Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meetings

20 & 21 April 2020

Agenda

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1. Introductions
2. Update on progress
3. Frequently Asked Questions
    1. Lopinavir-ritonavir
    2. Azithromycin
4. Tocilizumab and second randomisation
5. SAE reporting
6. Follow-up
7. Future plans
8. Q&A

Introductions

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- One of the central study team will talk to the agenda
- If you have questions about that particular topic please enter them into the “chat”
- Please save other questions for the general Q&A at the end

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UPDATE ON PROGRESS

RECOVERY trial design

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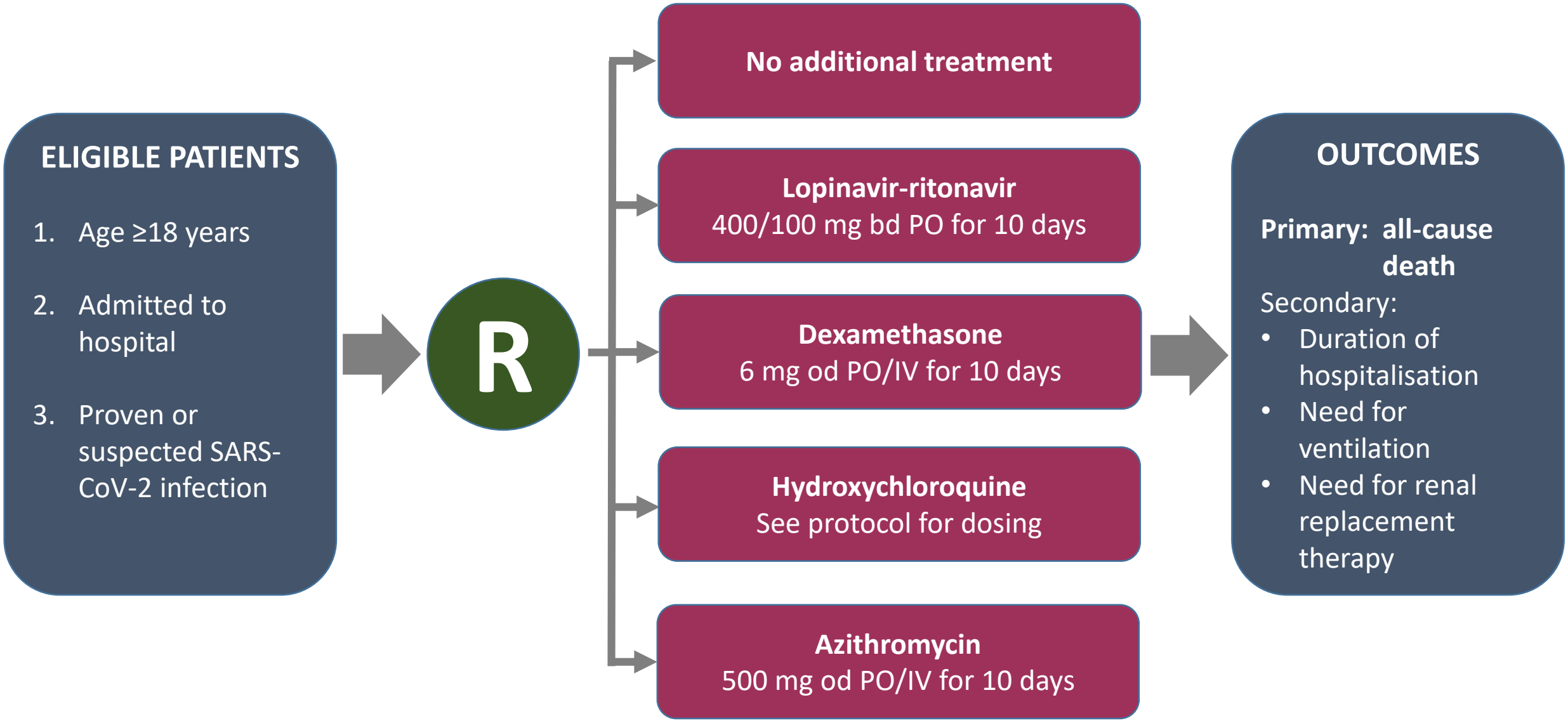
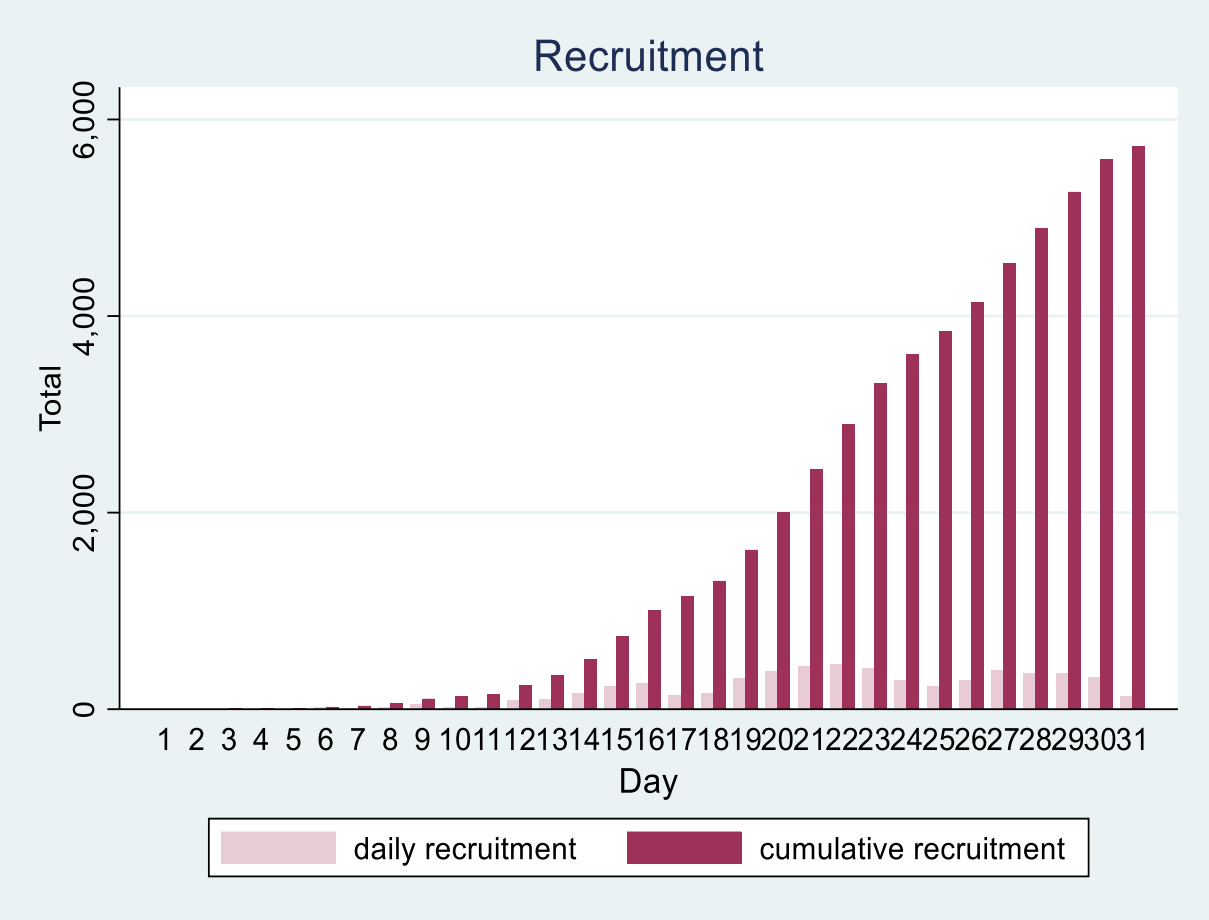
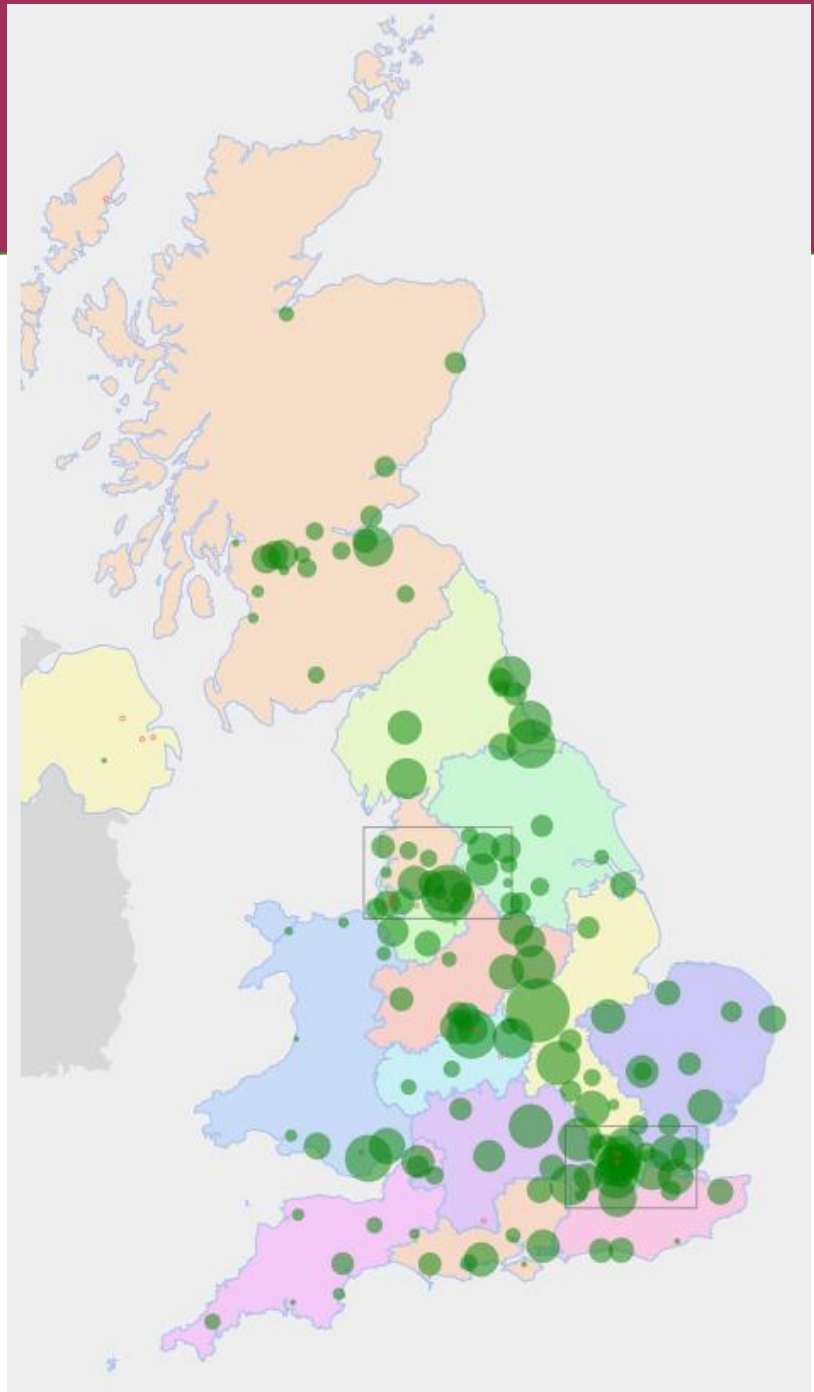


Update on progress





Characteristics at randomisation (n=5265)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		3525 (65%)
Age		65 (15)
Days since symptom onset		10 (6-14)
Days since hospitalisation		3 (2-6)
Severity of disease	No oxygen required	950 (18%)
	Supplemental oxygen only	3272 (62%)
	Ventilation/ECMO	1043 (20%)
Prior disease	Diabetes	1405 (27%)
	Cardiovascular disease	1281 (24%)
	Chronic lung disease	1035 (20%)

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FREQUENTLY ASKED QUESTIONS

Study treatments: Lopinavir-ritonavir

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- HIV drug with activity against SARS-CoV-2 in tissue culture

- Delivery can be difficult especially in patients unable to swallow
  - Liquid formulation is being acquired by PHE so will be available to order soon
  - REMAP-CAP method of tablet dissolution being discussed with MHRA

Study treatments: Azithromycin

- Can patients at sites that use azithromycin (or other macrolides) be recruited?

- If patient **already on a macrolide** at randomisation, then can enter trial but will not be allocated azithromycin or hydroxychloroquine
  - Macrolides and hydroxychloroquine both prolong QT interval

- If patient **not on a macrolide** at randomisation, can enter any suitable arm of the trial
  - If managing doctors which to prescribe macrolide later, they may but must consider risks

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TOCILIZUMAB AND SECOND RANDOMISATION

IL-6 and Tocilizumab

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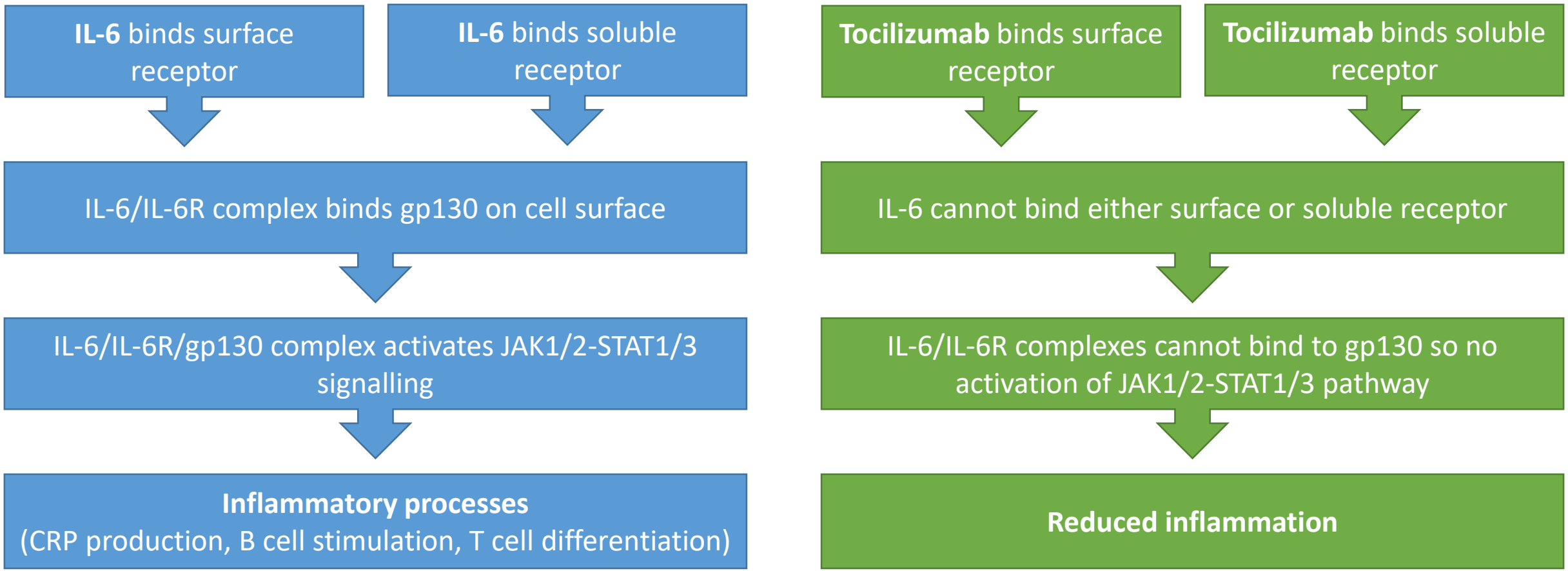

Tocilizumab

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- Humanized monoclonal antibody against IL-6 receptor
- Licensed for treatment in:
  - Rheumatoid arthritis
  - Cytokine release syndrome (CRS) after CAR-T cell therapy (new treatment for haematological malignancy)
- Also being tested in REMAP-CAP and COVACTA trials

RECOVERY second randomisation

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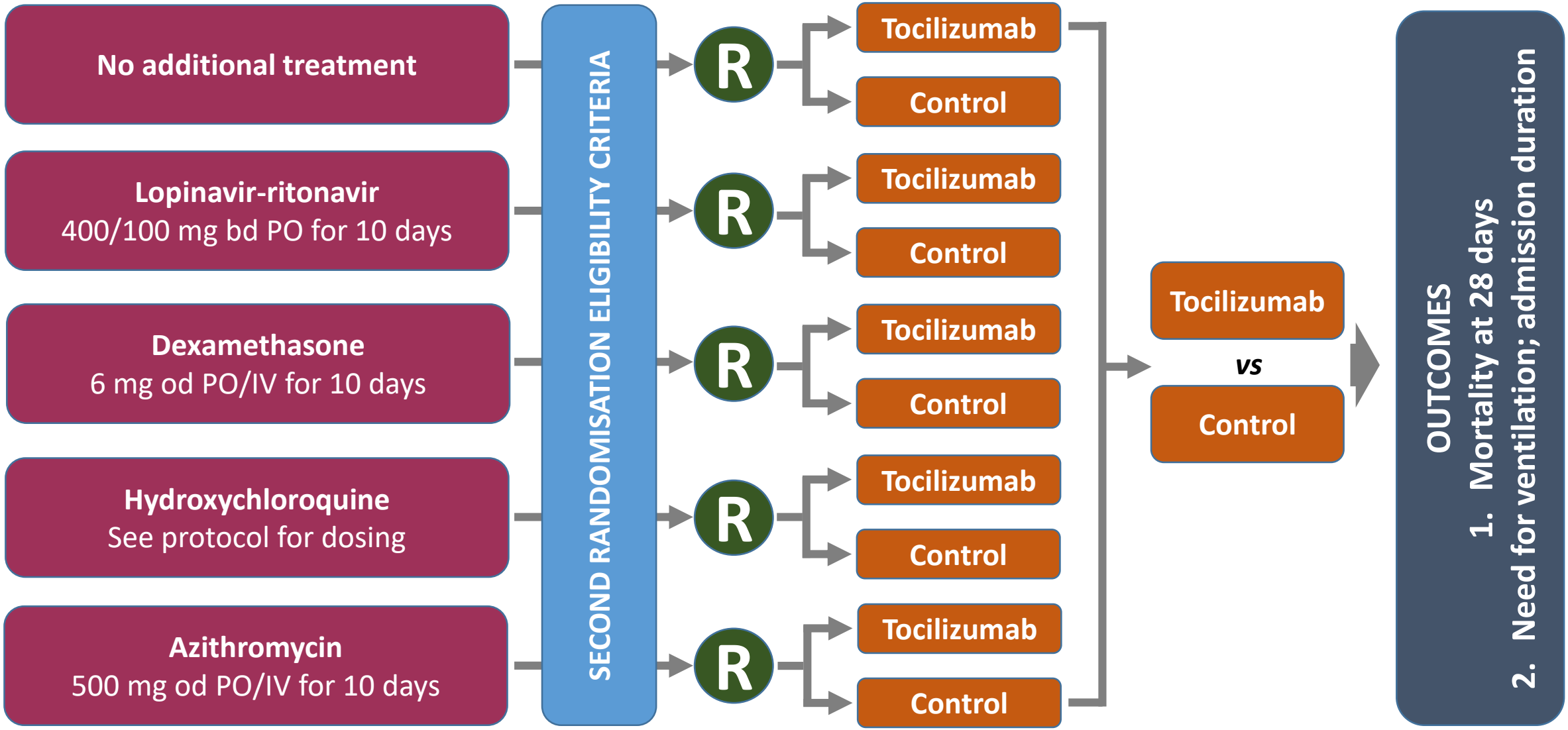

Second randomisation

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- Will not be conducted at all study sites due to limited drug supply
  - Sufficient for 4000 participants to be randomised between tocilizumab and control
- May be done at <u>any time</u> from immediately after first randomisation until 21 days later
- Consent included in main PIS/ICF (V4.1)
  - For participants recruited using earlier PIS/ICF may be included without re-consent

Second randomisation: eligibility

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- Eligibility criteria:
  - Receiving oxygen or oxygen saturations <92% on air
  - CRP ≥75 mg/L
  - No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if s/he were to participate in this aspect of the RECOVERY trial
    - e.g. clear evidence of secondary bacterial infection causing deterioration

Second randomisation: access

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- Access (i) via main randomisation system:

Logged in as: **Centre 1 (City 1)**

Menu

Latest 3 participants			
Study no	**NHS number**	**Date randomised**	**Time since randomisation**
1009913	8412658469	20/04/20 09:42	29 minutes
1009908	0274793385	20/04/20 09:26	45 minutes
1009896	5275396260	20/04/20 03:17	6 hours

Please select one of the following options:

1. **Enrol patient into study**
2. **View recent recruitment list**
3. **Enrol patient into second phase**
4. **Log out**

Second randomisation: access

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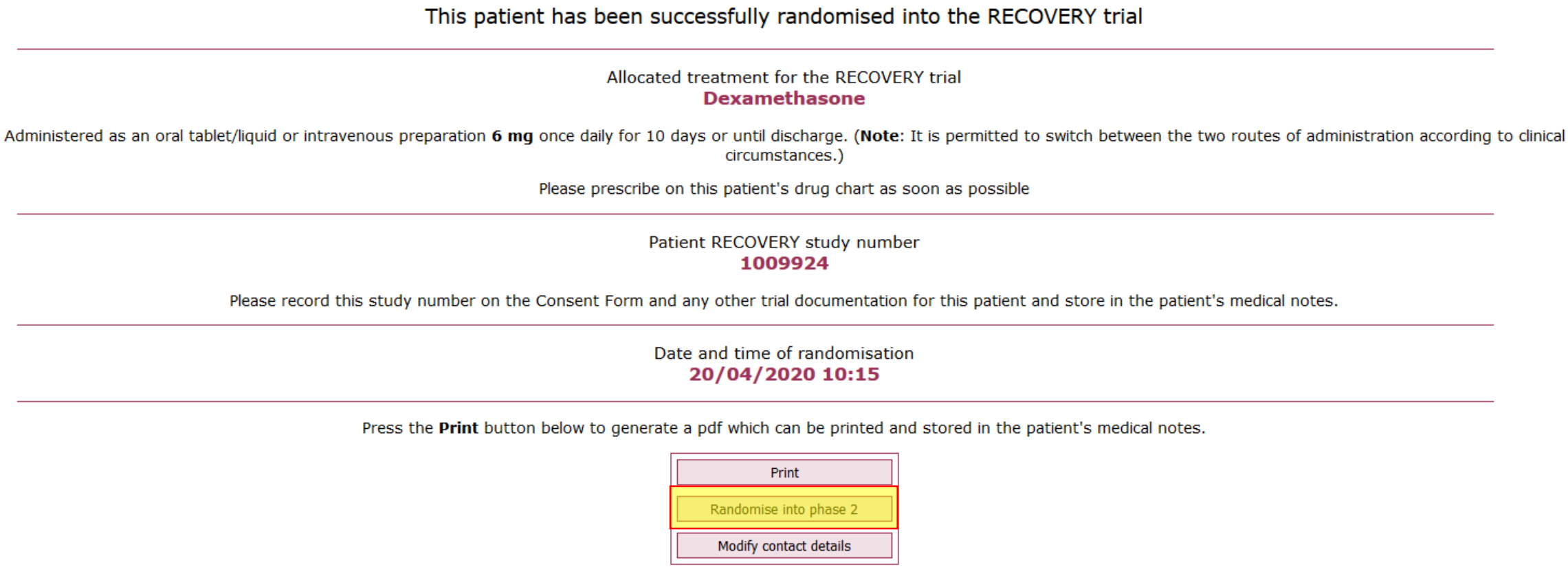
- Or (ii) access at end of main randomisation:



Second randomisation: process

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Patient details

Study no	1000000
Name	Forename Surname
A1. What is the patient's date of birth?	▾ / ▾ / ▾

Treating clinician

A2. Name of treating clinician	

Inclusion criteria

A3. Does the patient require oxygen?	▾
A4. Please select one of the following to describe the current level of ventilation support	None ▾
A5. Enter latest oxygen saturation measurement (%)	

Check that correct participant has been selected

Yes/No

Drop-down:
- CPAP
- NIV
- High-flow nasal O_2
- IMV
- ECMO

Second randomisation: process

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A6. Enter latest CRP measurement since admission to hospital (mg/L)
Enter 0 if below the limit of measurement
☐ Tick if not measured
☐ Tick if greater than limit of measurement

A7. Enter latest ferritin measurement since admission to hospital (ng/mL)
Enter 0 if below the limit of measurement
☐ Tick if not measured
☐ Tick if greater than limit of measurement

A8. Enter latest creatinine measurement since admission to hospital (µmol/L)
☐ Tick if not measured

Either enter result ("0" if below limit); or tick box if
1. not measured; or
2. Above limit (e.g. >250)

A9. Does the patient have any medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in this aspect of the trial?

Yes/No

Is the following treatment unsuitable for the patient?

A10.1 Tocilizumab

Is the following treatment available?

A11.1 Tocilizumab

Yes/No

Please sign off this form once complete

Tocilizumab prescribing

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- **Weight-based dose**
  - Can use estimated weight if measurement not available/possible

Weight	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

  - If weight ≤40 kg, prescribe 8 mg/kg
  - Single intravenous infusion over 60 minutes in 100 mL 0.9% sodium chloride

- **Second dose** can be given ≥12 <24 hours later if – in clinician's opinion – the patient's condition has not improved

Tocilizumab stock

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- Available via ImmForms/Movianto system

- Sites will be able to order sufficient for 20 patients initially; please contact coordinating centre once 10 patients treated

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SERIOUS ADVERSE EVENT REPORTING AND FOLLOW-UP

Serious Adverse Event reporting

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- Protocol specifies that adverse events only need to be reported if they are **both**:
  - **Serious;** and
  - Believed – with reasonable probability – to be **related** to study treatment

Serious Adverse Event reporting

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- As participants are inpatients already, can only be serious if:
  - Fatal or life-threatening
  - Prolong admission
  - Are another “important” event that requires intervention to avoid above

- Events should <u>not</u> necessarily be considered serious if:
  - Study treatment is discontinued
  - Do not require significant intervention (e.g. asymptomatic bradycardia)
  - They are recognised adverse effect of treatment but not otherwise serious (e.g. prolonged QTc interval without sequelae)

Serious Adverse Event reporting

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- Relatedness is based on “a reasonably probability”
  - Relationship to starting study treatment
  - Consideration of alternative causes
  - Not simply because “it can’t be excluded”

- Readmissions do not need to be reported unless related to study treatment

Follow-up

- All sites now have teams of people who can complete Follow-up forms on OpenClinica
- Form collects simple information on
  - Use of study treatments
  - Discharge or cause of death
  - Requirement for ventilation or dialysis

- Please ensure you track who requires form to be completed
- Coordinating Centre will provide reports in due course

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FUTURE PLANS

Future plans

- Trial now has 5 arms in main comparison and second randomisation
- No other arms to be added imminently
- Plans to include children in next protocol amendment
  - Need to identify paediatric co-investigator if you wish to recruit children at your site

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QUESTIONS AND ANSWERS

Q&A

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Q: What about transfer of patient to another hospital?

A: If for continuing acute care then should continue study treatment and not consider transfer to be “discharge”

If for rehabilitation then study treatment should stop and consider transfer to be discharge

Q: When will RECOVERY results be ready?

A: The quicker we recruit, the quicker the results will come! DMC review data every week.

Thank you!

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- Thank you very much for your collaboration in these uniquely challenging circumstances

- RECOVERY will provide reliable information on treatments for COVID-19 in the coming weeks to months which could influence management both in the UK and globally

- And a challenge…