

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

**Collaborators' Meeting
7th & 8th December 2020**

Agenda



1. Introductions
2. Update on progress
3. Tocilizumab
4. Colchicine
5. Convalescent plasma
6. Trial procedures
7. Q&A

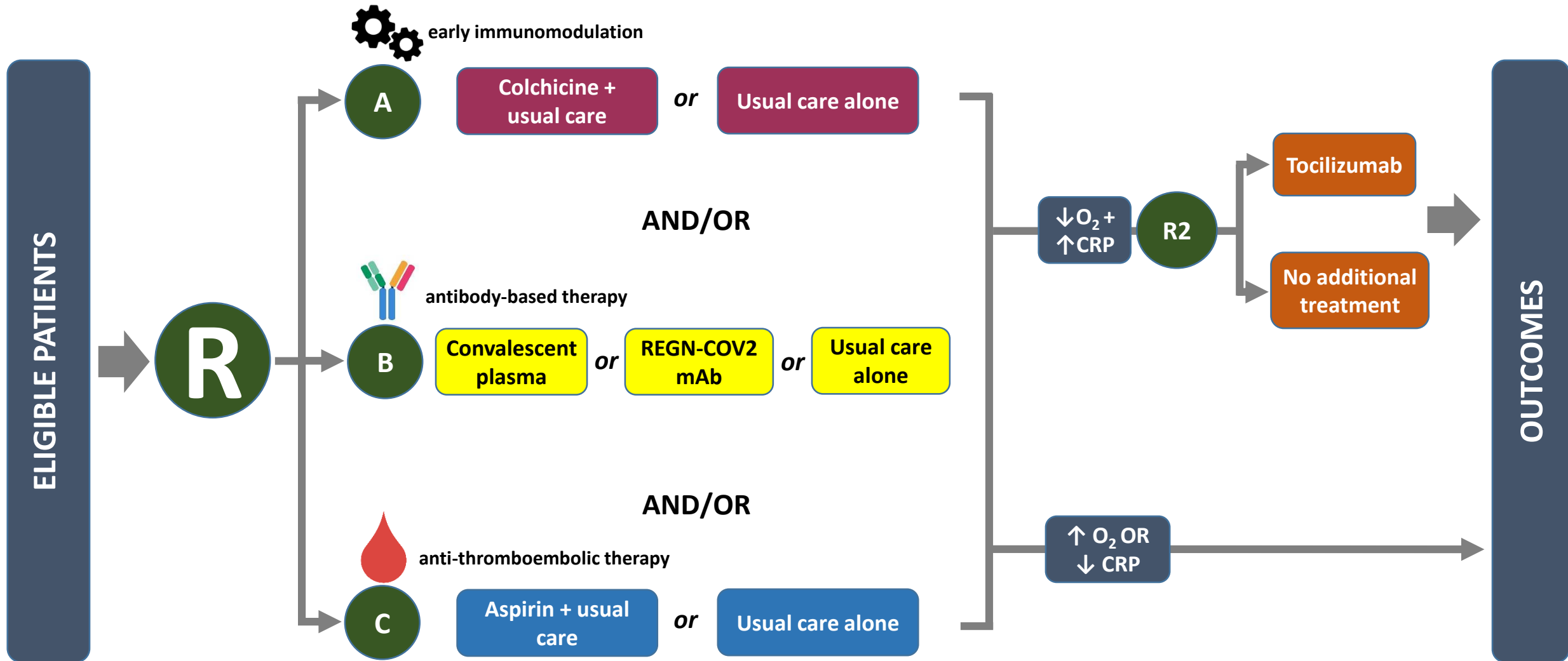
Introductions



- 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

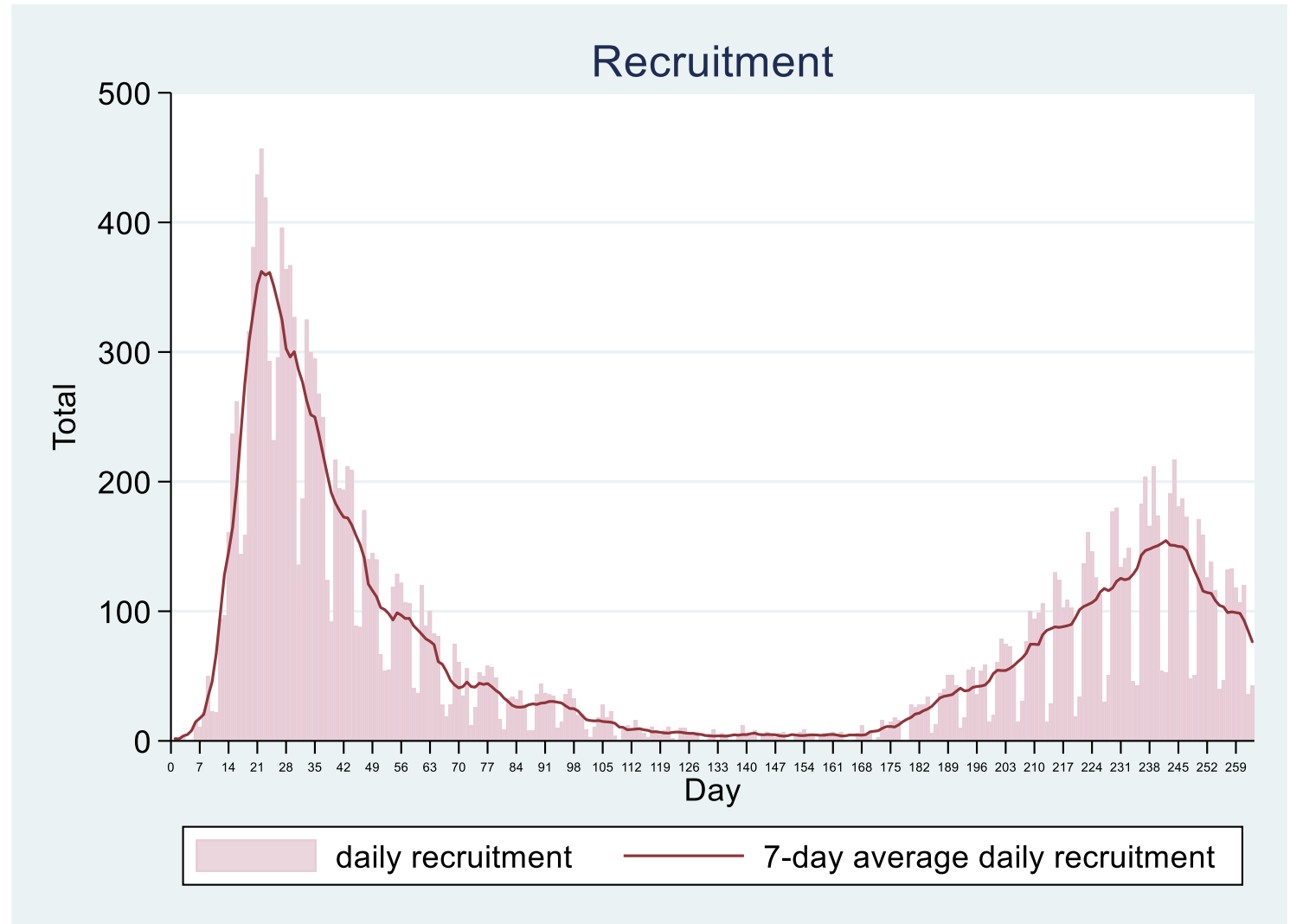
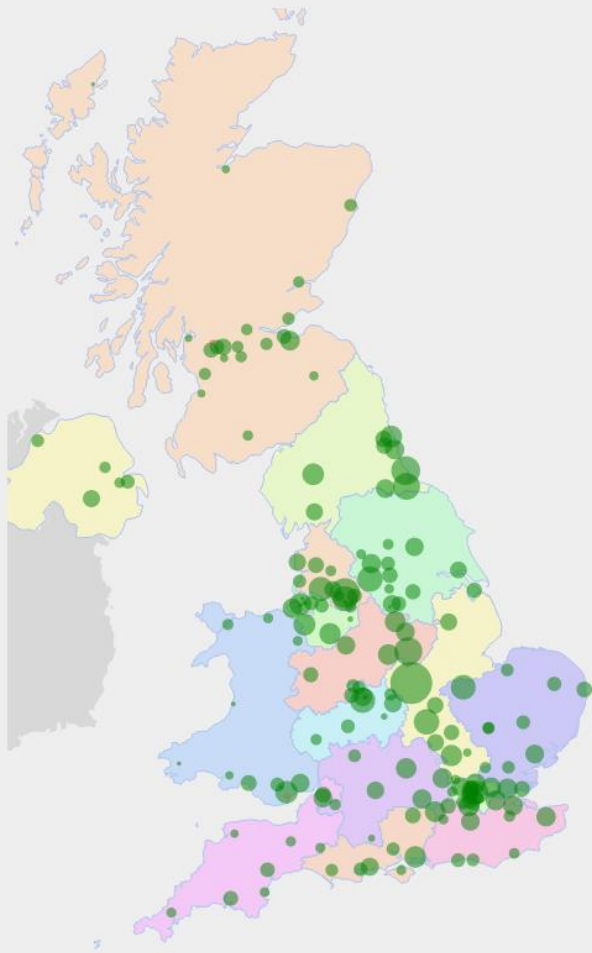
PROGRESS UPDATE

Design



Recruitment by site and by time

Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.
176	174	19948	2164	6756	1986



Recruitment



- Please continue to prioritise RECOVERY in accordance with its Urgent Public Health Priority 1A status (same as vaccine trials)
- Average recruitment remains at about 10% of all COVID-19 admissions, but with significant variation between regions and sites
- Please let us know how we could support recruitment at your site

Recruitment

- RECOVERY now active on Associate PI scheme
- Many applications now in process
- Further details available (including recorded webinar) at:

<https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040>

NIHR | National Institute for Health Research

Associate Principal Investigator (PI) Scheme

The NIHR Associate Principal Investigator (PI) scheme aims to develop junior doctors, nurses and allied health professionals to become the PIs of the future at the same time as helping to deliver studies to time and target. Registration is quick and easy, just follow the steps below.

Register study	Check if the study you want to register to be Associate PI for is on the list of registered studies . If not then complete the Associate PI Scheme Study Registration Form .
Register yourself	Register to the scheme by completing the API Scheme Applicant Registration Form once you have approval from the Site PI and CTU Study / Trial Manager
Complete Checklist	Once you are registered to the scheme you will be sent a welcome email with a link to the Associate PI Scheme Checklist which you need to complete and get signed off by your PI and the CTU Study / Trial Manager within six months of registering to the scheme.
Receive certificate	Once you have submitted your fully signed off Checklist the NIHR Associate PI Scheme Team will issue you with a certificate. You are then free to register to another study at the same or another site.

For further information about the scheme, please visit the [NIHR Associate PI Scheme website](#).
If you have any questions about the scheme please email the NIHR Associate PI Scheme Team on associatepischeme@nihr.ac.uk.

How long until the next result?



- Azithromycin recruitment now halted
- Please complete Follow-up forms as promptly as possible

TOCILIZUMAB

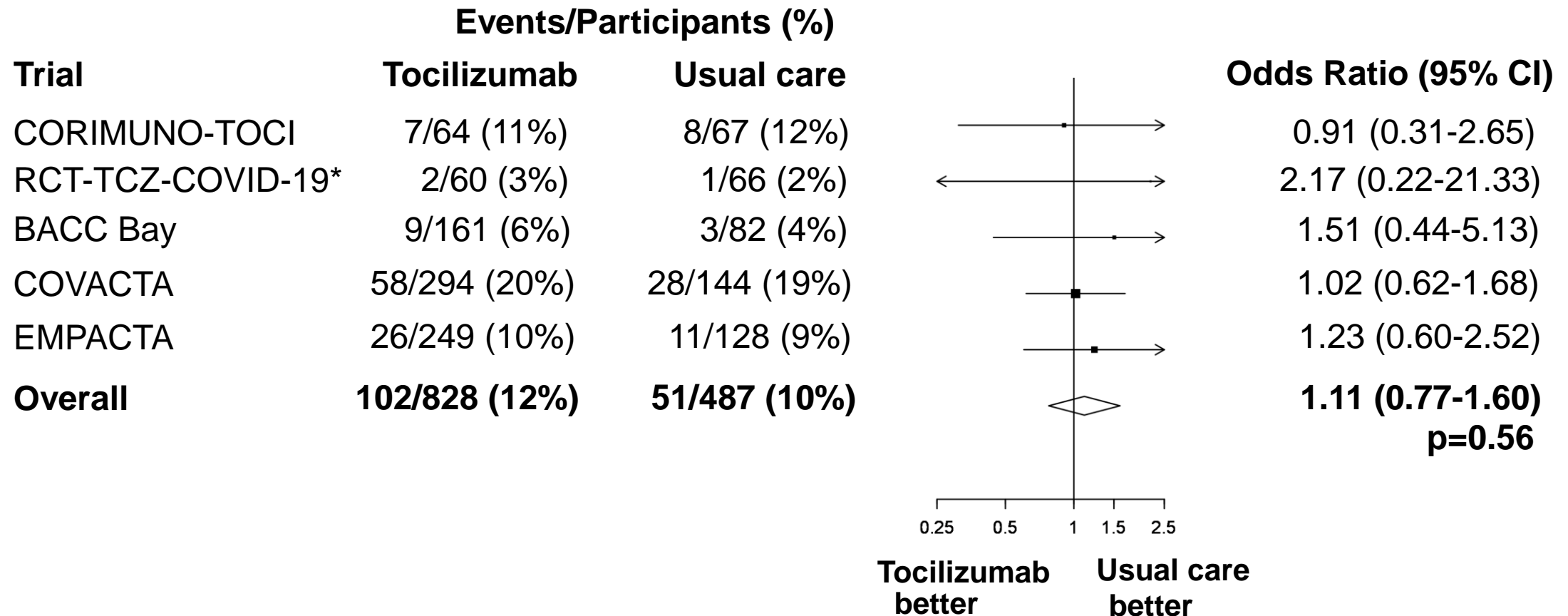
Tocilizumab in REMAP-CAP



- REMAP-CAP released preliminary results on 19 November
- Based on 303 participants randomised between usual care, tocilizumab, sarilumab, anakinra or interferon
- Estimated odds ratio of 1.87 for a better outcome with tocilizumab with high degree of statistical certainty (99.75% probability)
- Subsequent CAS alert from DHSC was not a directive to treat, but to ensure tocilizumab was available for licensed indications and gave permission to use it for patients who met REMAP-CAP criteria
- Randomisation into trials remains DHSC priority
 - NB REMAP-CAP are still randomising between tocilizumab and other immunomodulators (but have ceased usual care arm)

Tocilizumab in RECOVERY

- Substantial uncertainty remains, at least until details of REMAP-CAP results are released



Tocilizumab in RECOVERY



- 2150 randomised
- Sufficient tocilizumab supply for 4000 randomised.
 - Agreement from NHS England that NHS stock can be used where trial stock unavailable
- Please ensure you consider this randomisation for appropriate participants:
 - On oxygen (or sats <92%)
 - CRP ≥ 75 mg/L

COLCHICINE

Colchicine

- Well-known anti-inflammatory agent
- Commonly used in:
 - Gout
 - Familial periodic fever syndromes
 - Pericarditis
- Well-recognised side-effects e.g. diarrhoea

- **Contraindicated if:**
 - Women <55 years old (or older women with child-bearing potential)
 - Severe hepatic impairment
 - Significant cytopenia (neutrophil count <1; platelet count <50; reticulocyte count <20)
 - Concomitant use of strong CYP3A4 inhibitor (macrolide antibiotics; systemic azole antifungals) or P-gp inhibitors (cyclosporin, verapamil)
 - Hypersensitivity to lactose

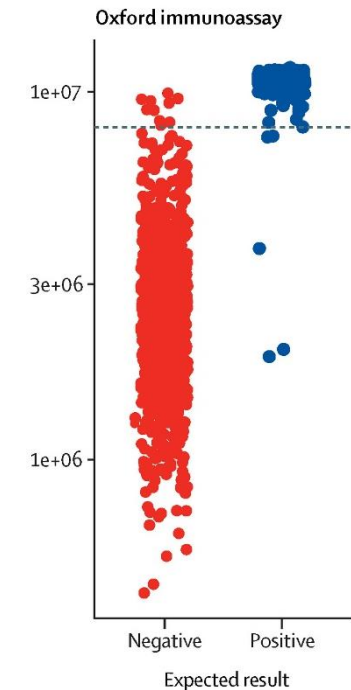
Colchicine

- **Caution if:**
 - Concomitant use of moderate CYP3A4 inhibitor (diltiazem)
 - eGFR <30 mL/min/1.73m²
 - Estimated body weight <70 kg
- In such patients use a reduced maintenance dose:
 - 1 mg at randomisation; 500 mcg 12 h later
 - 500 mcg **once** daily thereafter
- If a patient has >1 of these factors, responsible clinician should consider marking colchicine as “unsuitable”

CONVALESCENT PLASMA

Convalescent plasma

- Over 5500 participants in this comparison now
- Recent 'negative' trial from Argentina only included 300 participants
- Baseline serum samples now being analysed using Oxford immunoassay
 - Cut-off at 8 million for diagnosis

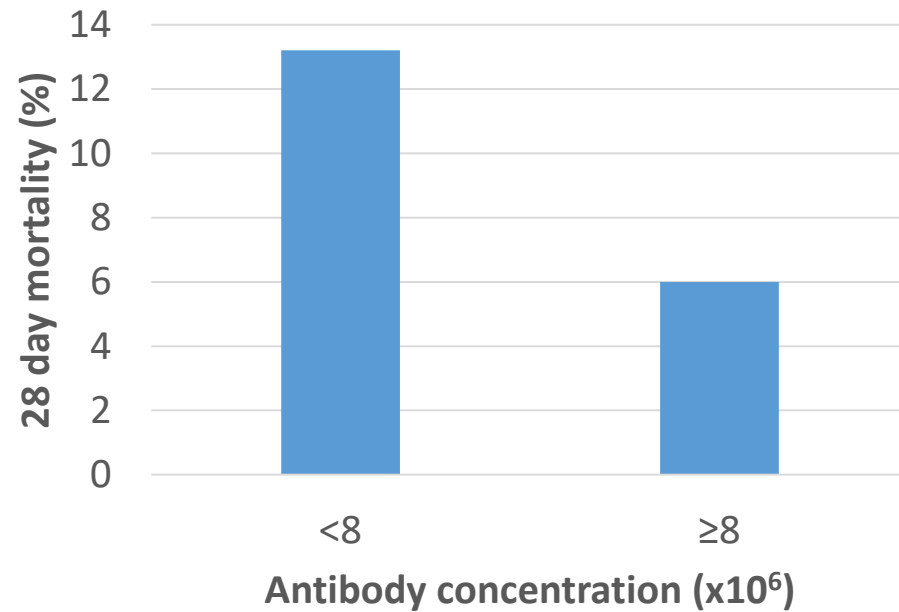


Antibody levels from 3668 participants

Characteristic		Median [IQR] (x10 ⁶)	Proportion >8 x10 ⁶
All participants		9.1 [4.6-10.0]	59%
Age	<70	9.3 [6.0-10.0]	64%
	≥70 <80	8.9 [3.7-10.0]	57%
	≥80	5.9 [2.1-9.7]	41%
Respiratory support	No oxygen	5.1 [1.8-9.5]	37%
	Oxygen only	9.1 [5.0-10.0]	60%
	Ventilated	10.0 [8.8-10.2]	79%
Days since symptoms	≤7	6.7 [2.5-9.6]	42%
	>7	9.7 [7.4-10.1]	71%

Antibody levels from 3668 participants

Baseline antibody level and risk of death



Baseline antibody level by arm

Recipient concentration	Convalescent plasma	Usual care
Available	73%	66%
Missing	27%	34%

Serum samples

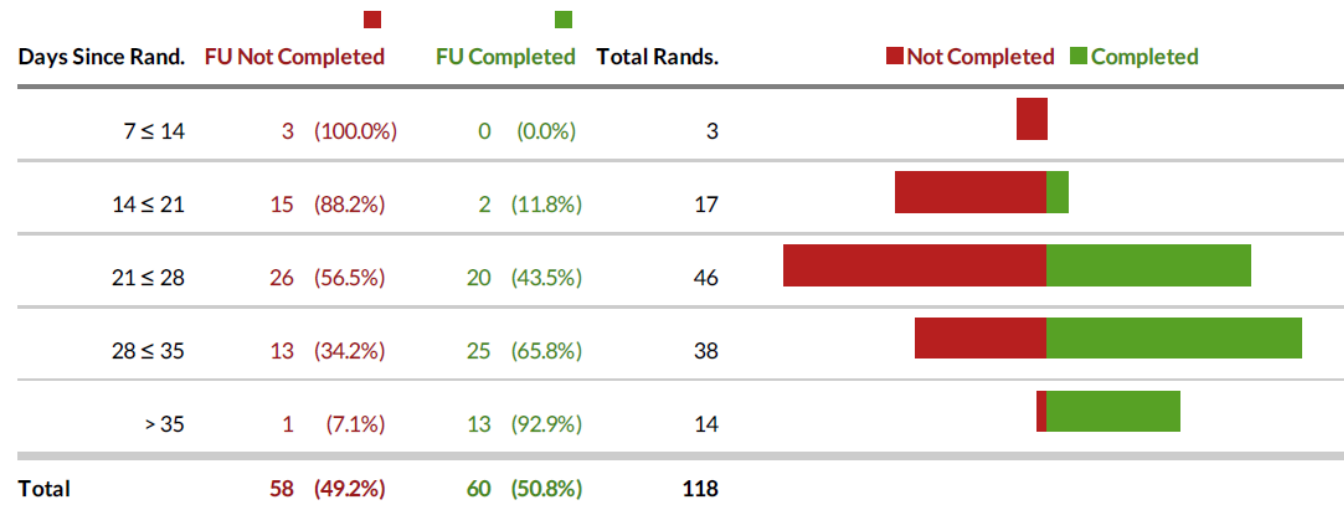
- **All** participants entering antibody comparison (CP vs mAb vs control) need to have serum sample collected prior to randomisation
- Must be taken for all participants in that comparison (regardless of allocation)
- **Please check whether any samples have not been returned to the central lab**

TRIAL PROCEDURES

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

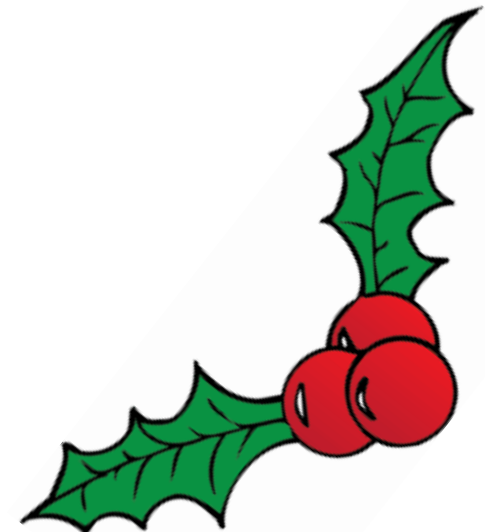
Follow-up form completion summary



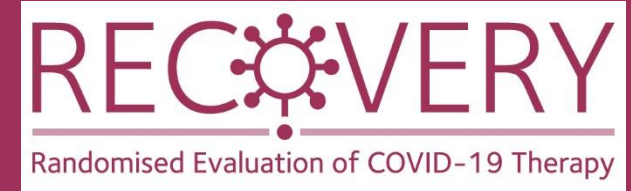
Christmas dates

- Trial inbox will be monitored on working days
- Urgent clinical enquiries: **0800 138 5451**
- Last orders for postage kits for serum samples: **18th December**
- Please post serum samples on days in green, not those in red:

December	21	22	23	24	25	26	27
	28	29	30	31			
January					01	02	03
	04	05	06	...			



Carry on recruiting!



- 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

Collaborators' Meeting for Pregnancy

7 December 2020

RECOVERY for pregnant women



1. Update on covid-19 and pregnancy
2. Update on adaptations
3. Update on UKOSS
4. Future plans
5. Q&A

Covid-19 and pregnancy

RESEARCH

OPEN ACCESS

Check for updates

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

Maternal, Newborn and Infant Clinical Outcome Review Programme



Saving Lives, Improving Mothers' Care

Rapid report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK

AJOG American Journal of Obstetrics & Gynecology

ORIGINAL RESEARCH: OBSTETRICS | ARTICLES IN PRESS

Pregnant women with severe or critical COVID-19 have increased composite morbidity compared to non-pregnant matched controls

Chelsea A. DeBolt, MD • Angela Bianco, MD • Meghana A. Limaye, MD • ... Elianna Kaplowitz, MPH • Jessica R. Overbey, MS, DrPH • Joanne Stone, MD, MS • Show all authors

Published: November 19, 2020 • DOI: <https://doi.org/10.1016/j.ajog.2020.11.022>

BMJ: first published as 10.1136/bmj.m2107 on 8 June 2020.

RESEARCH

OPEN ACCESS

Check for updates

FAST TRACK

Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

John Allotey,^{1,2} Elena Stallings,^{3,4} Mercedes Bonet,⁵ Magnus Yap,⁶ Shaunak Chatterjee,⁶ Tania Kew,⁶ Luke Debenham,⁶ Anna Clavé Llavall,⁶ Anushka Dixit,⁶ Dengyi Zhou,⁶ Rishab Balaji,⁶ Siang Ing Lee,¹ Xiu Qiu,^{7,8,9} Mingyang Yuan,^{1,7} Dyuti Coomaraswamy,¹ Madelon van Wely,¹⁰ Elizabeth van Leeuwen,¹¹ Elena Kostova,¹⁰ Heinke Kunst,^{12,13} Asma Khalil,¹⁴ Simon Tiberi,^{12,13} Vanessa Brizuela,⁵ Nathalie Broutet,⁵ Edna Kara,³ Caron Rahn Kim,⁵ Anna Thorson,⁵ Olufemi T Oladapo,⁵ Lynne Mofenson,¹⁵ Javier Zamora,^{3,4,16} Shakila Thangaratinam,^{2,17} for PregCOV-19 Living Systematic Review Consortium

Morbidity and Mortality Weekly Report

Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020

Laura D. Zambrano, PhD^{1,*}; Sascha Ellington, PhD^{1,*}; Penelope Strid, MPH¹; Romeo R. Galang, MD¹; Titilope Oduyebo, MD¹; Van T. Tong, MPH¹; Kate R. Woodworth, MD¹; John F. Nahabedian III, MS¹; Eduardo Azziz-Baumgartner, MD¹; Suzanne M. Gilboa, PhD¹; Dana Meaney-Delman, MD¹; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team

EDITORIALS

Check for updates

Include pregnant women in research—particularly covid-19 research

Adapting interventions and changing attitudes will drive scientific progress

Marian Knight,¹ R Katie Morris,² Jenny Furniss,³ Lucy C Chappell⁴

The UK Confidential Enquiries into Maternal Deaths have repeatedly highlighted inequities in the medical treatment of pregnant and postpartum women, noting that women are denied investigations and life preserving treatments simply because they are pregnant or breastfeeding.^{1,2} These inquiries emphasise that the default position should be to investigate and treat pregnant and breastfeeding women in the same way as non-pregnant women, unless there are clear reasons not to.¹ Clinical trials, particularly those of drug treatments, have typically automatically excluded pregnant or breastfeeding women—meaning data are unavailable or breastfeeding allows safety concerns to be allayed for women, their families, and healthcare professionals. Even if regulatory barriers have been overcome, gatekeeping or inertia may occur if local ethics committees take an overwhelming precautionary approach, overriding recognition of the potential benefits of including pregnant and breastfeeding women. This problem can be mitigated by a strong network of maternity researchers, familiar with delivering drug trials in pregnancy, who can be rapidly mobilised to help implement studies.

BMJ: first published as 10.1136/bmj.m3305 on 21

New National Restrictions from 5 November

9. Protecting people more at risk from coronavirus

If you are over 60 or clinically vulnerable, you could be at higher risk of severe illness from coronavirus. You:

- should be especially careful to follow the rules and minimise your contacts with others
- should continue to wash your hands carefully and more frequently than usual and maintain thorough cleaning of frequently touched areas in your home and/or workspace

Clinically vulnerable people are those who are:

- aged 70 or over (regardless of medical conditions)
- under 70 with an underlying health condition listed below (that is, anyone instructed to get a flu jab each year on medical grounds):
 - chronic (long-term) mild to moderate respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), emphysema or bronchitis
 - chronic heart disease, such as heart failure
 - chronic kidney disease
 - chronic liver disease, such as hepatitis
 - chronic neurological conditions, such as Parkinson's disease, motor neurone disease, multiple sclerosis (MS) or cerebral palsy
 - diabetes
 - problems with the spleen
 - a weakened immune system as the result of certain conditions or medicines they are taking (such as steroid tablets)
 - being seriously overweight (a body mass index (BMI) of 40 or above)
- **pregnant**

2 December

Follow the rules for your local area

[Find out what tier your area is in and what the local restrictions are](#)

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- aged 70 or older (regardless of medical conditions)
- under 70 with an underlying health condition listed below (that is, anyone instructed to get a flu jab each year on medical grounds):
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 - diabetes
 - a weakened immune system as the result of certain conditions or medicines they are taking (such as steroid tablets)
 - being seriously overweight (a body mass index (BMI) of 40 or above)
- **pregnant**

Covid-19 and pregnancy



Headline messages:

- Covid-19 affects pregnant women
- Additional risk factors have been identified (ethnic minority groups, increasing gestation, higher maternal age, high body mass index, pre-existing comorbidities)
- Pregnant and postnatal women need evidence-based treatments
- Pregnant and postnatal women should be actively included in research
- RECOVERY trial has changed clinical practice, including for pregnant women

Covid-19 and pregnancy: RCOG



Royal College of
Obstetricians &
Gynaecologists

Coronavirus (COVID-19) Infection in Pregnancy

Information for healthcare professionals

Version 12: Published Wednesday 14 October 2020

The interim results of the RECOVERY trial demonstrated a significant reduction in 28-day mortality for individuals with COVID-19 requiring oxygen who were given steroid therapy (age-adjusted rate ratio 0.83; 95% CI 0.75–0.93; $P < 0.001$),¹⁰³ and this has been recommended for use in the NHS.¹⁰⁴ The RECOVERY trial protocol for pregnancy recommends prednisolone 40 mg orally once daily, and, in women unable to take oral medicine, hydrocortisone 80 mg intravenously twice daily instead of dexamethasone treatment.^{16 105 106}

Remdesivir is currently subject to a therapeutic alert for pregnancy; it should be avoided unless benefits outweigh risks, following multidisciplinary discussion.¹⁰⁷ Remdesivir is an antiviral medication which has been shown to be associated with a reduction in time to clinical improvement in individuals with severe COVID-19, median 11 versus 15 days, rate ratio 1.32 (95% CI 1.12–1.55).¹⁰⁸

Pregnant women can be enrolled in the RECOVERY trial.

Where therapies or participation in trials are offered, they should also be considered for and offered to pregnant women.

RECOVERY for pregnant women



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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](#).

[RECOVERY Privacy Notice for Trial Staff](#)

INTERVENTION INFORMATION

[RECOVERY intervention sheet - colchicine](#)

[RECOVERY intervention sheet - aspirin](#)

[RECOVERY intervention sheet - dexamethasone \(now only recruiting children\)](#)

[RECOVERY intervention sheet - azithromycin](#)

[RECOVERY intervention sheet - tocilizumab](#)

[RECOVERY intervention sheet - assessing patients for risk of transfusion associated circulatory overload \(TACO\) prior to convalescent plasma transfusions](#)

GUIDES FOR SPECIFIC PATIENT GROUPS

[RECOVERY for paediatric patients](#)

[RECOVERY for patients with chronic kidney disease](#)

[RECOVERY for pregnant and breastfeeding women](#)

[RECOVERY and remdesivir](#)

COLLABORATORS' MEETINGS SLIDES

We apologise if you were unable to join the meetings.

16 November 2020	17 November 2020
26 October 2020	27 October 2020
5 October 2020	6 October 2020
3 & 4 August 2020	14 & 15 September 2020
13 July 2020	14 July 2020
29 June 2020	30 June 2020
15 June 2020	16 June 2020
1 June 2020 (plus obstetrics)	2 June 2020

Pregnancy information document

RANDOMISED EVALUATION OF COVID-19 THERAPY ([RECOVERY](#))

for pregnant and breastfeeding women

Pregnancy leads: Prof Lucy Chappell, 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 (clinically suspected or lab confirmed) iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Same eligibility
Interventions	First randomisation part A <ul style="list-style-type: none">Colchicine First randomisation part B <ul style="list-style-type: none">Convalescent plasmaSynthetic neutralising antibodies First randomisation part C <ul style="list-style-type: none">Aspirin Second randomisation <ul style="list-style-type: none">Tocilizumab	Same interventions <i>(with exception of colchicine for pregnant and breastfeeding women - do not undertake part A randomisation for pregnant women)</i> <u>Pregnant and breastfeeding women are eligible for all other treatments shown.</u>
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): <ul style="list-style-type: none">➤ 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

Eligibility = same

2.1 Eligibility

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

- (i) Hospitalised
- (ii) SARS-CoV-2 infection (clinically suspected¹ 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'

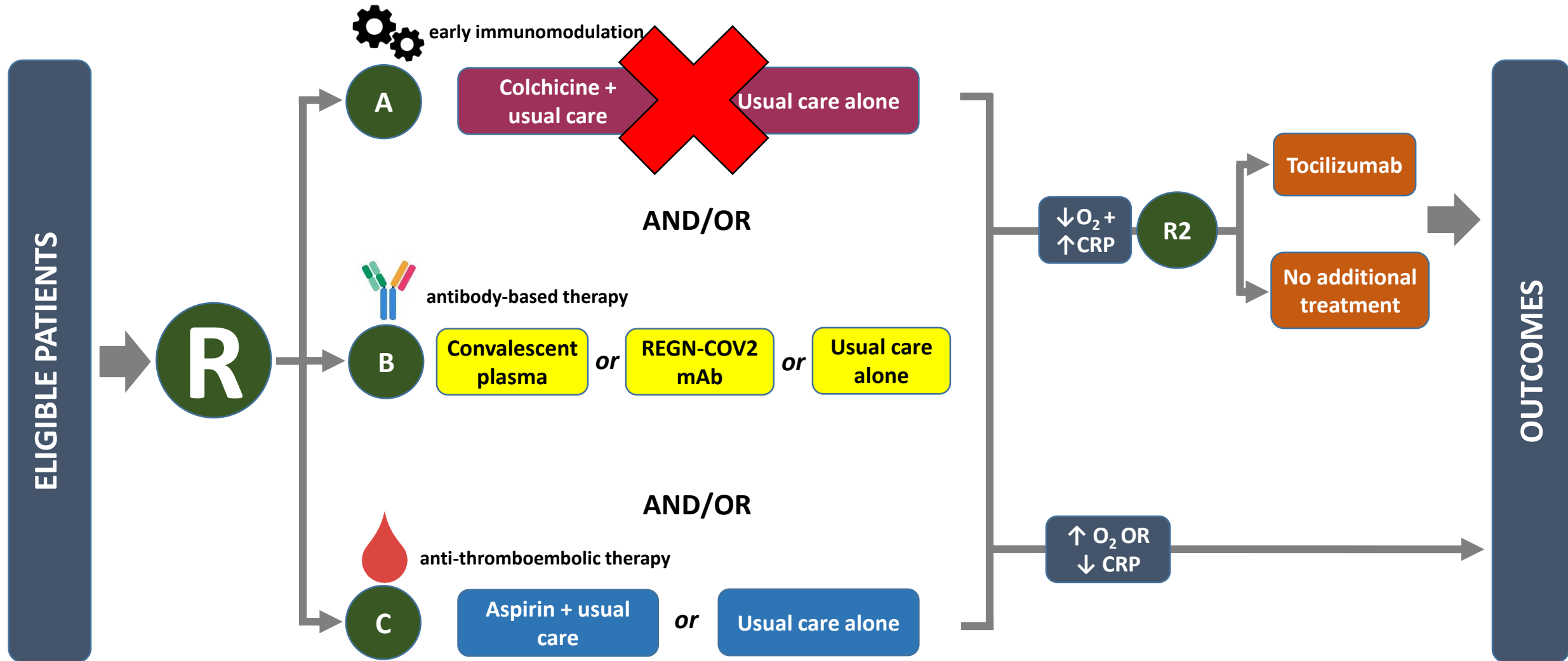
Offer the RECOVERY trial if...



- 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 provide the trial 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

Design for pregnant women



No colchicine allocation

Colchicine

This is not currently recommended for inclusion in the RECOVERY trial for pregnant or breastfeeding women.

The RECOVERY trial is excluding women aged less than 55 years old, but older women (aged 55 years and older) who might be pregnant should also not have colchicine included in their randomisation. Colchicine is a drug used to treat gout (not commonly seen in women of reproductive age) and familial Mediterranean fever (which is seen in pregnant women). A systematic review of colchicine use for pregnant women with familial Mediterranean fever has reported no increased risk of adverse pregnancy outcomes,[1] and this is reflected in the UKTIS information on colchicine:

<https://www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-IN-PREGNANCY/>

However, there are theoretical concerns over use in pregnancy, as colchicine has anti-mitotic properties with evidence of teratogenicity in animals, and the BNF advises against its use in pregnancy:

<https://bnf.nice.org.uk/drug/colchicine.html#pregnancy>.

In light of the uncertainty, we are not recommending colchicine for use in pregnant women (or those of reproductive age), but if a pregnant woman is unintentionally exposed to the drug, then the usual pathway should be followed (e.g. referral to a Fetal Medicine Unit and/ or discussion with the UK Teratology Information Service for advice).

Follow-up = the same, + linkage



Nuffield Department of
POPULATION HEALTH



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COVID-19 in Pregnancy



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

- [Key points](#)
- [Surveillance period](#)
- [Background](#)
- [Objective](#)
- [Research questions](#)
- [Case definition](#)
- [Funding](#)
- [Ethics committee approval](#)
- [Study registration](#)
- [Lead investigator](#)
- [Download the Data Collection Form \(DCF\)](#)
- [References](#)

Update on progress



- 160 pregnancy leads identified, supported by research midwives
- Midwife champions on board
- 44 antenatal women recruited and more postpartum women

Update from UKOSS this week



Nuffield Department of
POPULATION HEALTH
Medical Sciences Division



Notifications by week



ICNARC data (critical care)



Napier House
24 High Holborn
London WC1V 6AZ
email: COVID-19@icnarc.org
www.icnarc.org

ICNARC report on COVID-19 in critical care:
England, Wales and Northern Ireland
4 December 2020

Table 2. Patient characteristics: medical history

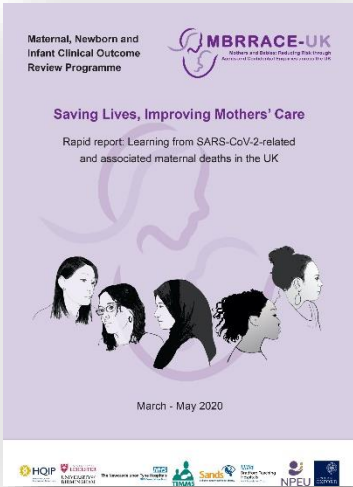
Medical history	Patients with confirmed COVID-19	
	Admitted from 1 Sep (N=6388)	Admitted up to 31 Aug (N=10,917)
Currently or recently pregnant, n (% of females aged 16-49) [N=455]		
Currently pregnant	37 (8.1)	29 (3.7)
Recently pregnant (within 6 weeks)	23 (5.1)	41 (5.2)
Not known to be pregnant	395 (86.8)	718 (91.1)

Recognition of severe illness



A woman in her third trimester of pregnancy presented to the Emergency Department with a one week history of symptoms of COVID-19. Her observations were documented using a National Early Warning Score (NEWS) and not a modified early obstetric warning score (MEOWS). She had a respiratory rate of 36 but this was not recognised as significant. Her first review by a member of obstetric staff was eleven hours after she attended, when a junior obstetrician identified no obstetric concerns. She deteriorated a few days later and was documented to need high dependency or intensive care but no beds were available in either high dependency or intensive care areas. Her care was discussed with a consultant obstetrician at the time of her deterioration and a decision made for a caesarean birth. Following the birth, it was again noted that no beds were available and she was transferred back to a general ward where she deteriorated. She was intubated and transferred to the intensive care unit but her condition continued to worsen and she died a few days later.

Ensure all pregnant or post-partum women with COVID-19 receive multidisciplinary team care and obstetric leadership with daily review. This is essential in order to ensure timely recognition of deterioration, early assessment of the need for iatrogenic birth to help respiratory function and identification of postnatal complications.



Next steps

- Anticipate ongoing new cases over coming weeks
- Check teams are ready for recruitment
- Talk to physicians in main hospital providing care for pregnant women
- Link with main RECOVERY research teams
- Think through pathways for notification of cases
- Use UKOSS as prompt to help (and for outcomes)
- Embed into usual practice
- Offer trial

Q&A