Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

19th 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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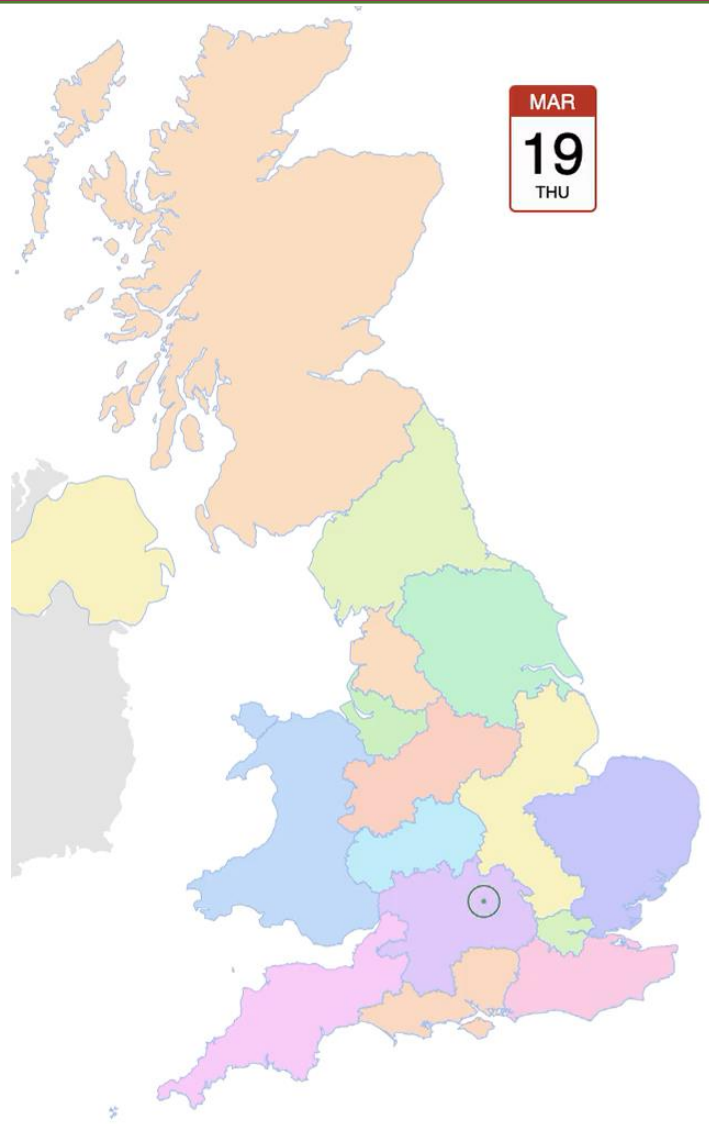

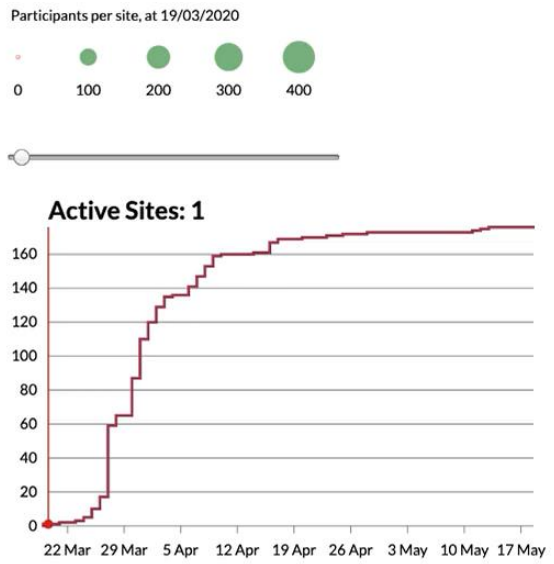

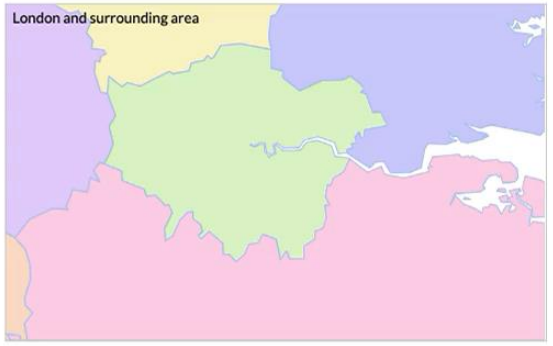

Recruitment progress

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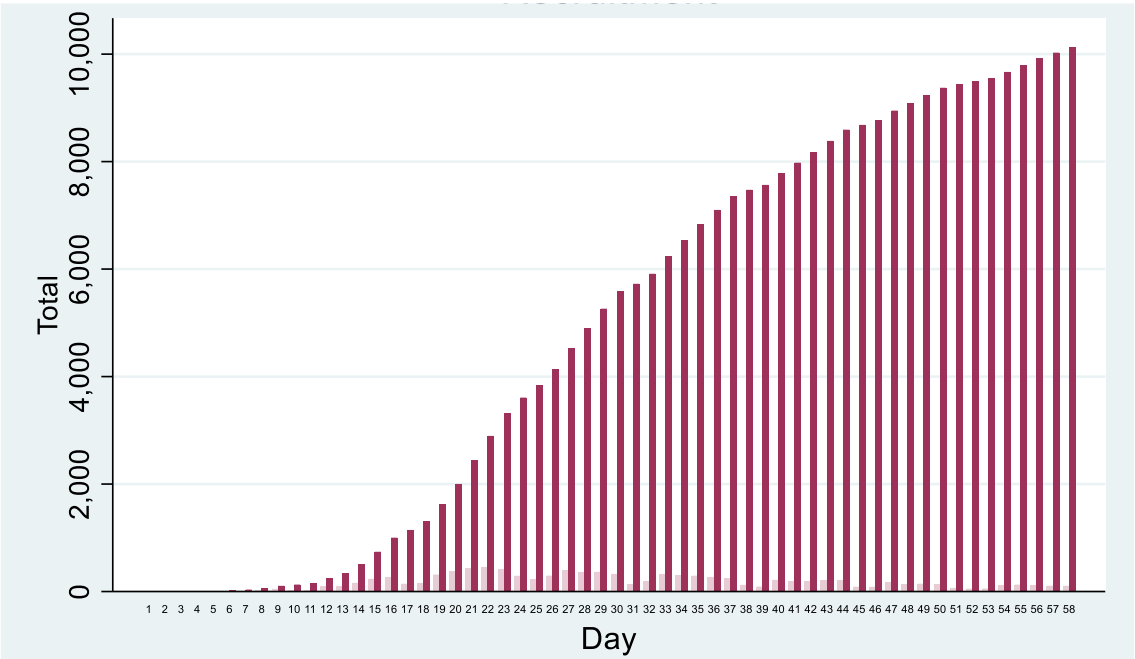
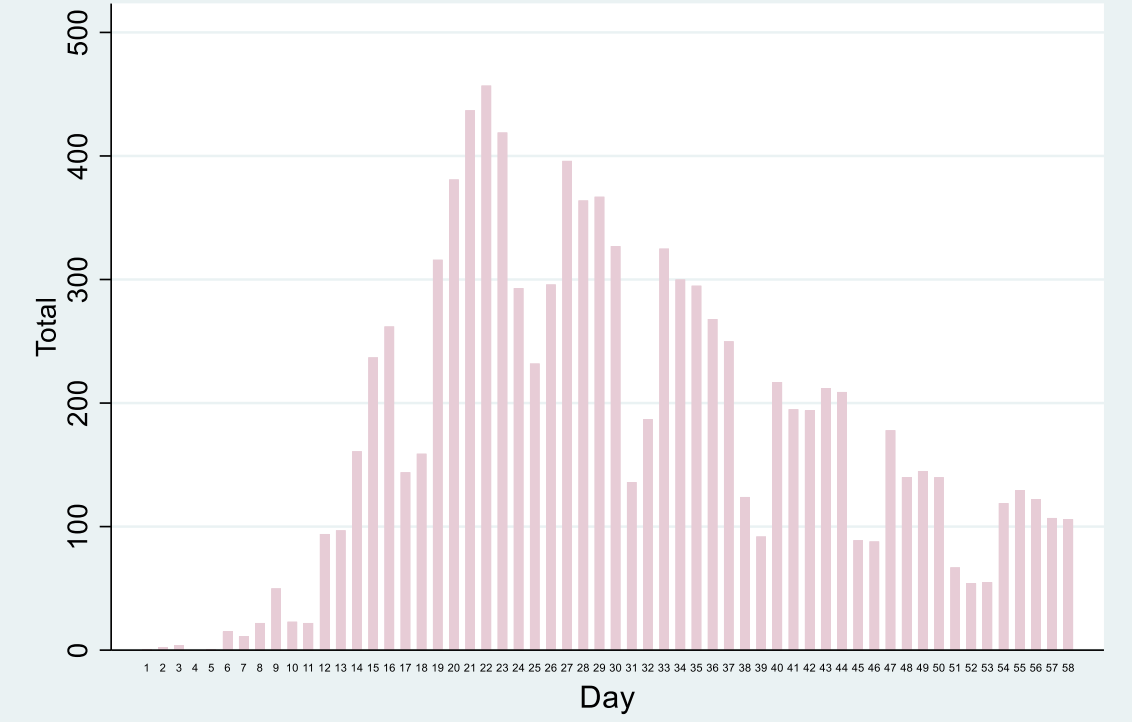
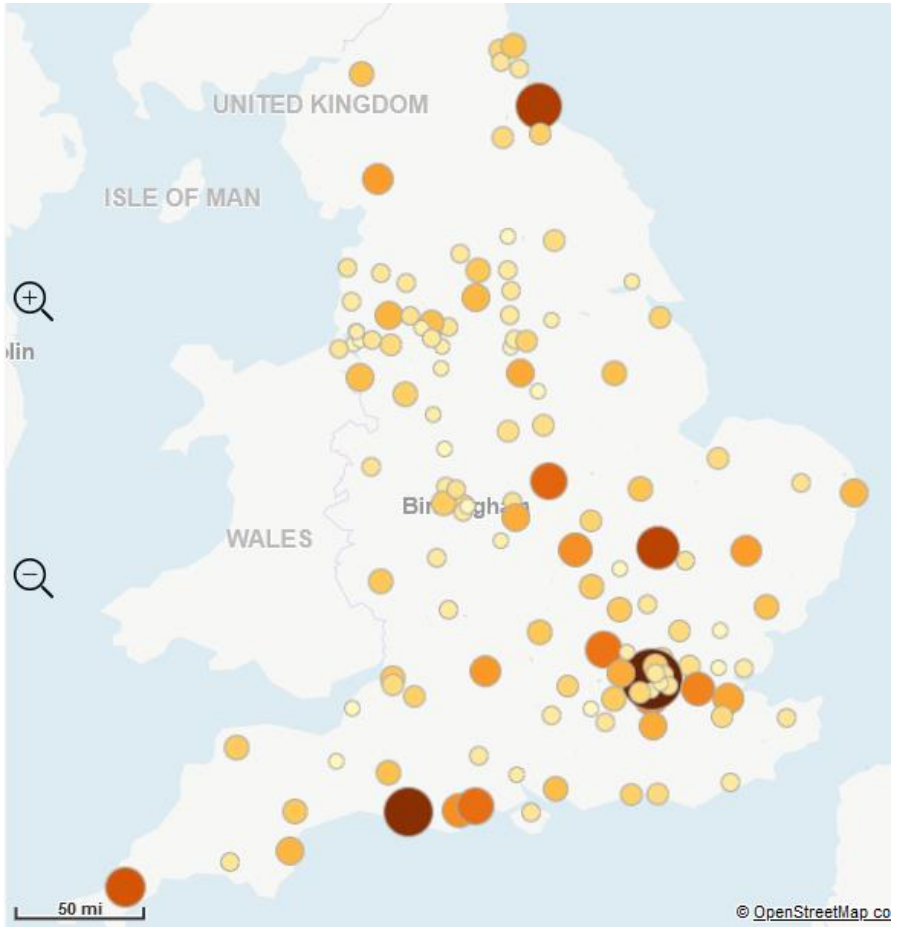
Total recruitment



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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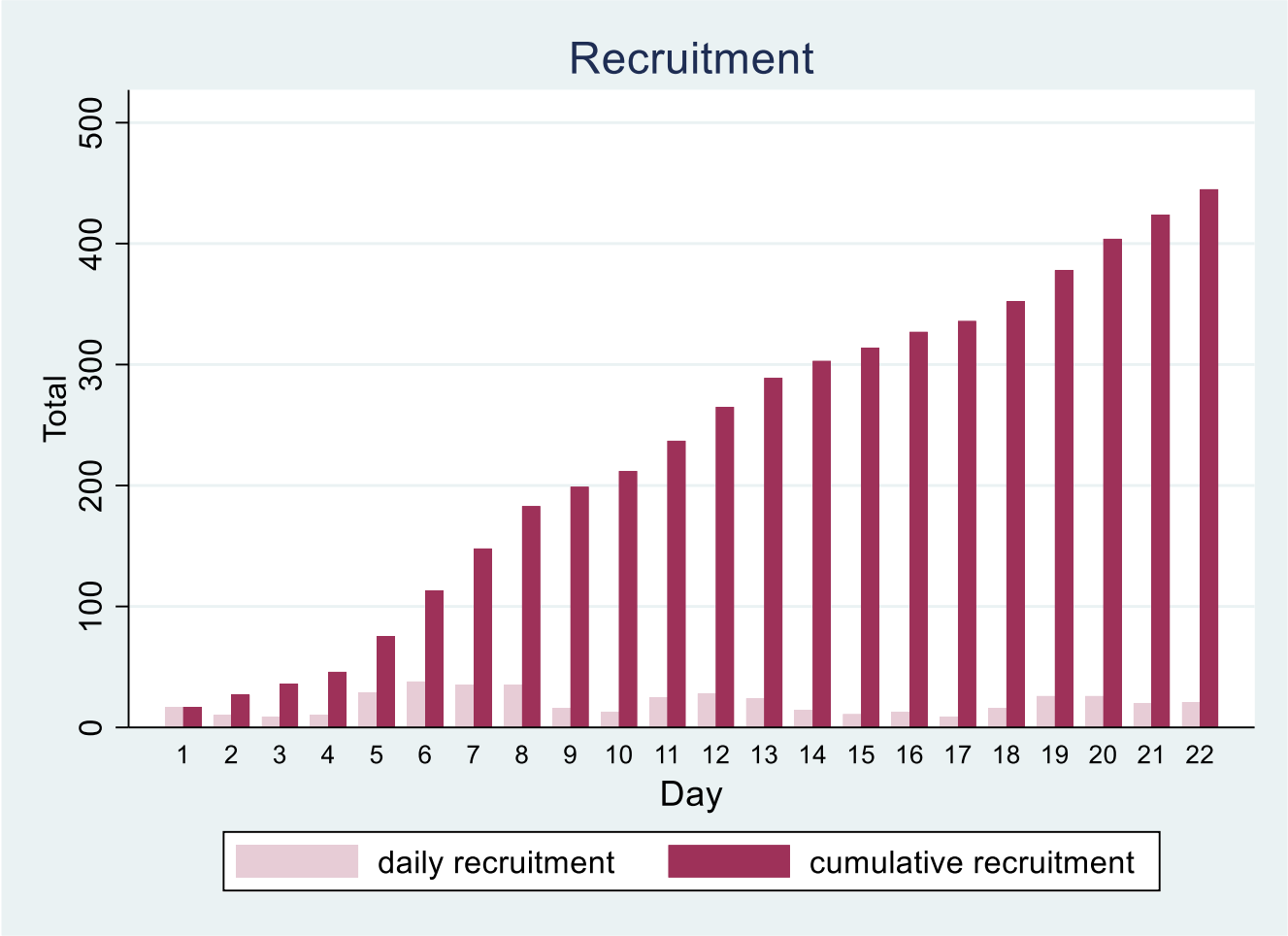

Characteristics at second randomisation (n=352)

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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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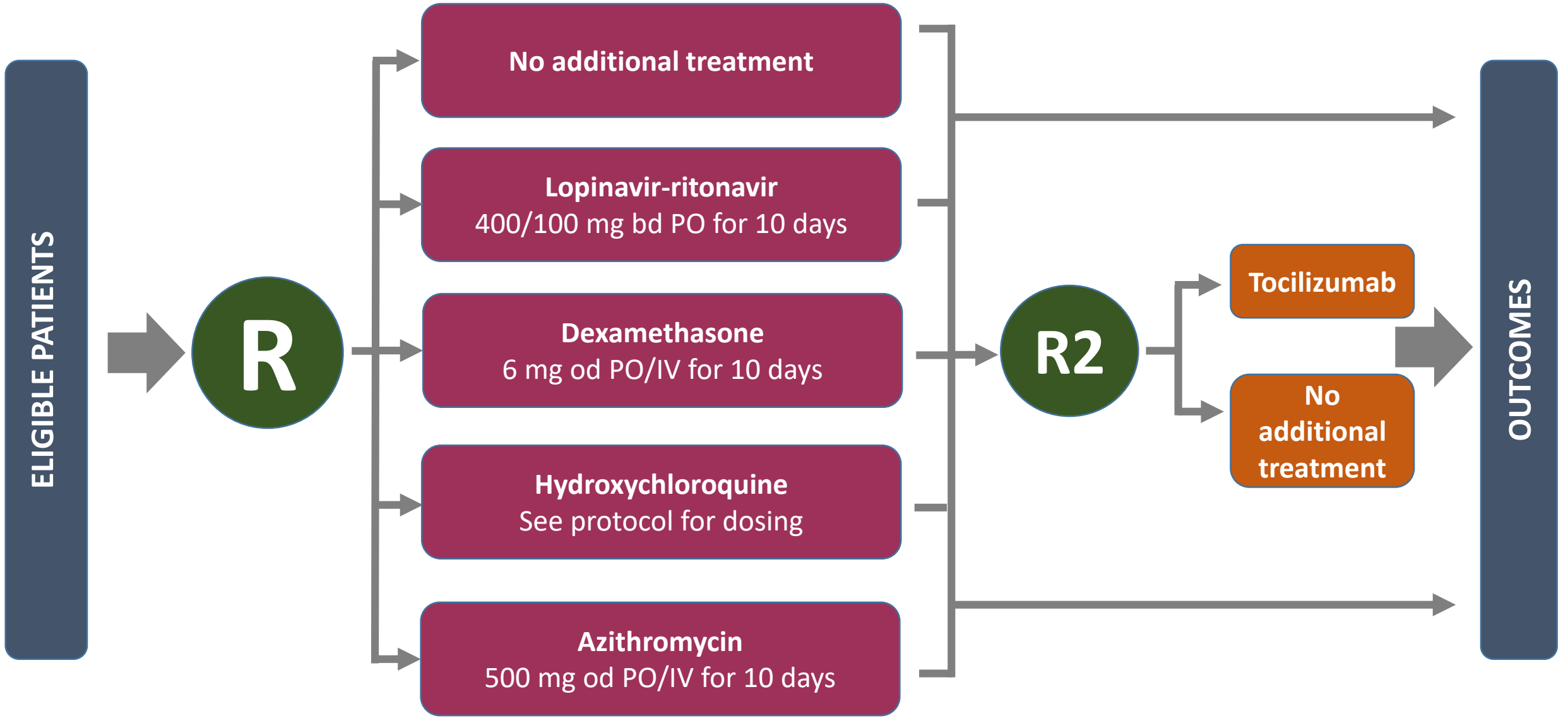

Adding convalescent plasma in factorial design

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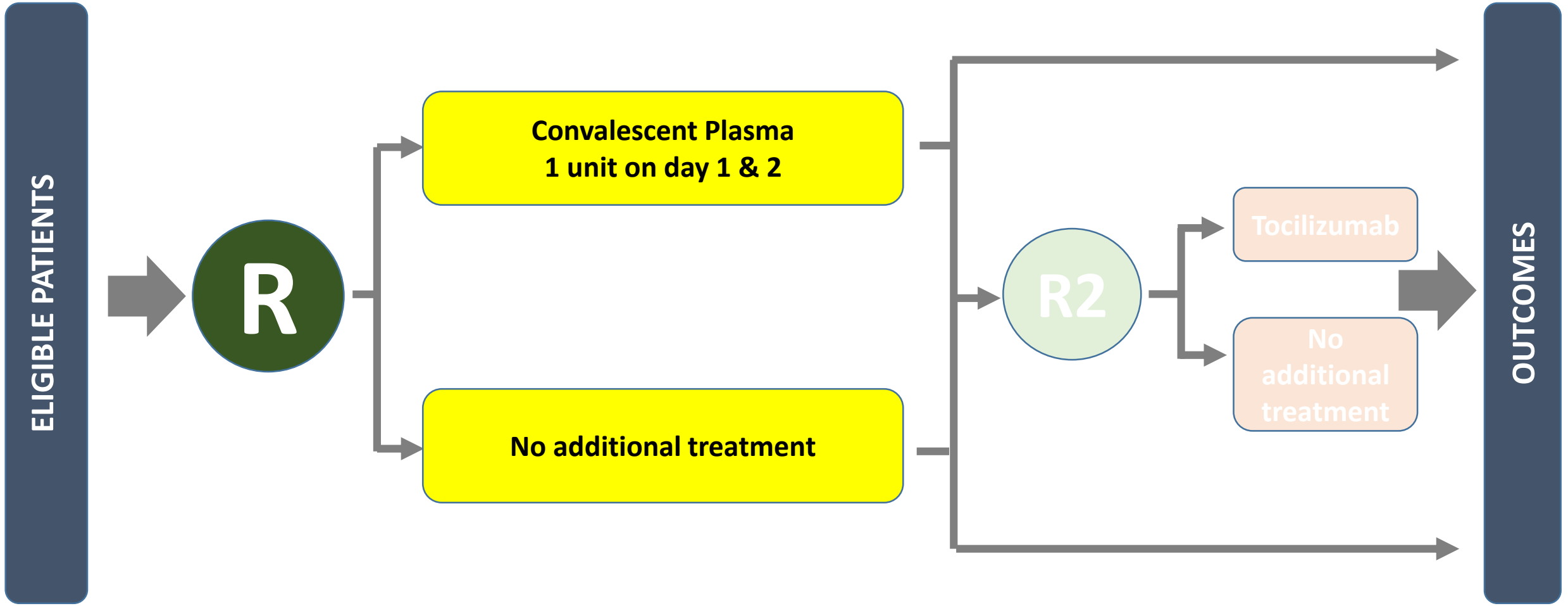

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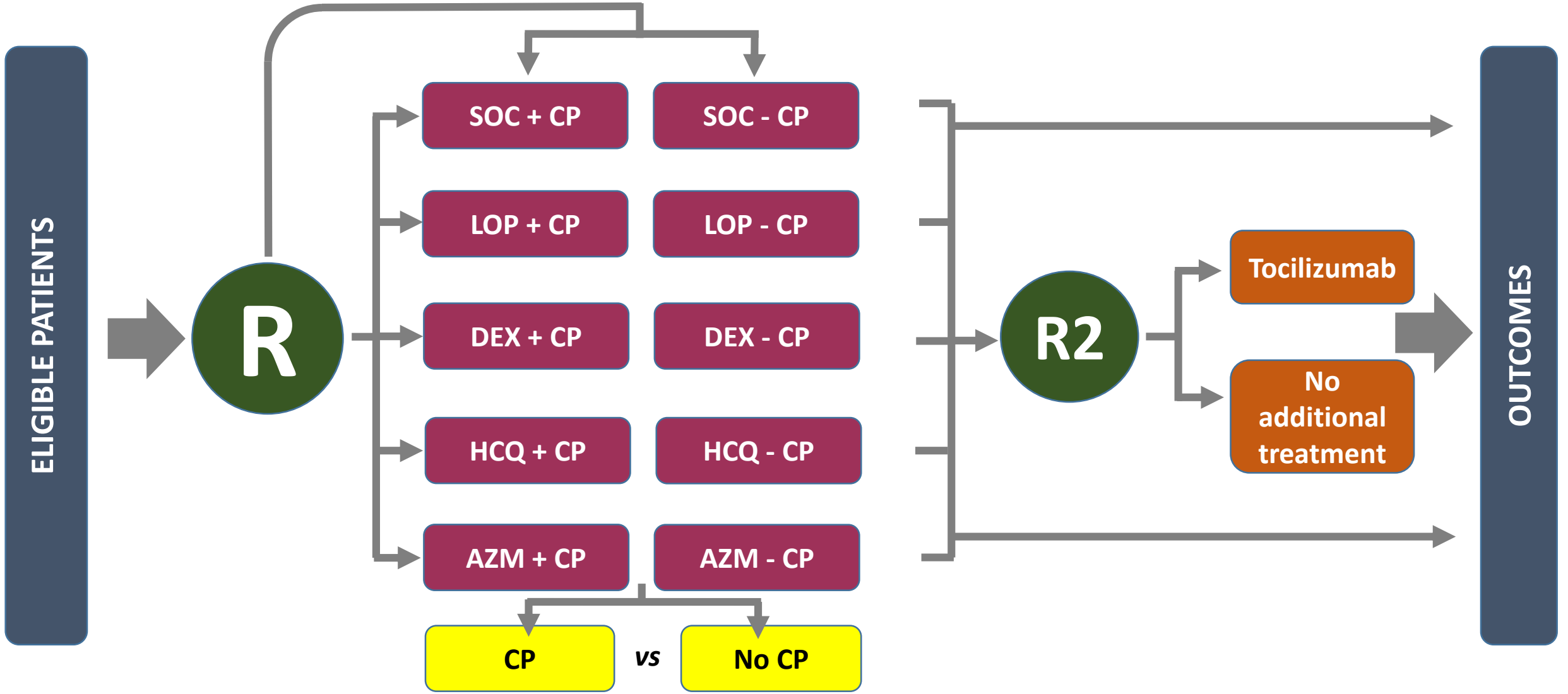

Convalescent plasma

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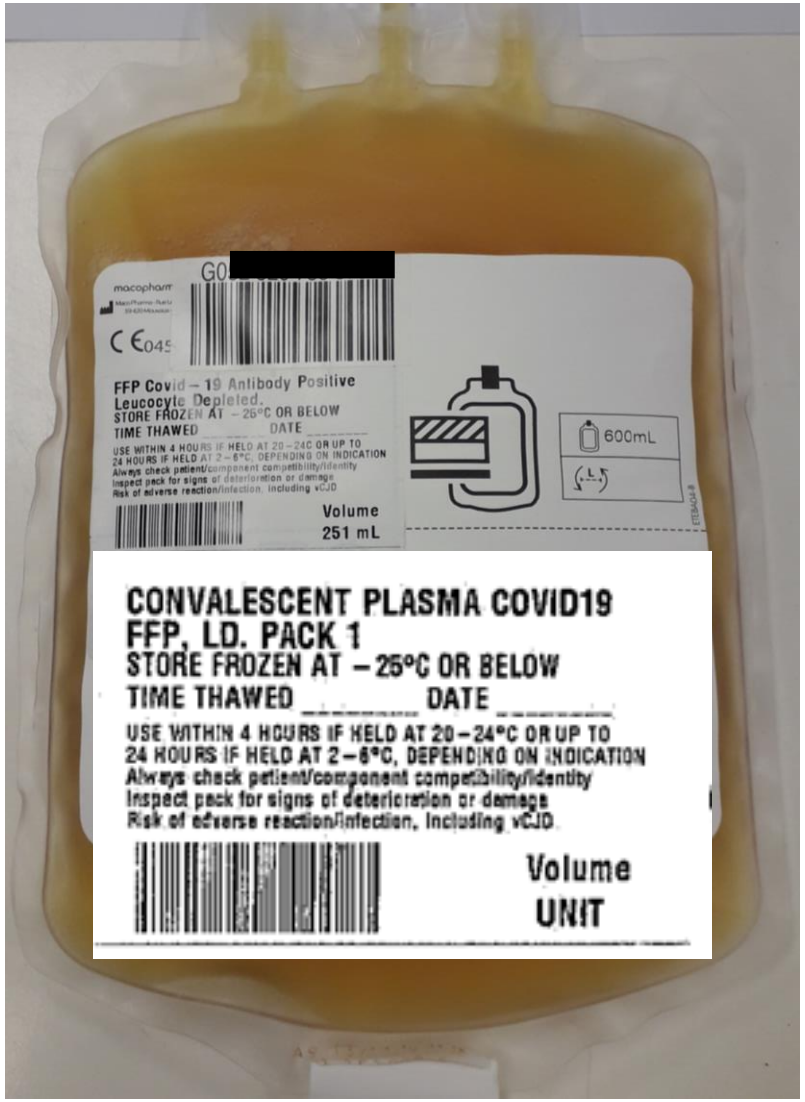
- Convalescent plasma COVID-19 FFP (CP) is plasma donated from patients who have recovered from COVID-19 and contains antibodies which may neutralise SARS-CoV-2 virus.
- Some low quality data to suggest it may be effective in viral pneumonia
- Need robust data from larger RCTs so has been included in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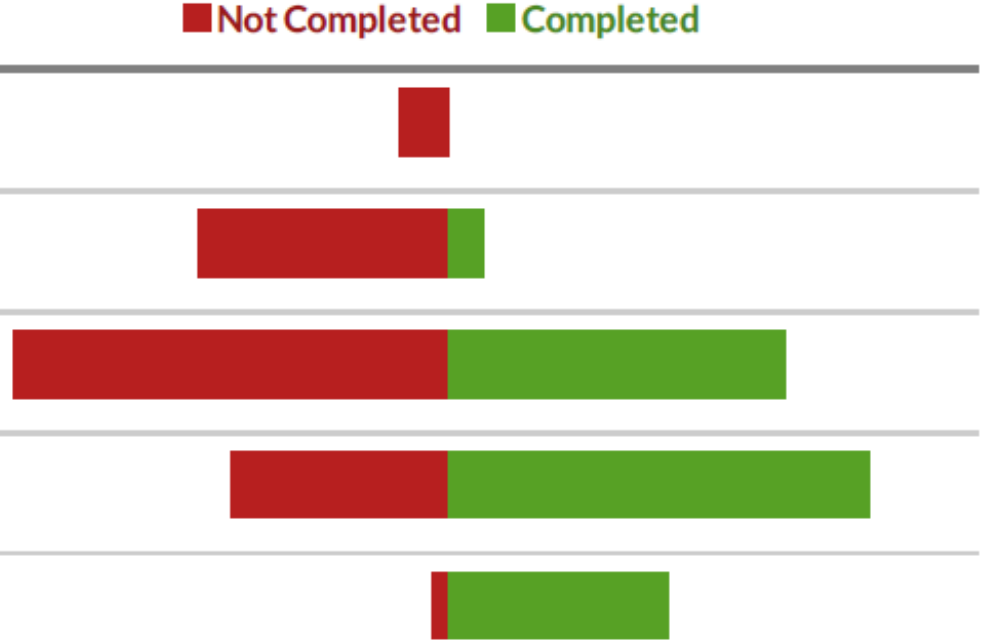
Follow-up form completion summary

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
- Thank you!

Paediatric multisystem inflammatory syndrome temporally associated with COVID -19

Athimalaipet V Ramanan

Professor of Paediatric Rheumatology

Bristol Royal Hospital for Children, Bristol, UK

University of Bristol, UK

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COVID-19

RCPCH
Royal College of Paediatrics and Child Health
Leading the way in Children's Health

Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Shares clinical features with-

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- Kawasaki disease
- Staphylococcal and streptococcal toxic shock syndrome
- Bacterial sepsis
- Macrophage activation syndrome

CASE DEFINITION

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- A child presenting with
  - persistent fever
  - inflammation (neutrophilia, elevated CRP and lymphopaenia)
  - evidence of single or multi-organ dysfunction

  (This may include children fulfilling full or partial criteria for Kawasaki disease)
- Exclusion of any other microbial cause, including
  - bacterial sepsis
  - staphylococcal or streptococcal shock syndromes
  - infections associated with myocarditis such as enterovirus
- SARS-CoV-2 PCR testing may be positive or negative

CLINICAL FEATURES

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- **All:**

  Persistent fever >38.5°C

- **Most:**
  - Oxygen requirement
  - Hypotension

- **Some**
- Abdominal pain ,vomiting, diarrhoea
- Confusion, headache
- Conjunctivitis
- Cough ,sore throat
- Lymphadenopathy
- Mucus membrane changes
- Rash
- Swollen hands and feet

LABORATORY MARKERS

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- Abnormal Fibrinogen
- Absence of potential causative organisms (other than SARS-CoV-2)
- High CRP
- High D-Dimers
- High ferritin
- Hypoalbuminaemia
- Lymphopenia
- Neutrophilia in most
- Raised LDH

IMAGING AND ECG

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- Echo and ECG – myocarditis, valvulitis, pericardial effusion, coronary artery dilatation
- CXR – patchy symmetrical infiltrates, pleural effusion
- Abdo USS – colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly
- CT chest/ CXR – may demonstrate coronary artery abnormalities if with contrast

MANAGEMENT

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- Look for multisystem involvement (liver, renal, neurological etc.).
- Empiric antibiotics as per local protocols.
- Consider IVIG and aspirin early if fulfils criteria for Kawasaki Disease.
- Consider IVIG if fulfils criteria for toxic shock syndrome.

Deterioration can be rapid

MONITORING FOR WORSENING INFLAMMATION

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Clinical

- Worsening fever
- Cardiorespiratory deterioration
- Worsening gastrointestinal symptoms
- Increasing hepatosplenomegaly or lymphadenopathy
- Extending rash
- Worsening neurological symptoms

Laboratory

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- Falling blood cell counts
- Rising ferritin
- Unexpectedly low or falling ESR
- Rising fibrinogen or new onset low fibrinogen
- Rising ALT, AST or LDH
- Rising triglycerides
- Rising D-dimers
- Low serum sodium with worsening renal function

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THANK YOU

Inclusion of infants 0 – 28 days with suspected or proven COVID-19 infection in the RECOVERY trial

Charles C Roehr

NPEU

University of Oxford

COVID-19 infection in the neonatal period

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- 27 publications incl. 217 newborns with suspected COVID-19:
  - 7 (3%) had evidence of SARS-CoV-2 infection , of these
  - 3 had positive serum levels of IgG and IgM antibodies with negative PCR tests, 4 SARS-CoV-2 PCR +ive (Shalish W et al. Am J Perinatol. 2020 May 2)
- NY-City study: Of 326 deliveries, 31 (9.5%) mothers testing +ive for SARS-CoV-2: 15 (48%) were asymptomatic and 16 (52%) symptomatic (Perlman, J. pers. communication)
- Beyond the immediate postnatal period, several case studies report positive SARS-CoV-2 tests in symptomatic newborns in the first month of life, and new reports are published frequently

Case presentation

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BBC news, May 15th

Leia, twin 1. Age of infant undisclosed

Kawasaki-like Syndrome

Supportive management, including nasal cannula oxygen and a naso-gastric feeding tube

She is about to be discharged in good condition

https://www.bbc.co.uk/news/uk-wales-52682460

Coronavirus: Baby's life-threatening reaction to Covid-19

15 May 2020 Share

Coronavirus pandemic

The illness left baby Leia fighting for her life in hospital

Should we be treating babies with suspected or proven COVID-19?

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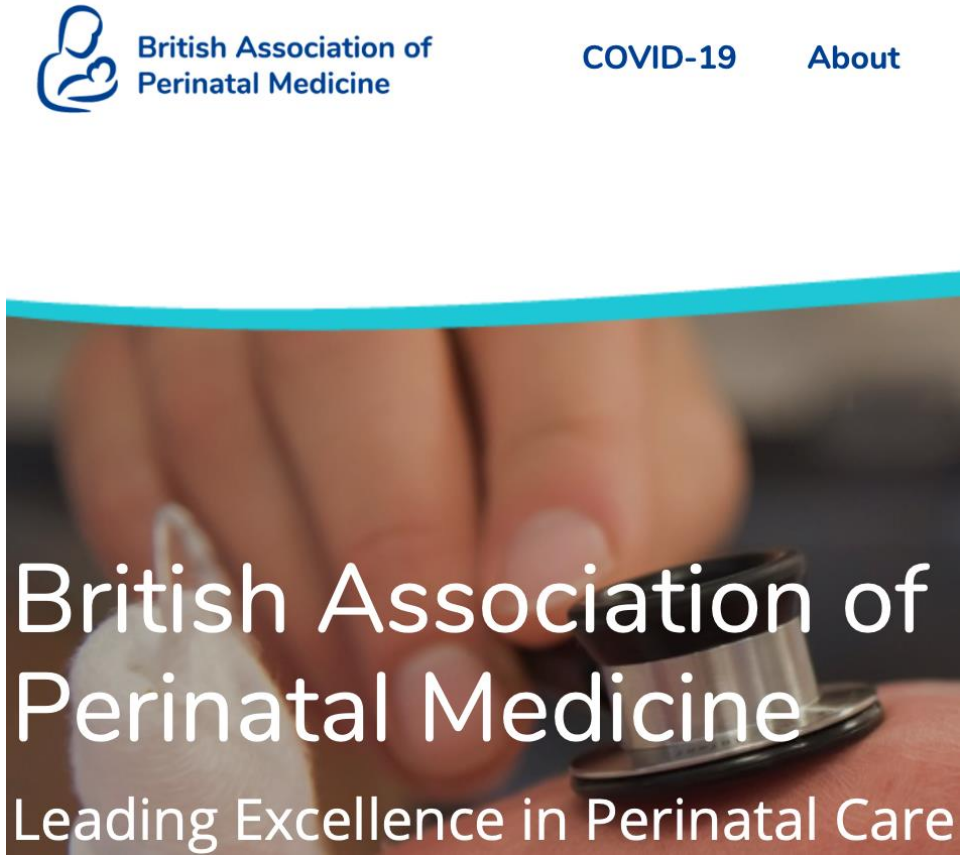
- For the few babies who develop suspected or confirmed infection, a robust evidence base is essential to guide the use of effective treatments and to avoid potential harm from severe or life-threatening disease.
- There are currently no proven treatments for COVID-19 for children.
- The Royal College of Paediatrics and Child Health (RCPCH) and the BAPM recommend that treatments for COVID-19 should only be used in the context of a treatment trial.



BAPM – guidance:
https://hubble-live-assets.s3.amazonaws.com/bapm/redactor2_assets/files/511/COVID-FAQs_7.5.20final.pdf

Considering treatment despite uncertainty about COVID-19 phenotype in babies?

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- Clinicians may chose to treat infants of any gestation on the basis of clinical signs alone, if there is a high index of suspicion for COVID-19 infection

- This may especially be the case where the clinical deterioration is not explained by existing neonatal conditions

- Where the cause of clinical deterioration or collapse is unknown, the possibility of COVID-19 infection should be strongly considered

Considering treatment in babies

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Disease severity	Intervention
Severe/critical disease • An increase in respiratory support to maintain oxygen saturations within agreed acceptable limits that is new or above a baby's baseline • Signs of sepsis with shock • Encephalopathy • Multi-organ failure	• Supportive care AND • Consider enrolment into a treatment evaluation trial

Considering treatment in babies

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Severe/critical disease • An increase in respiratory support to maintain oxygen saturations within agreed acceptable limits that is new or above a baby's baseline • Signs of sepsis with shock • Encephalopathy • Multi-organ failure	• Supportive care AND • Consider enrolment into a treatment evaluation trial • RECOVERY Trial protocol includes a choice of treatments see next slides

Neonatal patients - drugs and doses

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- Treatments for neonates:
  - Standard of care
  - Azithromycin: *10 mg/kg OD,* (for infants >16 kg or preterm infant)
  - Corticosteroids
    - At the discretion of the treating clinician:
      - Dexamethasone / Prednisolone / Methylprednisolone, as per protocol
    - For infants with corrected gestation age of < 40 weeks:
      - Hydrocortisone 0.5mg/kg BD for 7d, thereafter 0.5mg/kg OD for 3d
  - Convalescent plasma (coming up)

https://www.recoverytrial.net/files/recovery-protocol-v5-0-2020-04-24.pdf

Neonatal patients - drugs and doses

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- Drugs NOT open to babies and young children include:
  - Lopinavir-Ritonavir (<42 weeks or babies with postnatal age of < 14 days)
  - Hydroxychloroquine (postnatal age of < 180 days)
- Second randomisation to Tocilizumab is NOT available to children < 1 year
- For details, pls. see comprehensive frequently asked questions (FAQs) section, incl. a specific paediatric guidance document includes infants <28 days of life.

https://www.recoverytrial.net/files/recovery-protocol-v5-0-2020-04-24.pdf

Questions

Looking forward to answering your questions