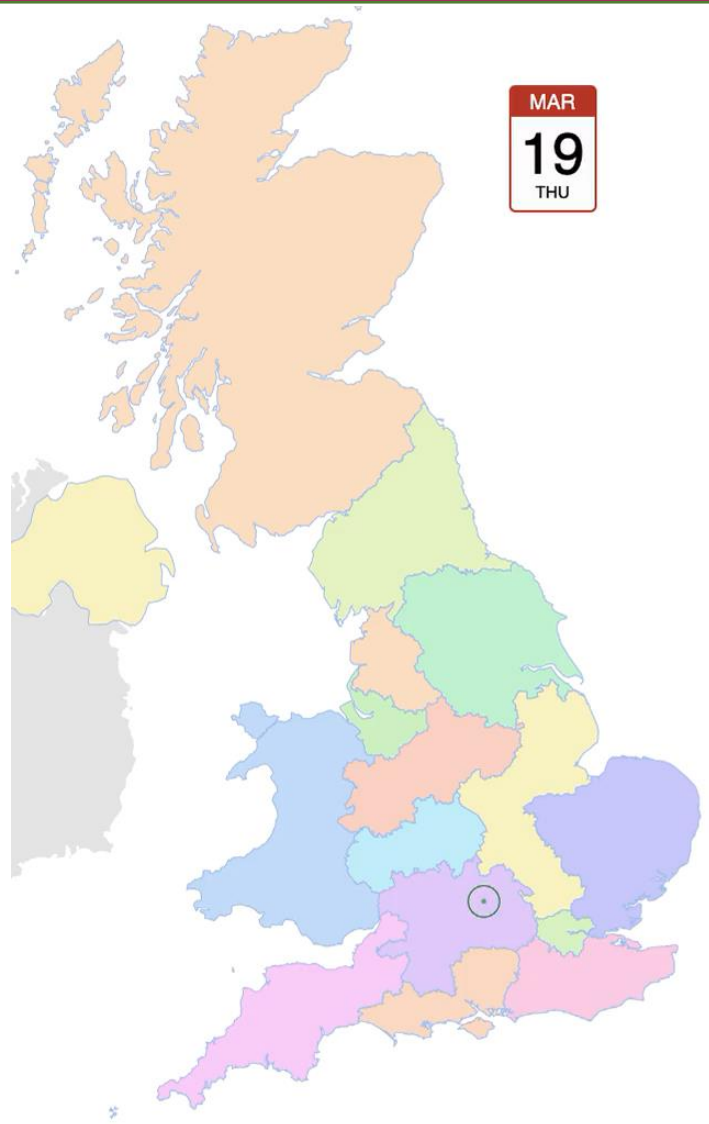

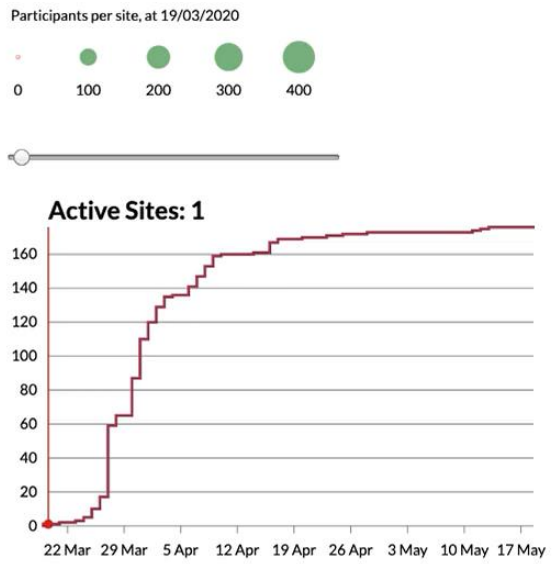

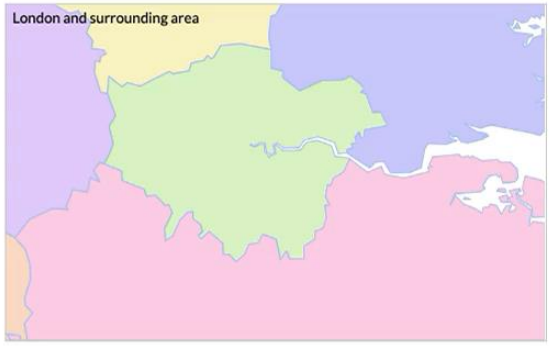

Recruitment progress

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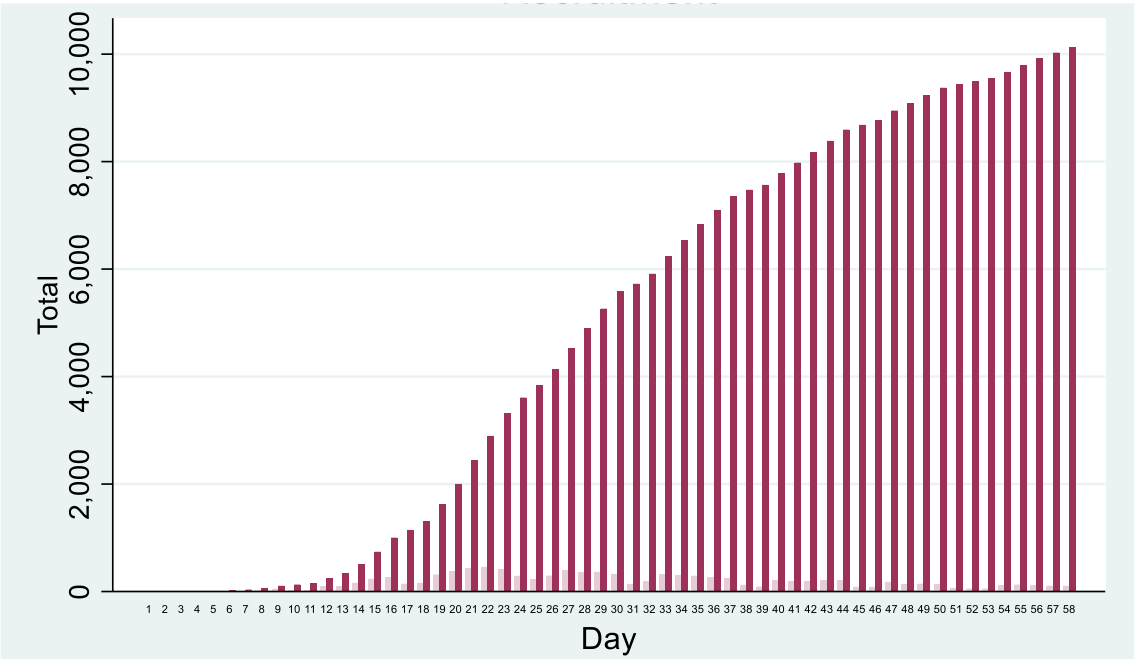
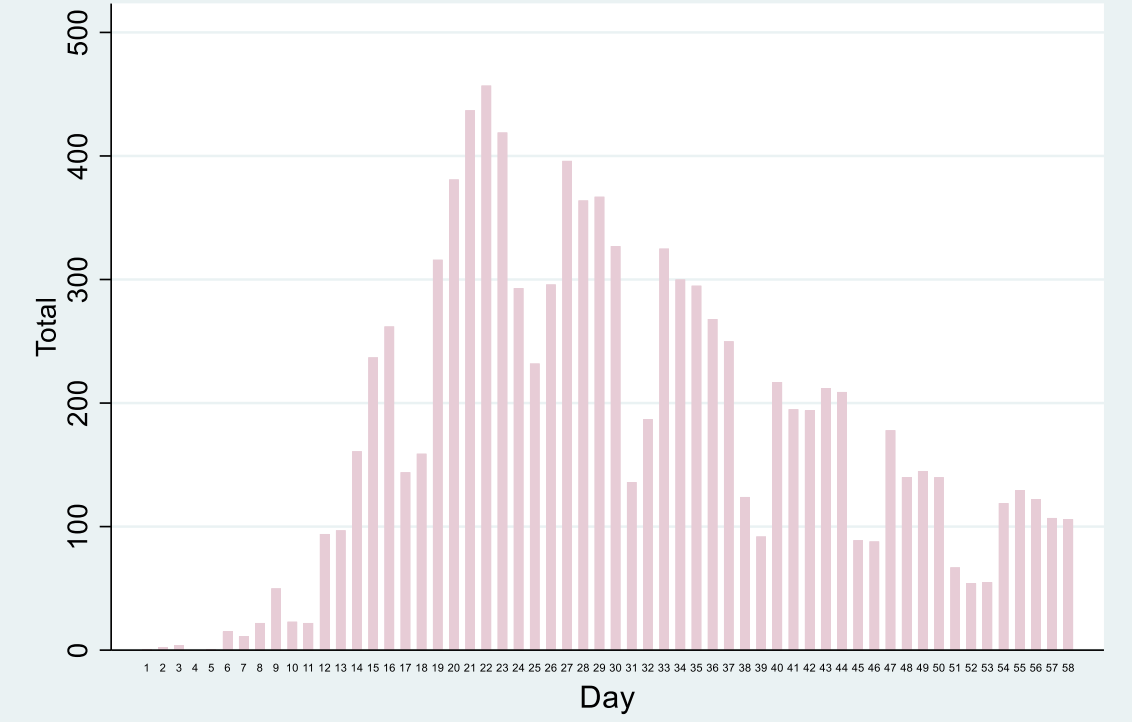
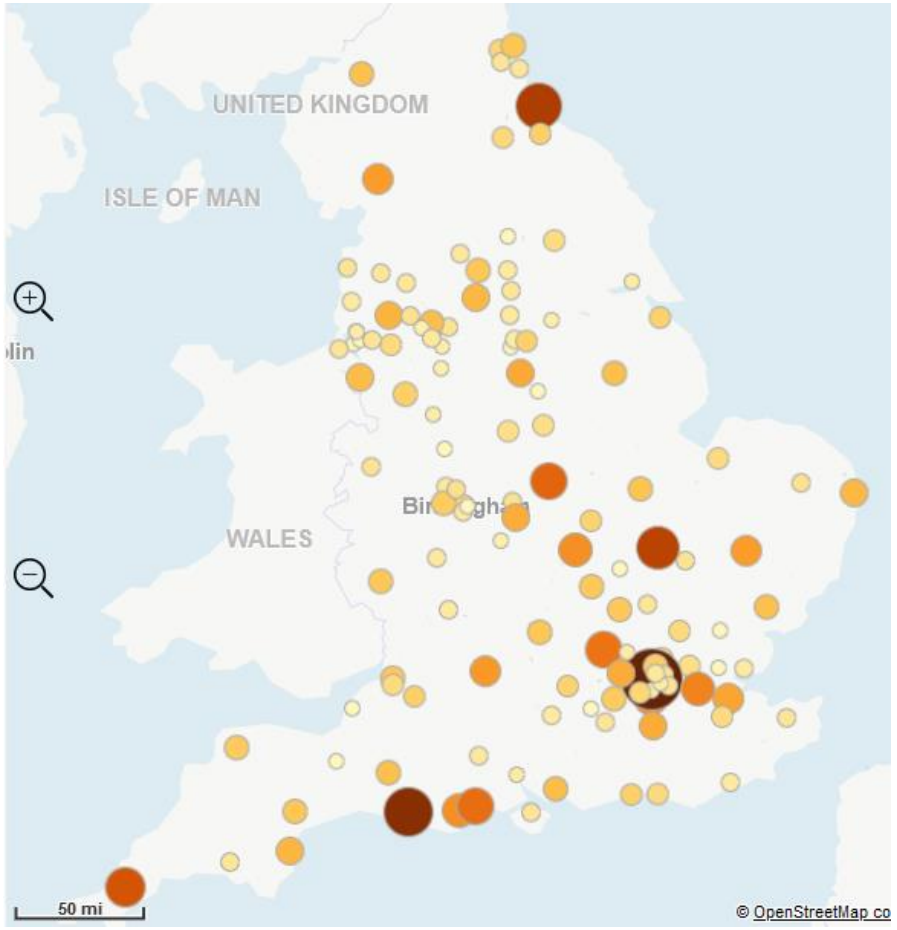
Total recruitment



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 58% (nearly 40 fold!)

Characteristics at main randomisation (n=9968)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		6142 (64%)
Age		66 (15)
Days since symptom onset		9 (5-13)
Days since hospitalisation		2 (1-5)
Severity of disease	No oxygen required	2229 (23%)
	Supplemental oxygen only	5983 (62%)
	Ventilation/ECMO	1458 (15%)
Prior disease	Diabetes	2600 (27%)
	Cardiovascular disease	2497 (26%)
	Chronic lung disease	2047 (21%)

When will we get some answers?

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- Although over 10,000 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 13th May)

Second randomisation

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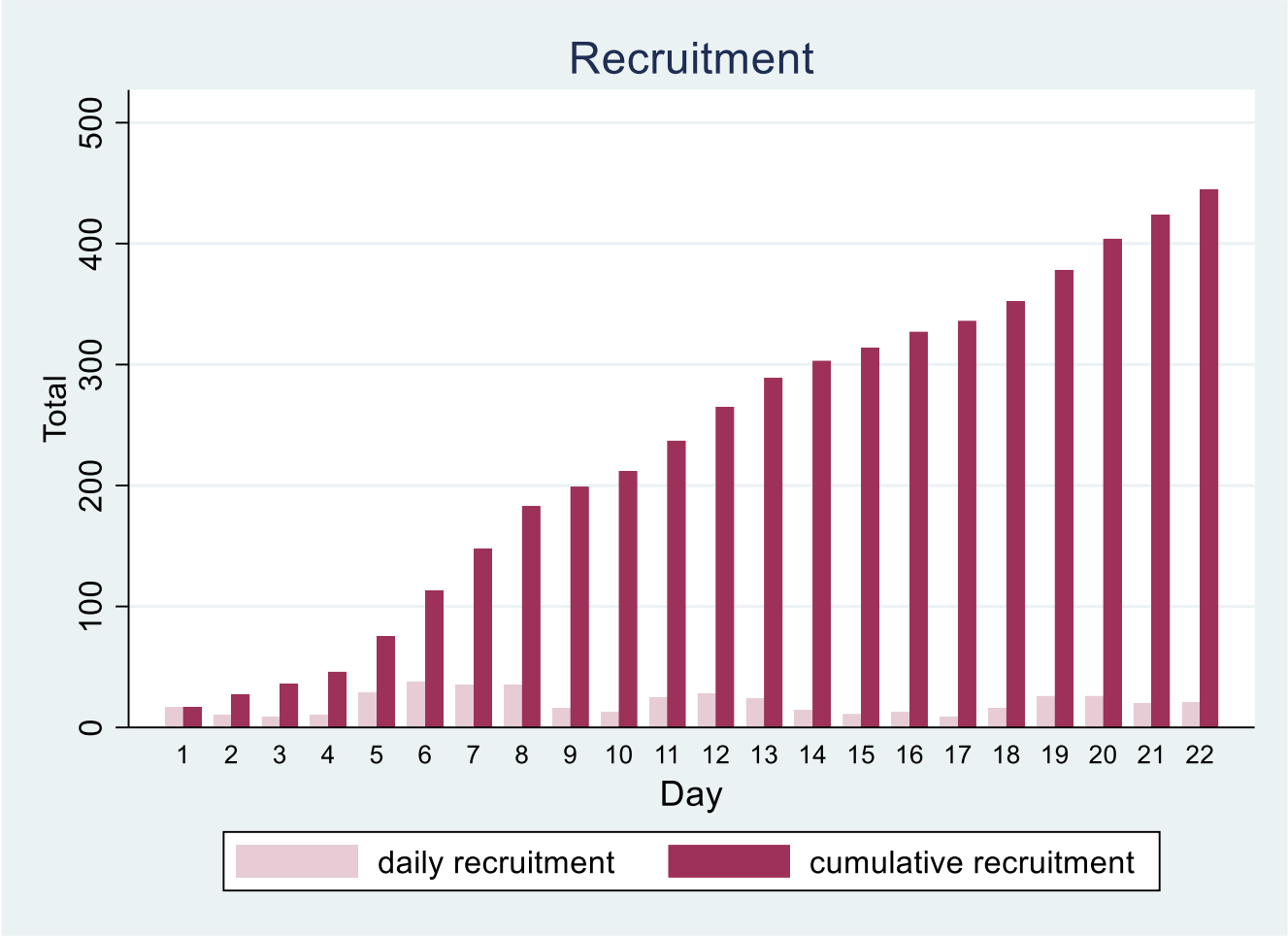

Characteristics at second randomisation (n=352)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		237 (67%)
Age		62 (13)
Days since symptom onset		13 (8-19)
Days since hospitalisation		4 (2-9)
Ventilation support	None	125 (36%)
	CPAP/NIV/HFNO	110 (31%)
	Ventilation/ECMO	117 (33%)
Biochemistry	CRP (mg/L)	178 (118-251)
	Ferritin (ng/mL)	1193 (534-2332)
	Creatinine (µmol/L)	74 (54-109)

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CONVALESCENT PLASMA

Trial design

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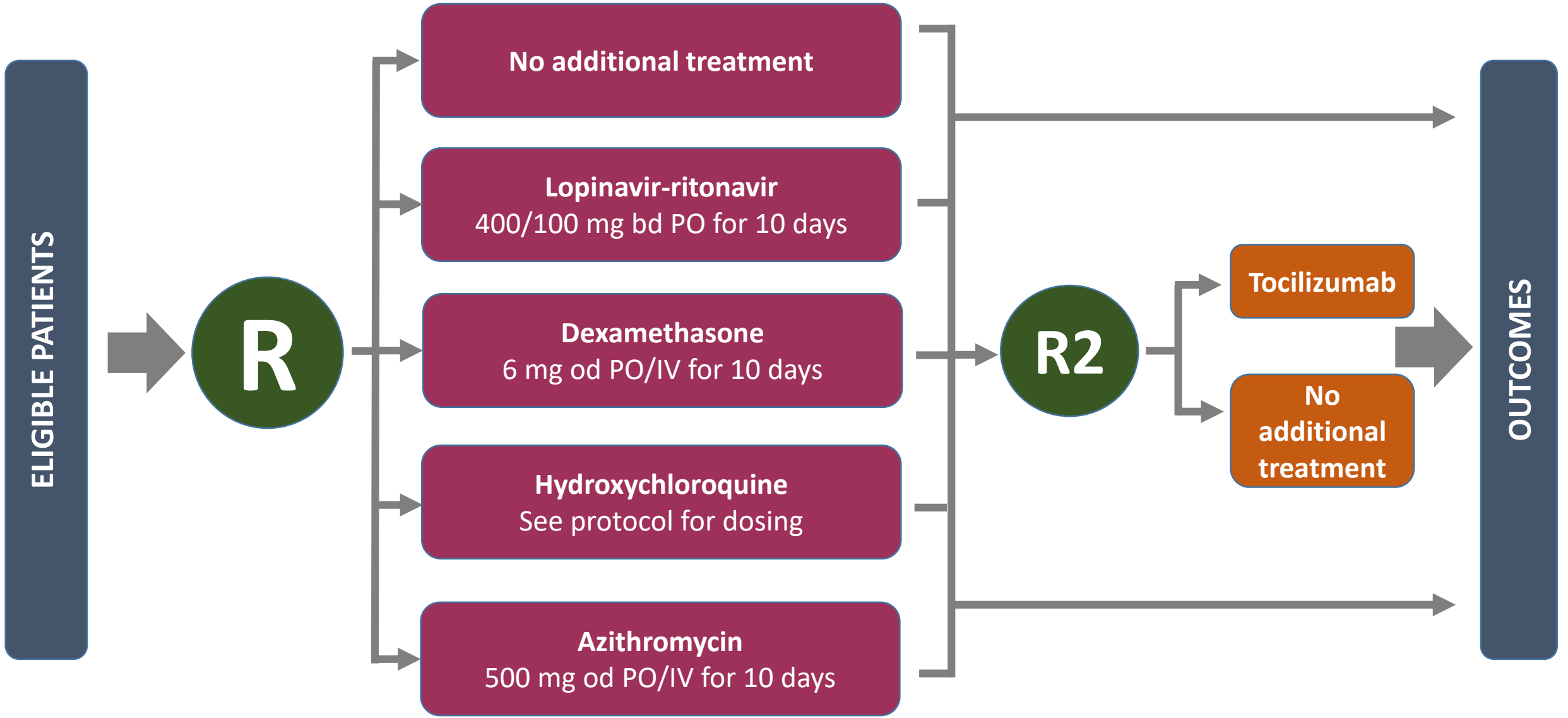

Adding convalescent plasma in factorial design

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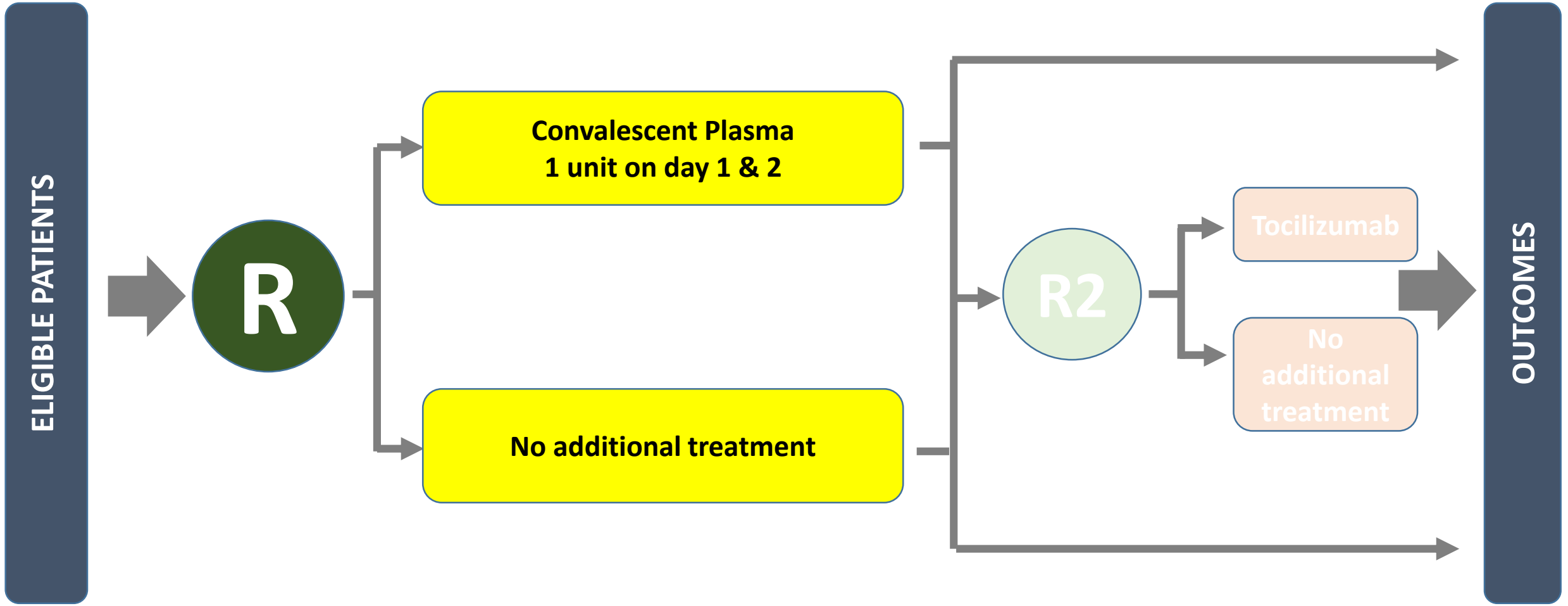

Adding convalescent plasma in factorial design

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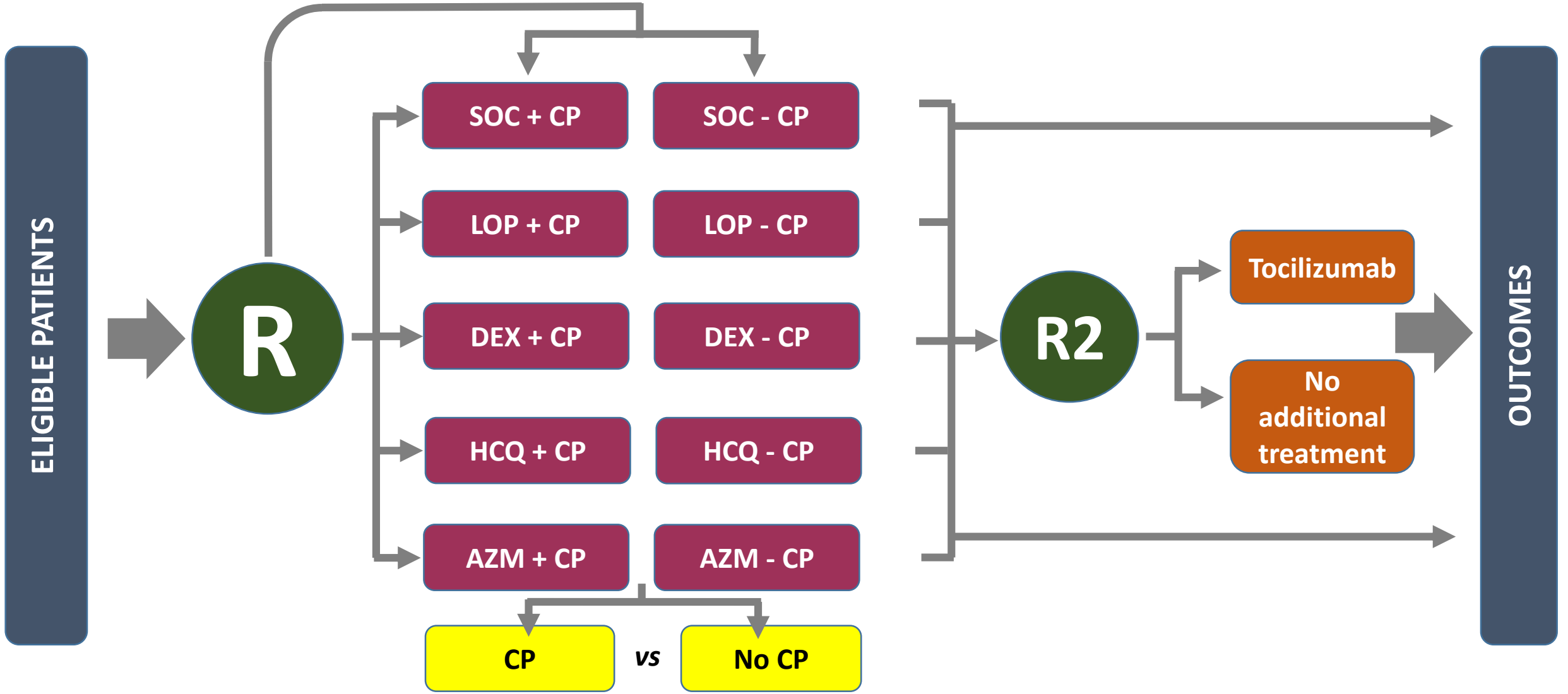

Convalescent plasma

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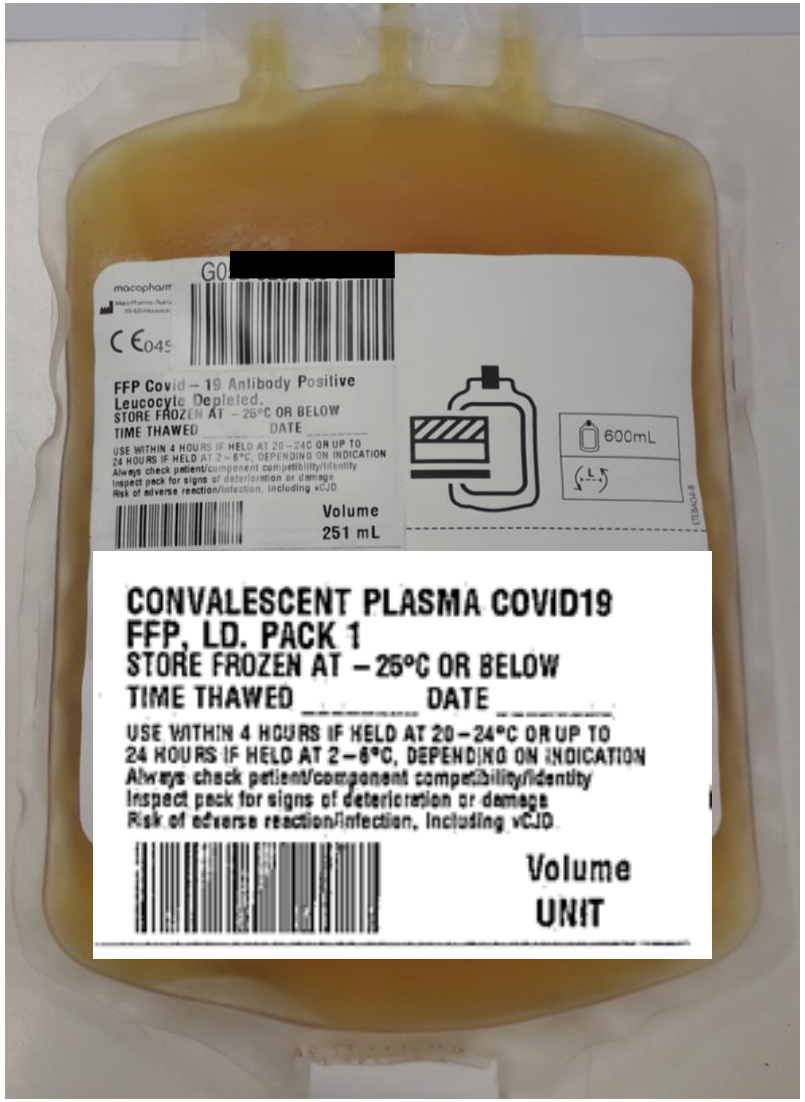
- Convalescent plasma COVID-19 FFP (CP) is plasma donated from patients who have recovered from COVID-19 and contains antibodies which may neutralise SARS-CoV-2 virus.
- Some low quality data to suggest it may be effective in viral pneumonia
- Need robust data from larger RCTs so has been included in RECOVERY and REMAP-CAP protocols



NHS
Blood and Transplant

Consent and Randomisation

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- RECOVERY PIS+ICF V5.0 has information on CP and extra line on consent form:

6. OPTIONAL: Convalescent plasma: I am aware that I may be offered convalescent plasma as one of the treatments I may receive. I have indicated my agreement (or not) to receive this by initialing the appropriate box.	**I agree**	**I do not agree**

- Randomisation form has questions on:
  - Participant's willingness to receive CP (i.e. the answer above)
  - Participant's suitability for CP
  - Availability of CP

Potential hazards of CP

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- Antibody-dependent enhancement
  - Theoretically antibodies may promote viral entry into cells and accelerate disease
  - No clear evidence of this in humans
- Transfusion-associated circulatory overload (TACO)
  - Assess patient's volume status and risk of circulatory overload before prescribing CP
- Hypersensitivity reaction to plasma

Allocation and access to CP

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- Allocations will be displayed:

Allocated treatment for the RECOVERY trial
Usual standard management

AND

Allocated treatment for Part B
Convalescent plasma

- **BEFORE** convalescent plasma can be supplied by transfusion lab:
  - Two Group & Screen samples must have been sent to laboratory (taken at separate times)
- **BEFORE** administering convalescent plasma:
  - Assess for potential transfusion associated circulatory overload

Prescription of CP

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- Adult dose: One unit (275 ± 75 mL) on days 1 and 2
  - At least 12 hours apart
- Paediatric dose = 5 mL/kg
  - See protocol for neonatal details
- Should be handled according to standard procedures
  - Prescribed as for FFP
  - Administer as soon as possible and within 4 hours of defrosting if at room temperature or up to 24 hours if refrigerated between 2 - 6^{o}C
  - All standard administration checks and records

Additional early safety data collection for first 200 CP recipients/controls

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- In first 72 hours after randomisation, has the participant had:
  - Sudden worsening in respiratory status
  - Severe allergic reaction
  - Temperature >39°C or ≥2°C rise above baseline
  - Sudden hypotension (defined as either (i) sudden drop in systolic blood pressure of ≥30 mmHg with systolic blood pressure ≤80 mmHg; or (ii) requiring urgent medical attention)
  - Clinical haemolysis (defined as fall in haemoglobin plus one or more of the following: rise in lactate dehydrogenase (LDH), rise in bilirubin, positive direct antiglobulin test (DAT), or positive crossmatch)

- How many units of CP were given and were any stopped early
- This information will be collected on additional OpenClinica form
- Standard SHOT reporting will also be used for all participants receiving CP

Will my site be a CP site?

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- Availability of convalescent plasma quite limited at present
- Transfusion laboratory and practitioners need training (as well as trial staff)
- Centres will be contacted as this part of trial is rolled out across the UK

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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

Reminder e-mails

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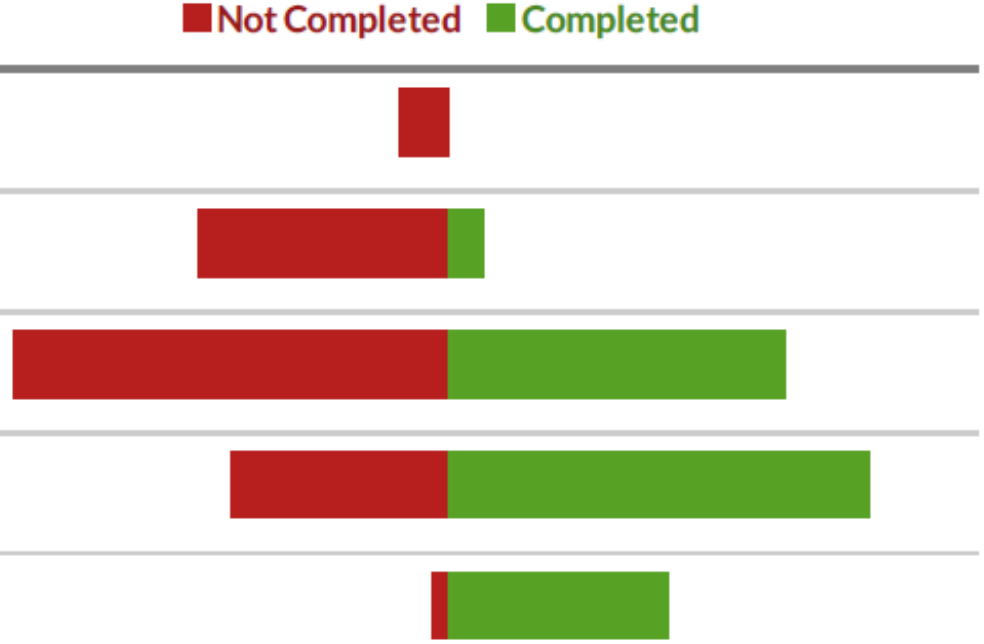
Follow-up form completion summary

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**



Reminder e-mails

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Patients recruited at this site with at least one Follow-up CRF due

Patient study no.	CRF due	Due by	Due from	Status	Days overdue
1038179	Follow-up	10/05/20	*this site*	not started	7
1045224	Follow-up	12/05/20	*this site*	started by [redacted]	5
1046744	Follow-up	13/05/20	*this site*	not started	4
1051941	Follow-up	14/05/20	*this site*	not started	3
1052319	Follow-up	14/05/20	*this site*	not started	3
1052540	Follow-up	14/05/20	*this site*	started by [redacted]	3
1052557	Follow-up	14/05/20	*this site*	not started	3
1052950	Follow-up	15/05/20	*this site*	not started	2
1053030	Follow-up	15/05/20	*this site*	not started	2

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

International Clinical Trials Day

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What? Celebrate all those involved in clinical trials
Raise awareness of clinical trials amongst the 'general' public

When? Wednesday 20 May

How? Social media #CTD2020 #RECOVERYtrial directing to https://www.recoverytrial.net/ - and in person

More info https://www.clinicaltrialsday.org/

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
- Please stay on the line if you want to hear more about RECOVERY for pregnant women
- Otherwise, thank you!

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PREGNANT WOMEN

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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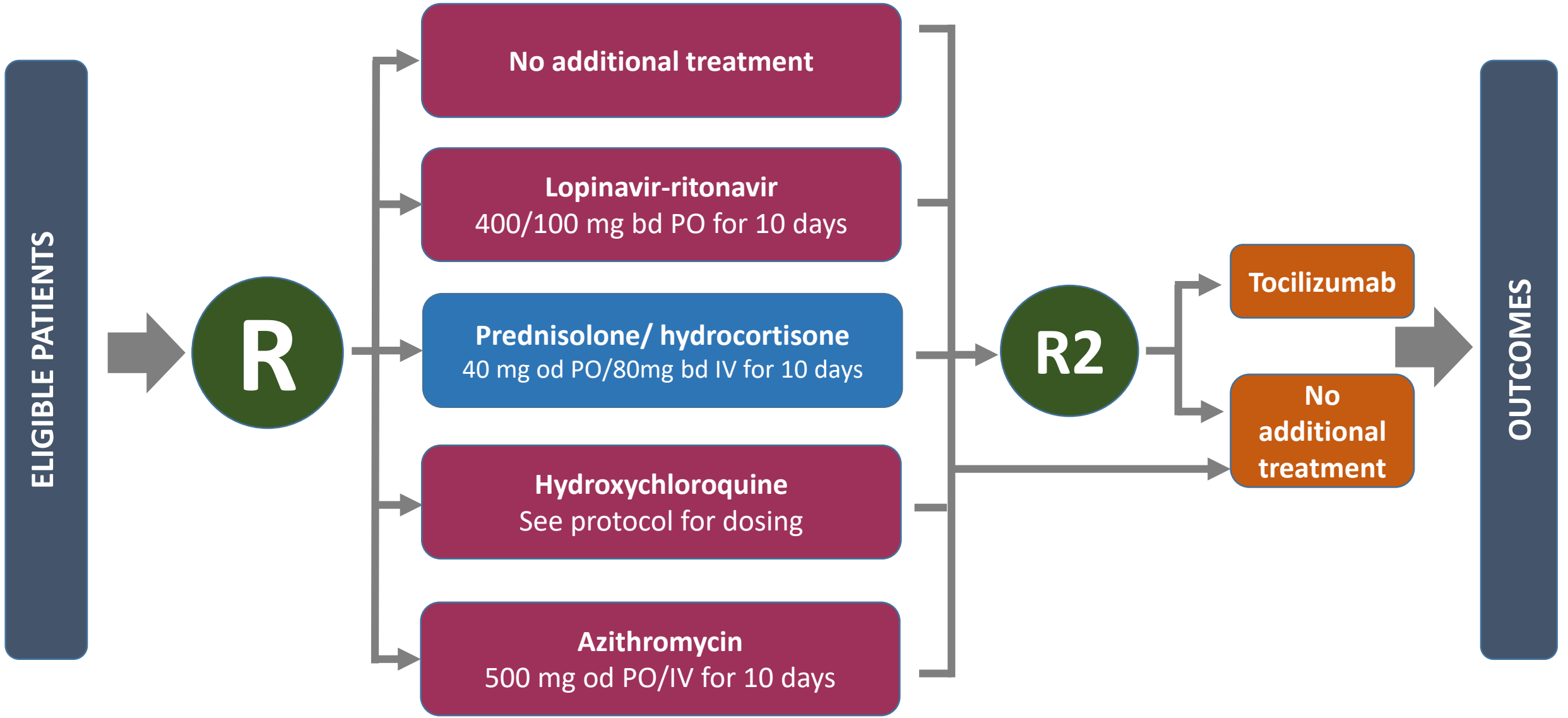

Use of drugs in pregnancy

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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

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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/

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

- 158 pregnancy leads identified, supported by research midwives
- Midwife champions on board
- 11 women recruited

- Ask yourself whether every woman reportable to UKOSS can be offered the trial…

Future plans

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Health

Coronavirus: Thousands signal interest in plasma trial

- Forecasting of case numbers in coming months?

Q&A

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