Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

27th October 2020

Agenda

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1. Introductions
2. Update on progress
3. REGN-COV2
4. Tocilizumab
5. Other developments
6. Trial procedures
7. Neonatal update
8. 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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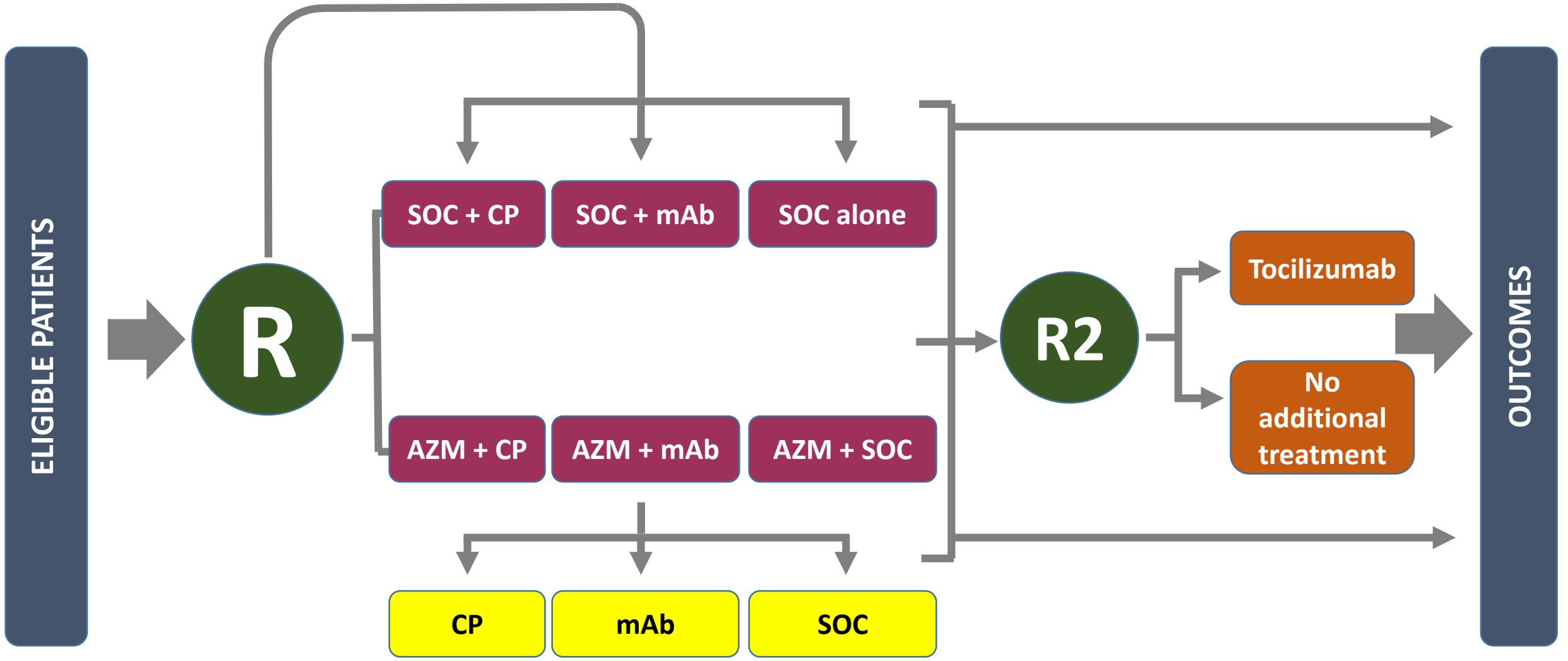

Recruitment by site and by time

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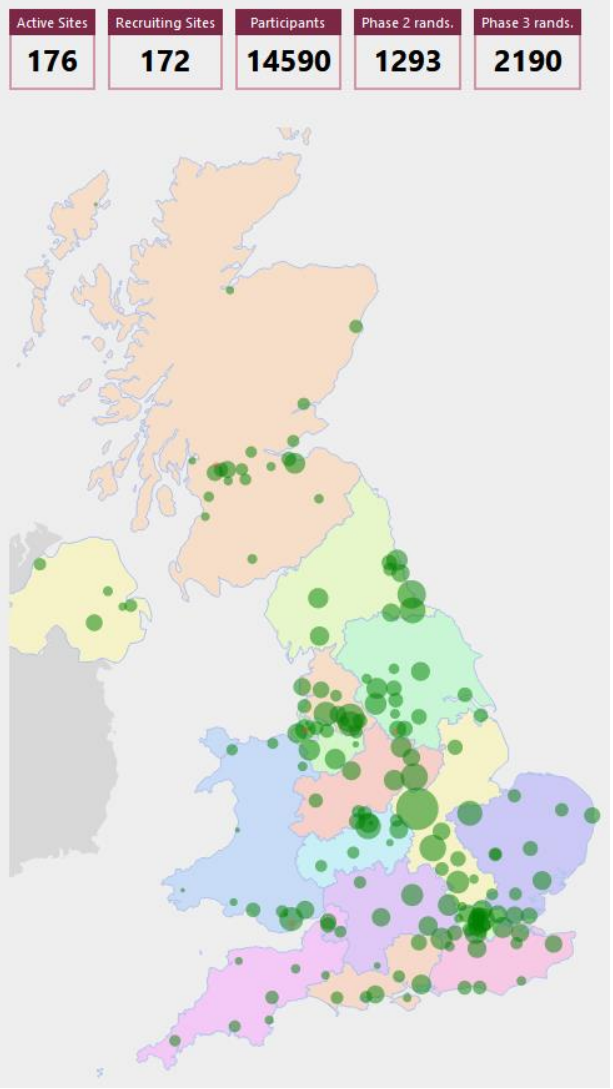

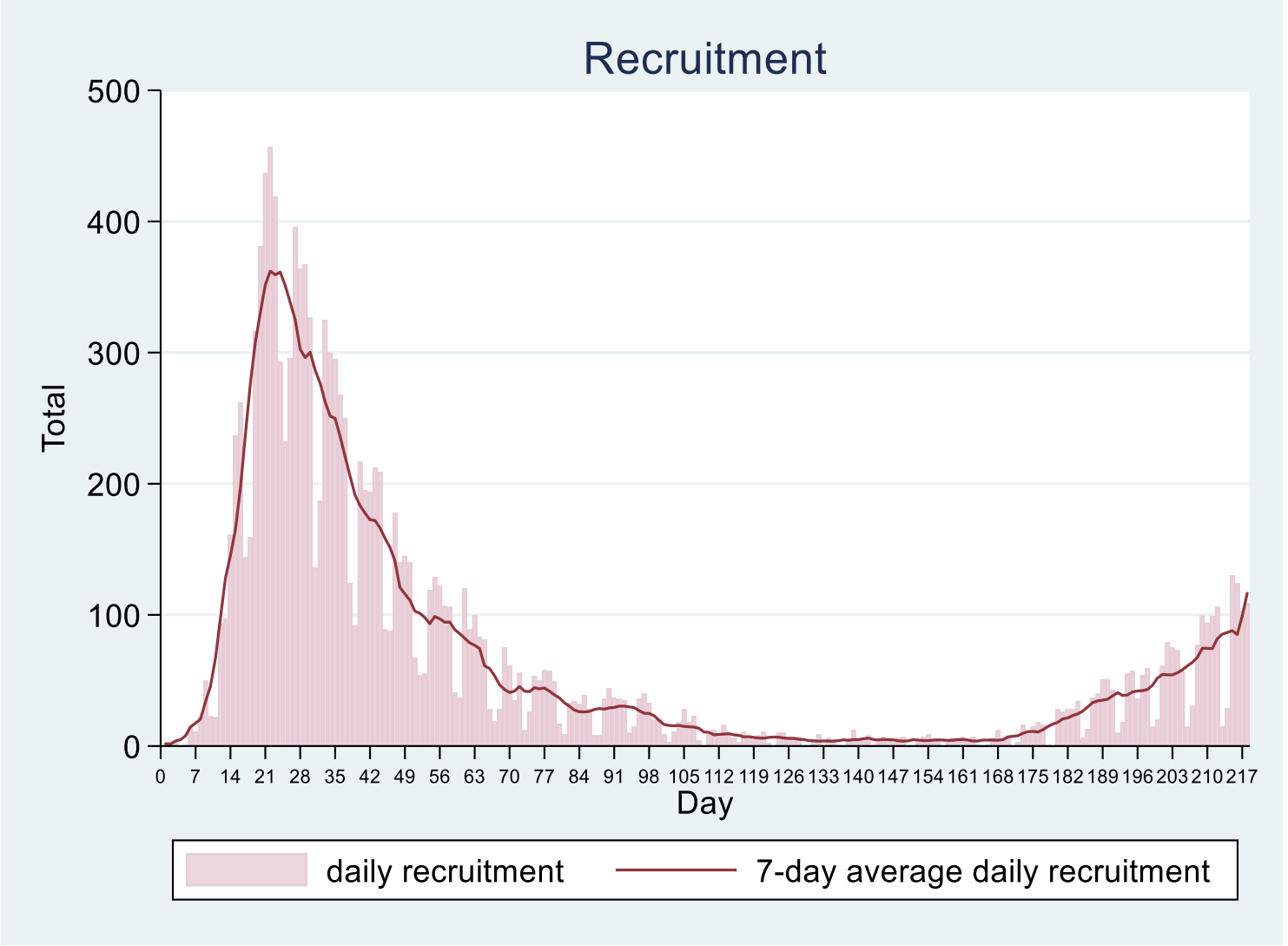

Recruitment

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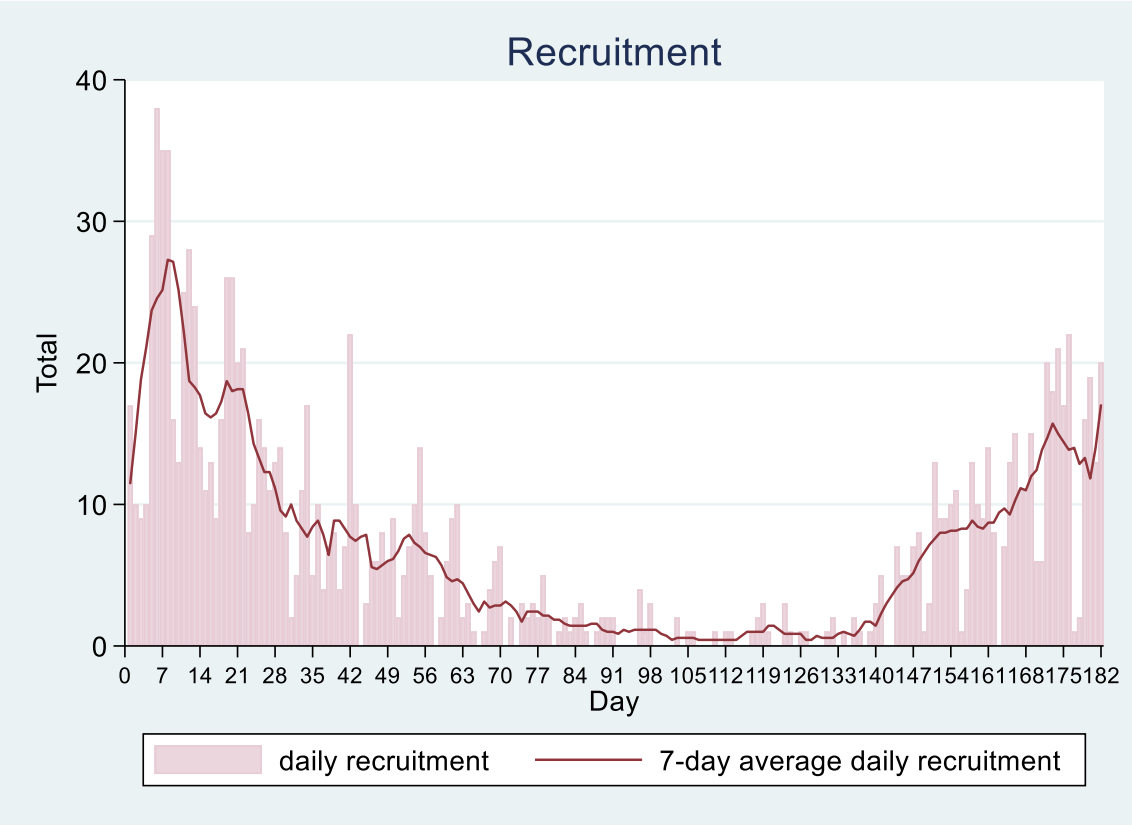
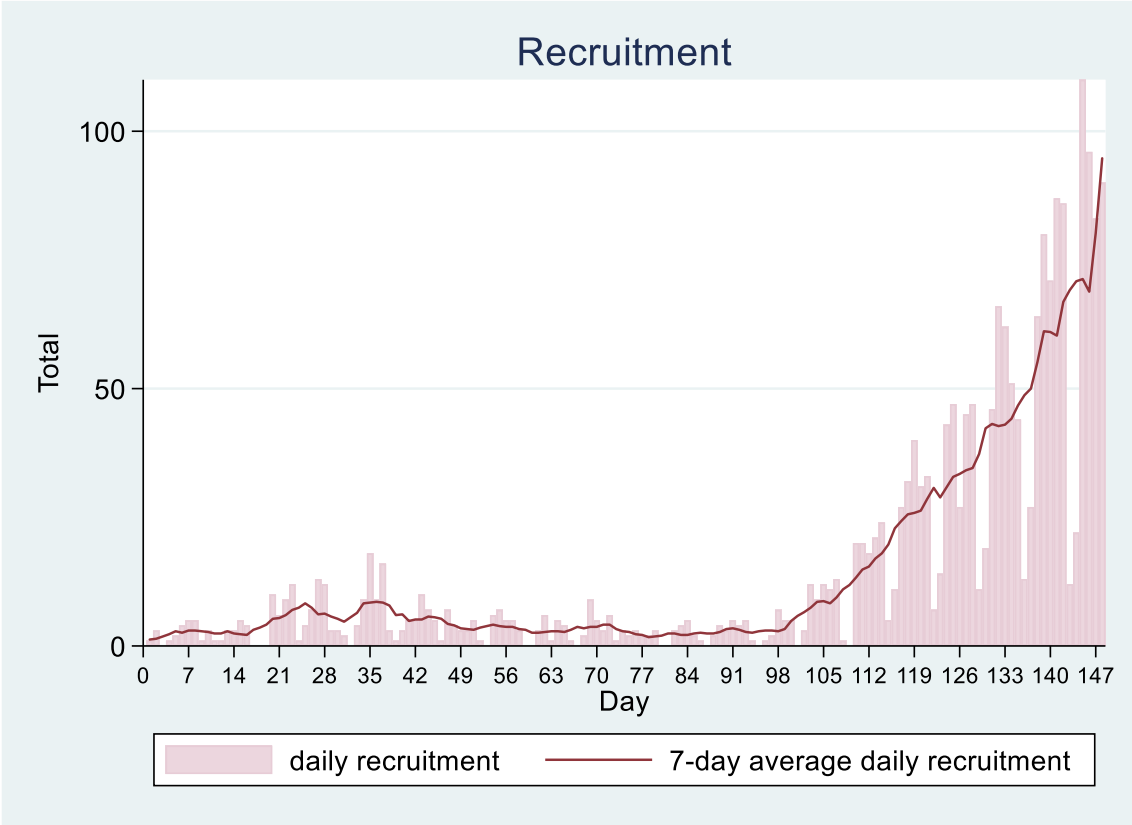
- Tocilizumab vs control



- Convalescent plasma vs REGN-COV2 vs control



Recruitment

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- As local outbreaks occur, please consider discussing with your teams how to ensure that all available admissions with Covid-19 are identified and enrolled if possible
  - Daily catch-up with admitting teams
  - Links with laboratory for all positive swabs among patients to be reported

- Average recruitment remains at about 12% of all COVID-19 admissions, but with significant variation between sites

Recruitment

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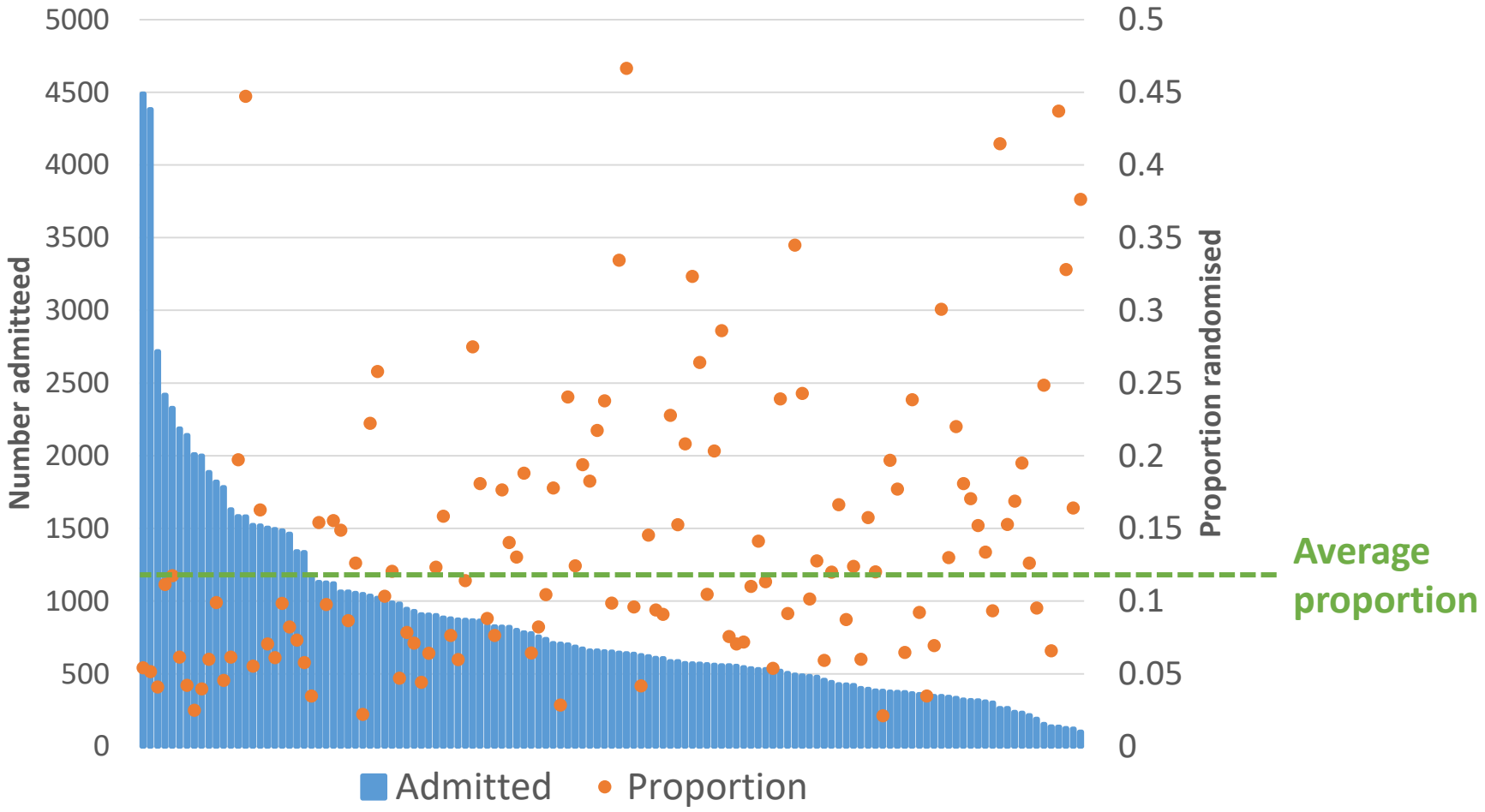

Recruitment

- Pilot of additional funding for weekend working in November

- Potential adoption onto NIHR Associate PI scheme (more details will follow)

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REGN-COV2

REGN-COV2

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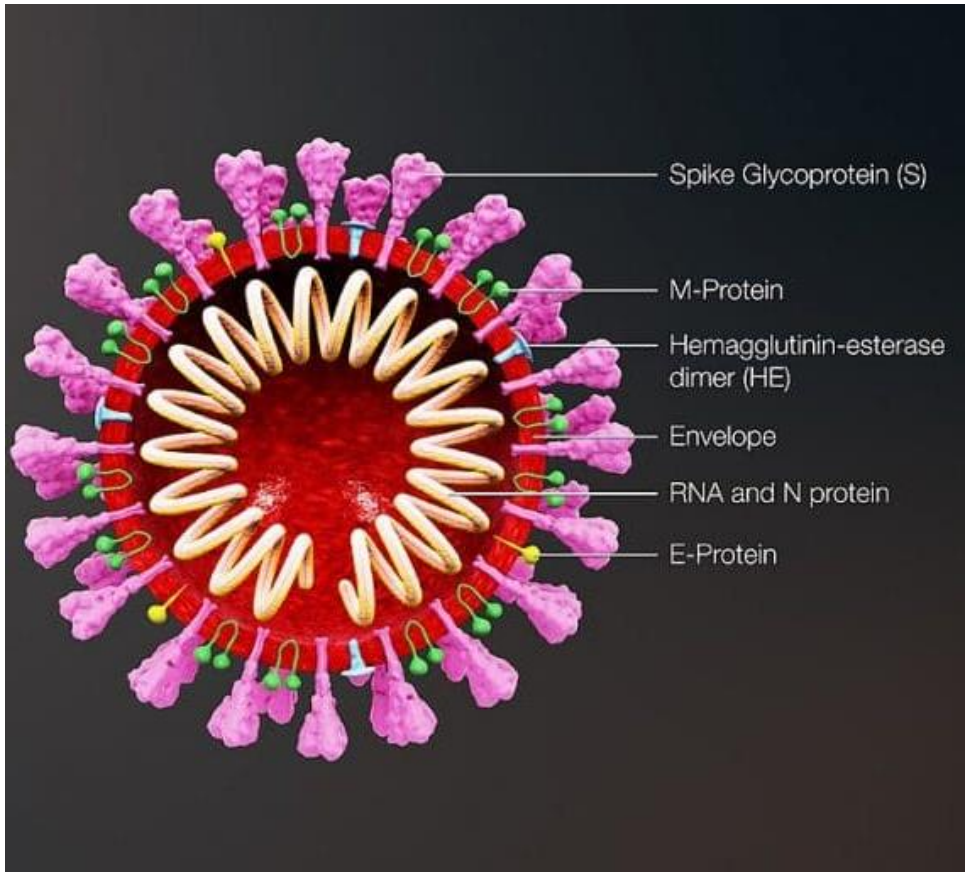
- REGN-COV2 is a mixture of two monoclonal antibodies (mAbs: REGN10933 and REGN10987)



- These are fully human antibodies directed against spike protein

- Two different antibodies mean that if virus mutates its spike protein such that one antibody doesn't bind so well, the other antibody probably still will

REGN-COV2 site setup

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1. Local PIs need to complete online training and confirmation form
   - They should ask other staff involved at site to also do this, but not require before site activation

2. Pharmacy need to be ready to support new arm
   - Review Pharmacy Manual on website and complete local risk assessment to determine where mAb will be prepared
   - Confirm staff details to RECOVERY team
   - Indicate when they will be ready to:
     1. Receive drug
     2. Support allocation to a trial participant

REGN-COV2 dos and don’ts

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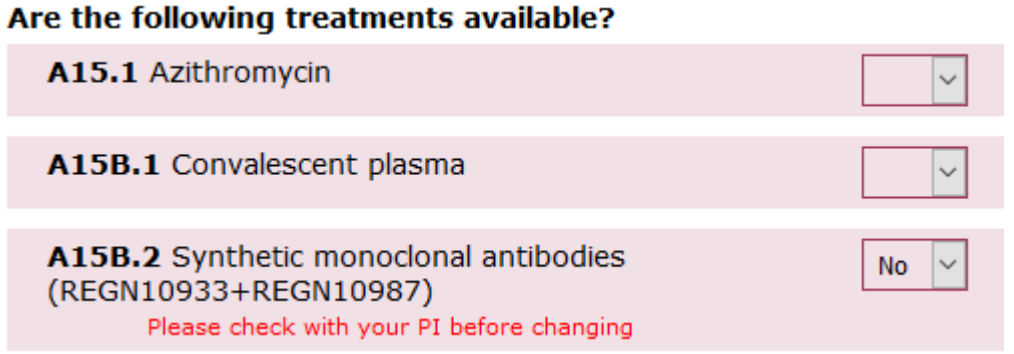
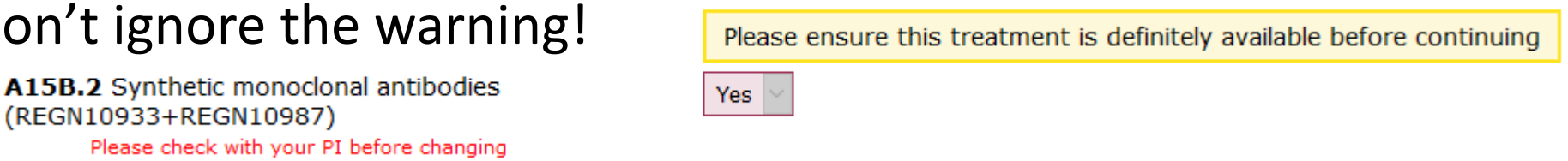
- Please **DO NOT** indicate REGN-COV2 is available if system suggests it is not *unless you are absolutely sure!*



- Please don’t ignore the warning!



- Otherwise the participant may be allocated a treatment they can’t have ☹

When to include REGN-COV2

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- REGN-COV2 should be administered as soon after randomisation as possible

- If being prepared in pharmacy, this may not be until next working day

- If delay is likely to be longer (e.g. at weekend), please indicate that mAb is unavailable on randomisation form so it will not be allocated

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TOCILIZUMAB

Tocilizumab

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- Several recent publications

Trial name	Number of participants	Number of deaths	HR (95% CI)
RCT-TCZ-COVID-19	126	4	2.1 (0.2-22.6)
CORIMUNO-19	131	15	0.92 (0.33-2.53)
BACC	243	12	1.52 (0.41-5.61)
COVACTA	438	86	1.02 (0.62-1.68)*
EMPACTA	389	~37*	not estimable

* Estimated from published data

- JAMA editorialist: “I plan to wait out the torrent of positive observational studies and reconsider tocilizumab’s use in COVID-19 if, and only if, more compelling data from randomized trials emerges.”

Tocilizumab

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- Nearly 1300 randomised
- Sufficient tocilizumab supply for 4000 randomised, but all now at sites
- Please ensure you consider this randomisation for appropriate participants:
  - On oxygen (or sats <92%)
  - CRP ≥75 mg/L

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OTHER DEVELOPMENTS

CTAP

Department of Health & Social Care

Guidance

Guidance: making a proposal for COVID-19 therapeutics clinical trials

Published 17 August 2020

Contents

Introduction

Given the success of the Phase III RECOVERY platform in delivering a single platform trial across the NHS, the UK Government has increased investment in an expanded platform which will operate for the next 24 months. This will include new treatments tested in Phase II and Phase III studies which will now be delivered through the RECOVERY platform (RECOVERY+) in patients admitted to hospital.

New treatments can be proposed for inclusion in the RECOVERY+ platform for both Phase II and Phase III trials. They will be considered by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP).

Subcommittees that have met to date:

- Antiviral
- Anticoagulation
- Immunomodulation
- Renin-angiotensin system

- One recommendation from CTAP is being discussed with manufacturer

- Outcome from anticoagulation subcommittee imminent

Pharmacogenomic substudy

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- Azithromycin known to prolong QT interval, but genetic determinants unknown

- Substudy for interested sites which requires:
  - ECG prior at baseline and 48h (uploaded to OpenClinica)
  - Co-enrolment into GenoMICC or ISARIC-4C encouraged (for genetic samples)

- Please e-mail recoverytrial@ndph.ox.ac.uk if interested

SOLIDARITY

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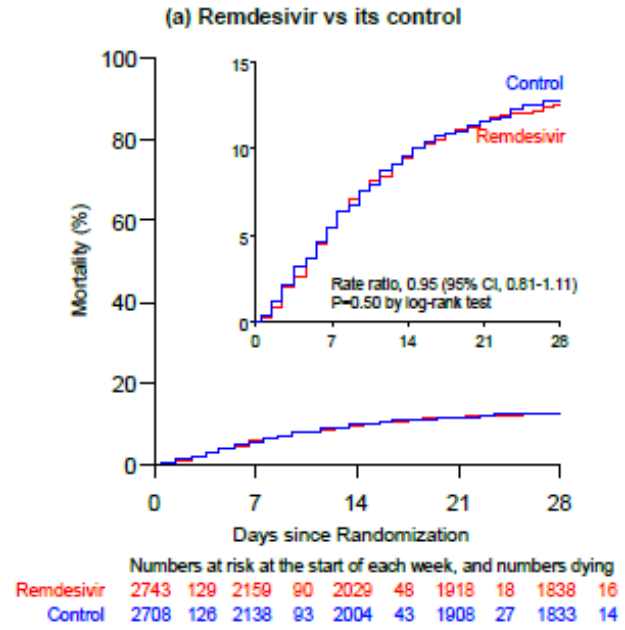
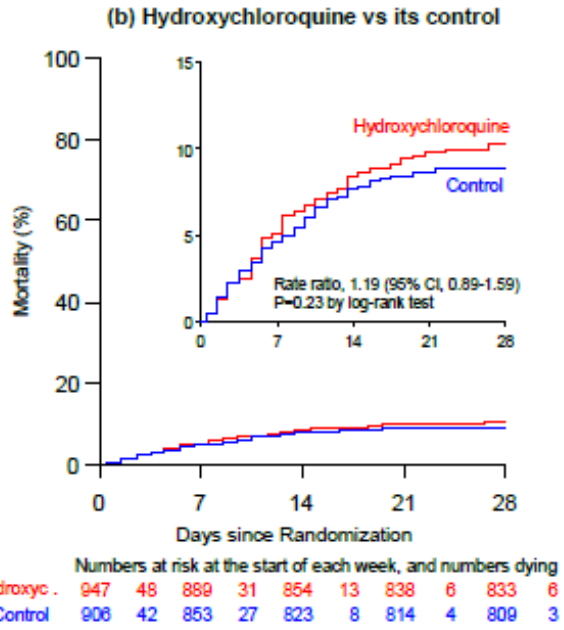
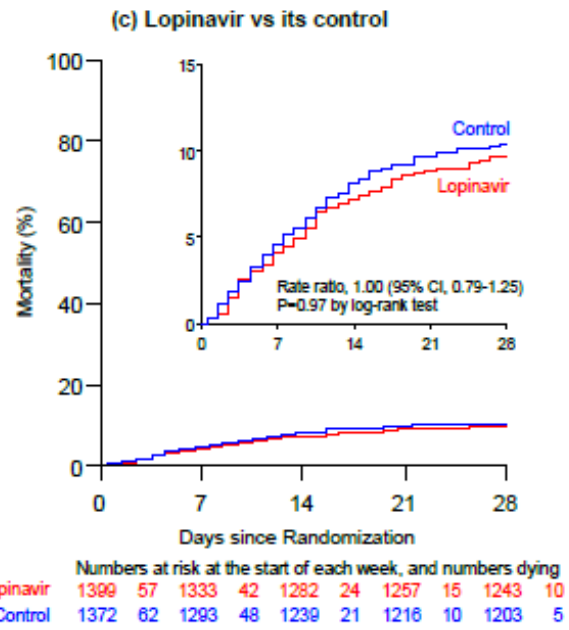
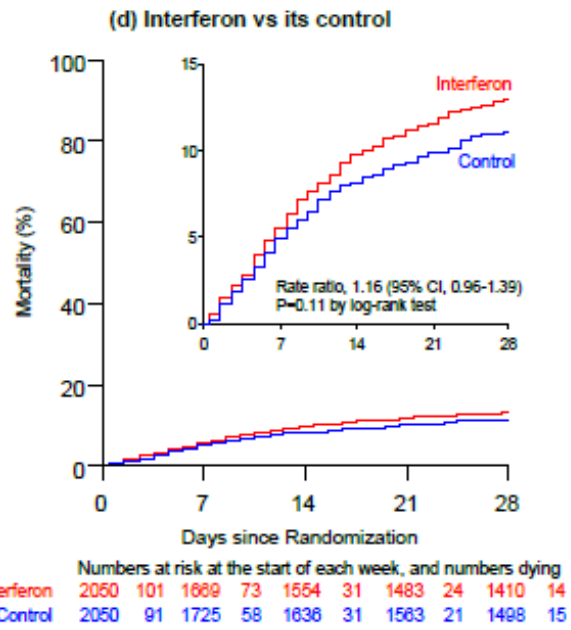
- 11,266 participants randomised in 30 countries









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TRIAL PROCEDURES

Serum samples

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- **All** participants entering antibody comparison (CP vs mAb vs control) need to have serum sample collected prior to randomisation

- Can be taken with G&S sample after consent prior to randomisation to limit venepunctures

- Must be taken for all participants in that comparison (regardless of allocation)

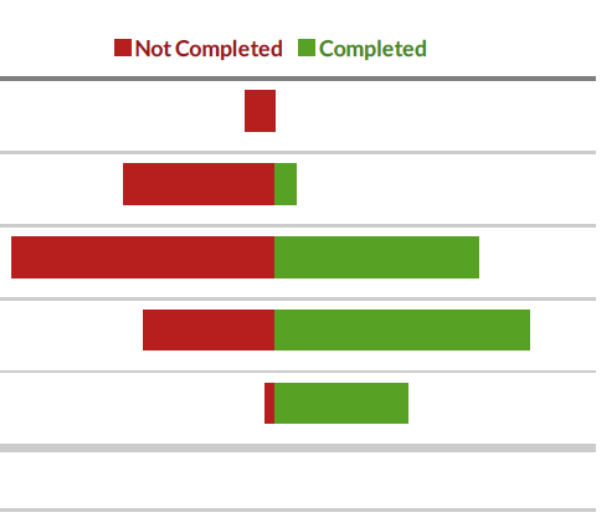
Completeness of follow-up

- Weekly reminders highlighting participants randomised >28 days ago without complete form **and also** those needing an Antibody Comparison 72h safety 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**



Carry on recruiting!

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- RECOVERY remains the largest global trial in COVID-19 and is an exemplar of what trials can do (both in and after pandemic)
- Current therapies are exciting, but need reliable data before they should be used routinely
- Thank you for your support!

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Specific information for

Infants <44 weeks corrected gestational age

27/10/2020

Background

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- Transmission of COVID-19 from a mother to her unborn baby is very unlikely and there is a low risk of babies being infected at birth even if born to a confirmed COVID-19 positive mother.
- Infection in the neonatal period (less than 28 days old) has been described, but is very rare. The majority of babies who develop COVID-19 present with mild symptoms or are asymptomatic.
- Symptomatic babies can present days to weeks after birth.

Background, continued …..

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- Up to 44 weeks corrected gestational age, 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 considered.

Background, continued …..

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- For the few infants 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 (*BAPM guidance, link as below*)

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

Background, continued …..

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- For the few infants 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 (*BAPM guidance, link as below*)
- The Royal College of Paediatrics and Child Health (RCPCH) 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

Background, continued …..

- It is anticipated that any child with suspicion of COVID-19 being considered for treatment (over and above supportive care), should be enrolled in RECOVERY.

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

RCH criteria for offering treatment to children:
www.rcpch.ac.uk/resources/covid-19-clinical-management-children-admitted-hospital-suspected-covid-19

Background, continued …..

- It is anticipated that any child with suspicion of COVID-19 being considered for treatment (over and above supportive care), should be enrolled in RECOVERY.

- Criteria for treating infants who are <44 weeks corrected gestational age include the following, these should also be considered as criteria for entry to RECOVERY:
  - Increase in respiratory support to maintain oxygen saturations within accepted limits that is new or above a baby's previous baseline,
  - signs of sepsis with shock,
  - encephalopathy,
  - multi-organ failure.

www.rcpch.ac.uk/resources/covid-19-clinical-management-children-admitted-hospital-suspected-covid-19

Patient information leaflets and Co

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- Parents of infants and children <10 years of age should be provided with the ‘younger’ child’s information leaflet. The parent / guardian should sign the consent form.

- Witnessed consent may be obtained over the telephone or web video link if hospital visiting rules or parental infection mean a parent / guardian cannot be physically present.

Treatments for infants <44 weeks corrected gestational age

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- For first stage interventions, options open to babies <44 weeks corrected gestational age (CGA):

Randomisation 1A:	Randomisation 1B:
Azithromycin	Convalescent plasma
Hydrocortisone	No additional treatment
No additional treatment (SOC)	

- The hydrocortisone option is specific to infants CGA <44 weeks and is not available to older infants and children
- The second randomisation to Tocilizumab vs no additional treatment is NOT available to children < 1 year.
- Specific neonatal and paediatric drug dosing and administration is available in the Frequently Asked Questions document on the RECOVERY website

Further guidance: Frequently asked questions document

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https://www.recoverytrial.net/for-site-staff/training/children-and-neonates-1

GUIDES FOR SPECIFIC PATIENT GROUPS

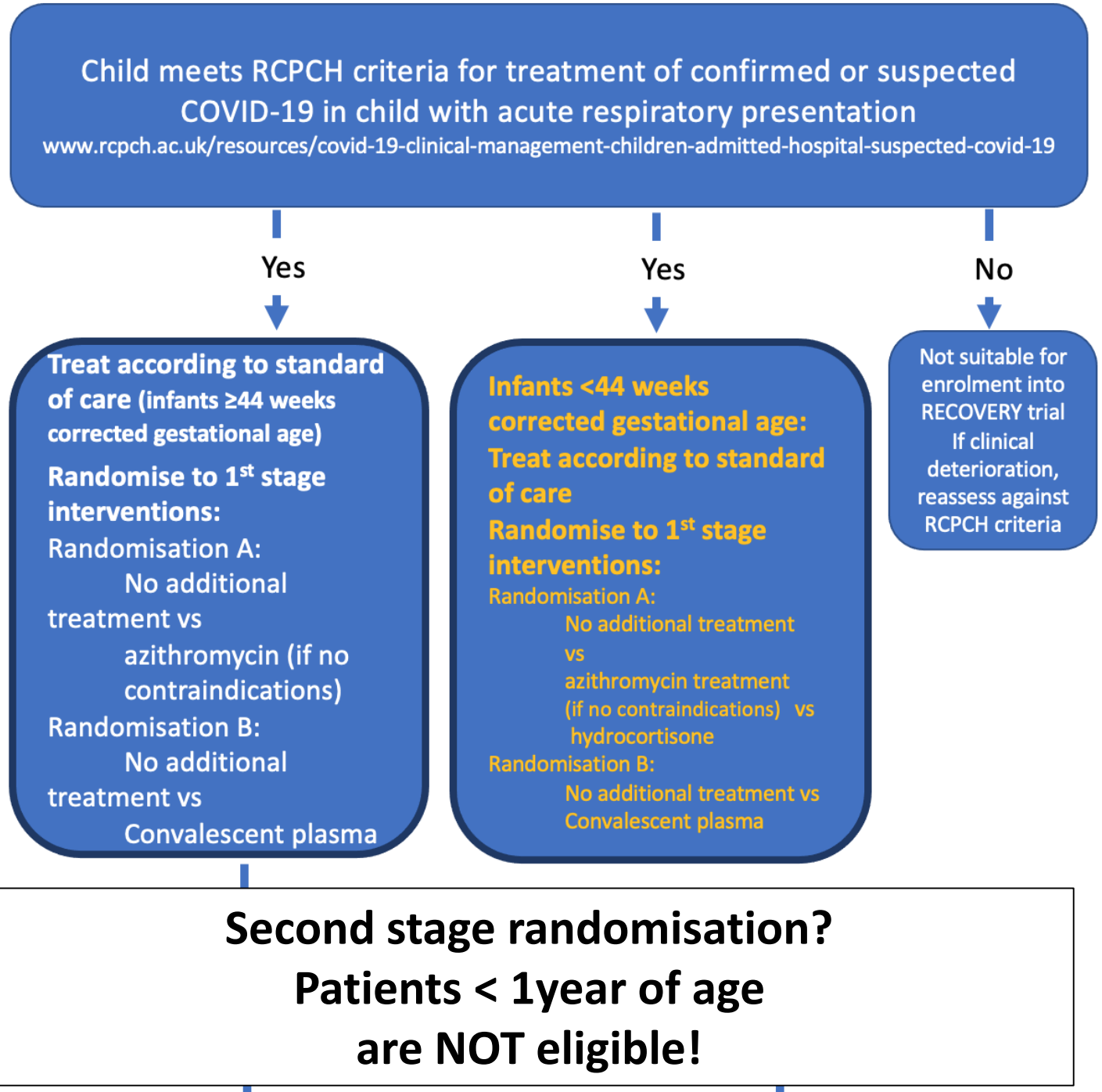
- RECOVERY for paediatric patients
- RECOVERY for patients with chronic kidney disease
- RECOVERY for pregnant and breastfeeding women
- RECOVERY for neonatal inclusion
- RECOVERY and remdesivir

Paediatric Patients

Adaption for paediatric patients
Children and infants of all ages are included in RECOVERY **Please see FAQs "Recruitment and randomisation" on page 2 and 3 for details on which children should be offered participation in RECOVERY.**
Same options but in randomisation part A, the arms are: - No additional treatment - Corticosteroid arm **remains open** with different dosing options for patients with PIMS-TS phenotype (high dose methylprednisolone) and for neonates/infants <=44 weeks gestation with acute respiratory COVID-19 (low dose steroids). - Intravenous immunoglobulin - Azithromycin Lopinavir-Ritonavir and hydroxychloroquine arms are **closed.**

RECOVERY trial – inclusion flow chart

for infants and children < 1year of age – special considerations



Questions?

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Thanks for listening!

:-)