Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

14th July 2020

Agenda

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. Introductions
2. Update on progress
3. Recruitment
4. Future plans
5. Q&A
6. Paediatric update
7. 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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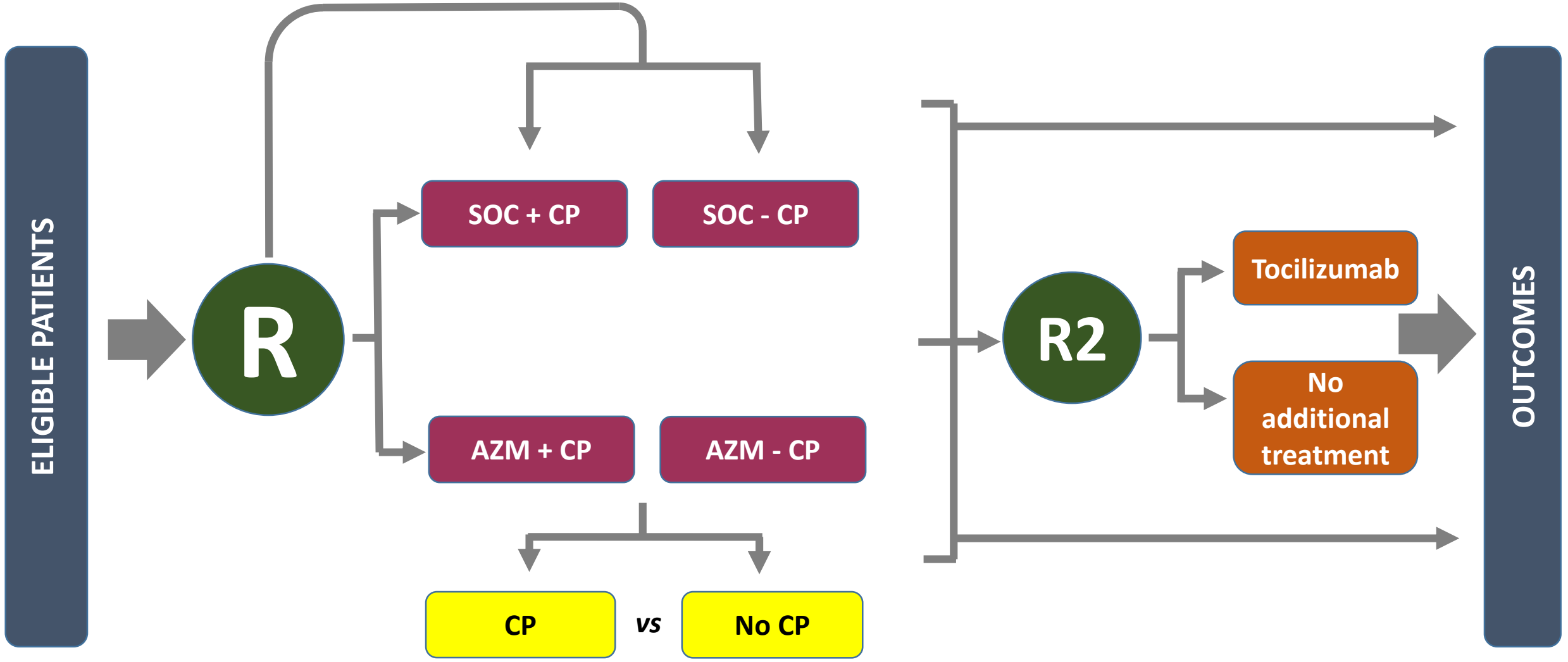

Recruitment by site and by time

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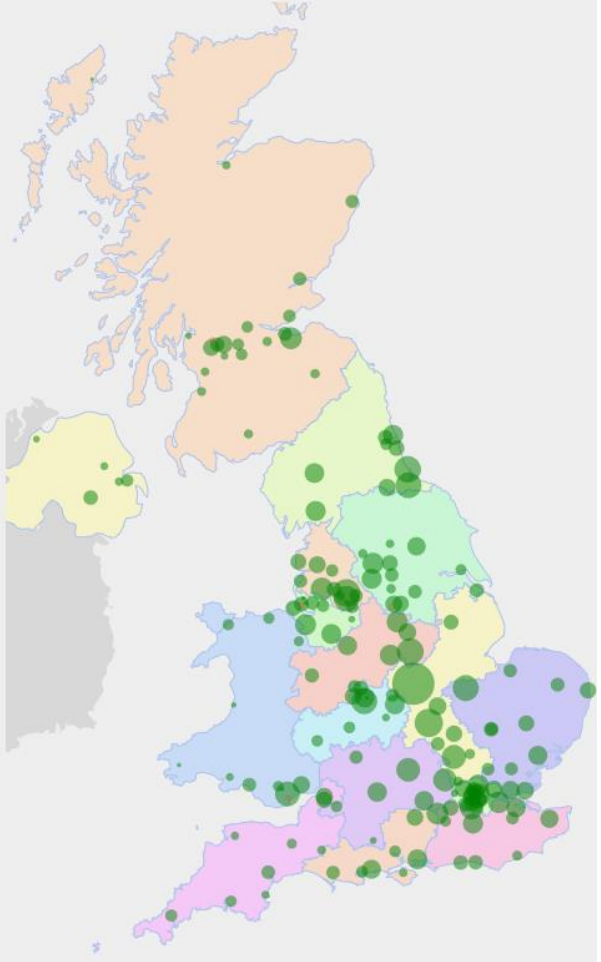
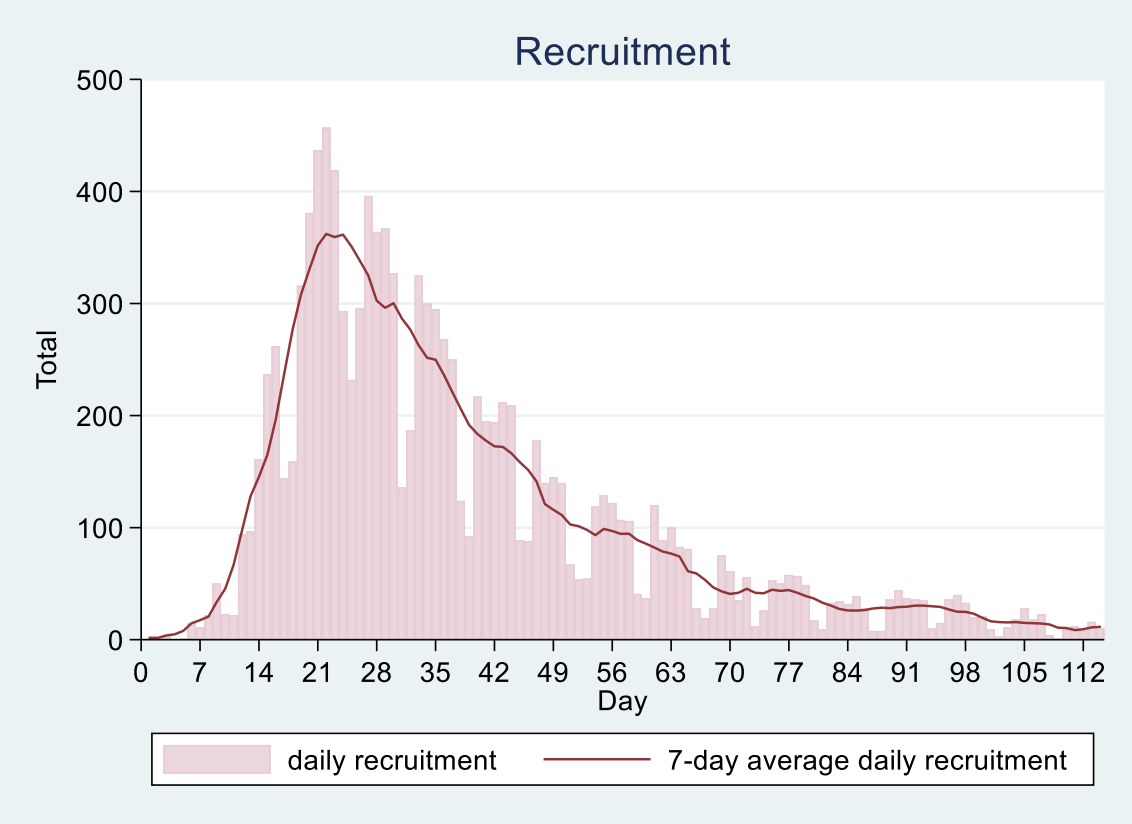
Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.
176	172	12034	808	216





Recruitment proportion

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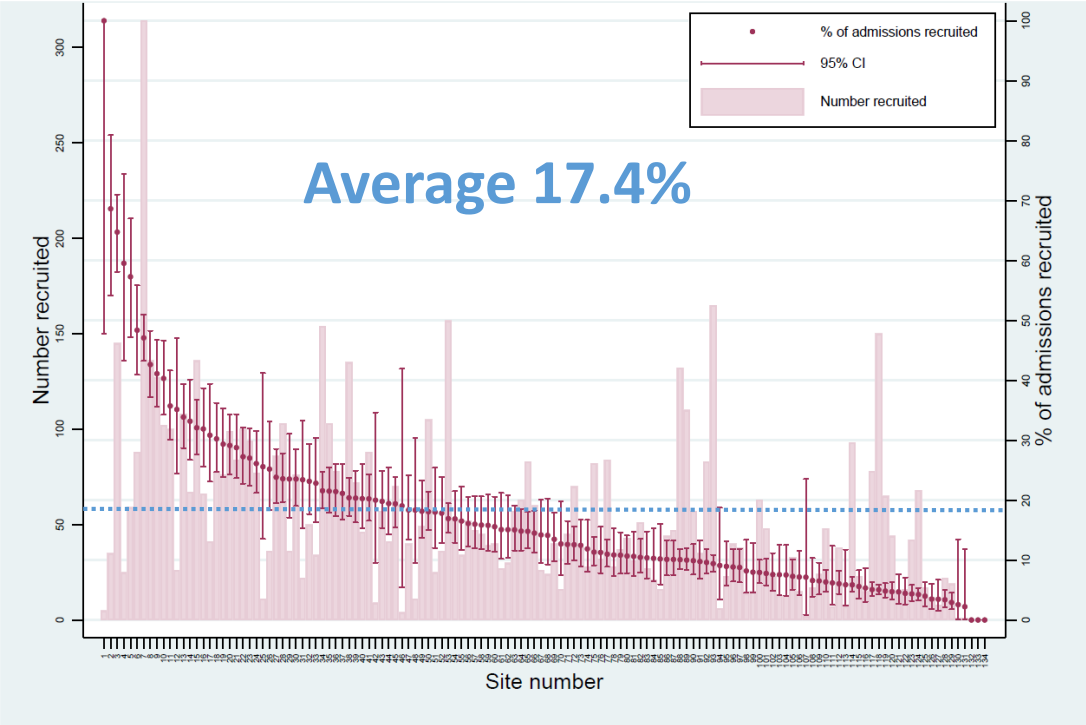
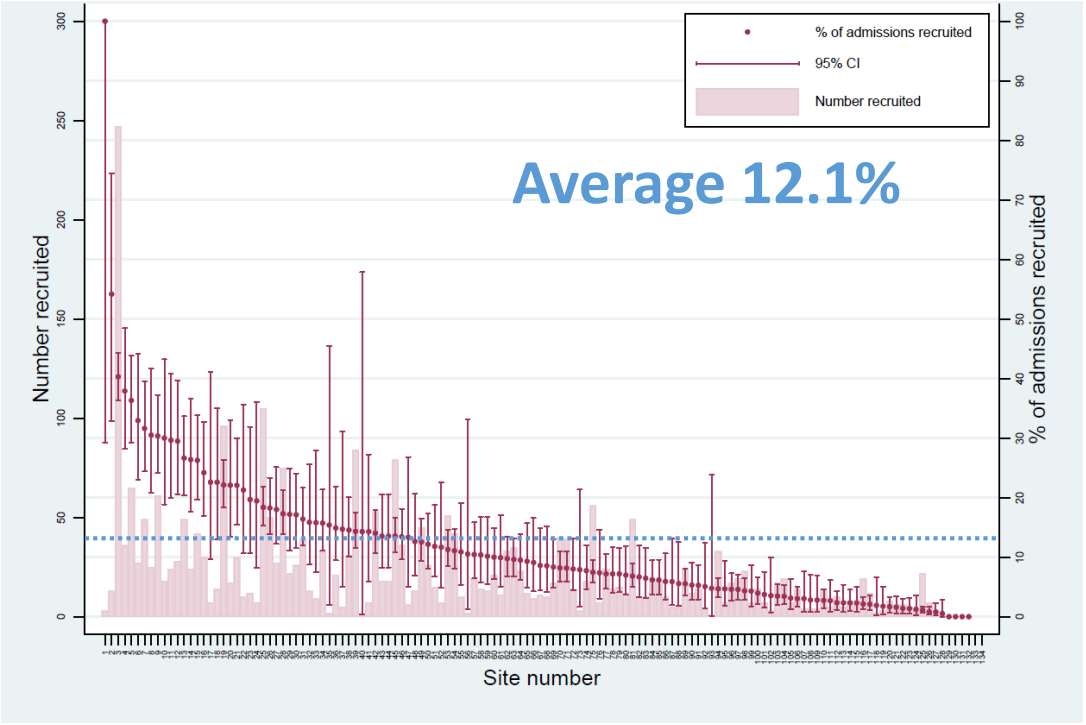
Proportion recruited 20 March – 30 April



Proportion recruited 30 April – 7 July



Recruitment proportion

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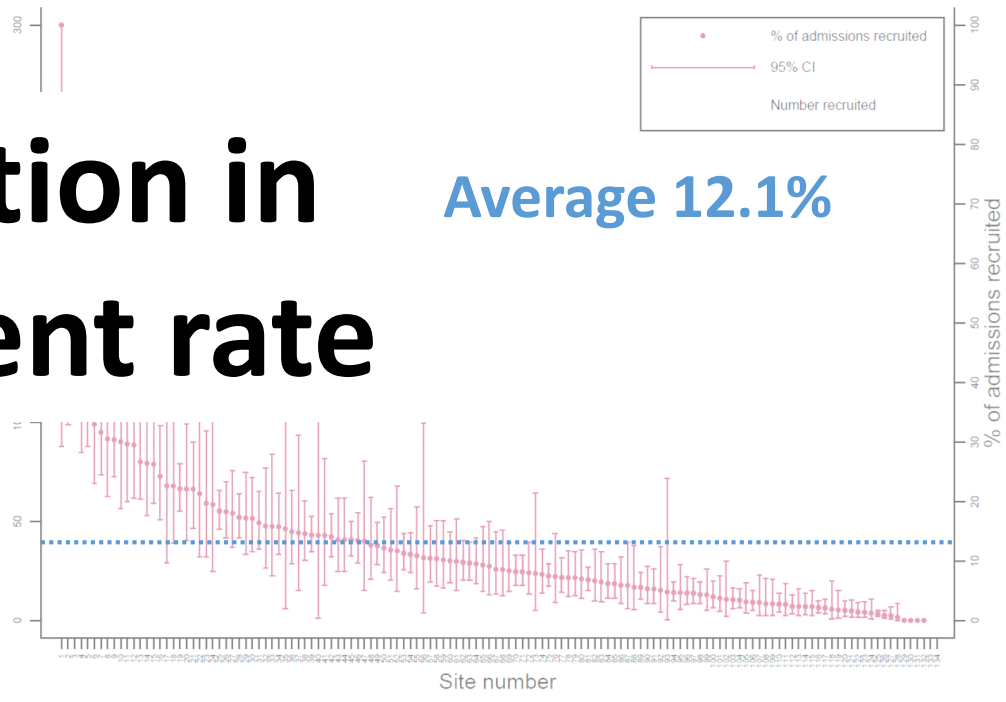
Proportion recruited 20 March – 30 April

Average 17.4%

⅓ reduction in recruitment rate

Proportion recruited 30 April – 7 July



Average 12.1%

Recruitment proportion: change in rate between two periods

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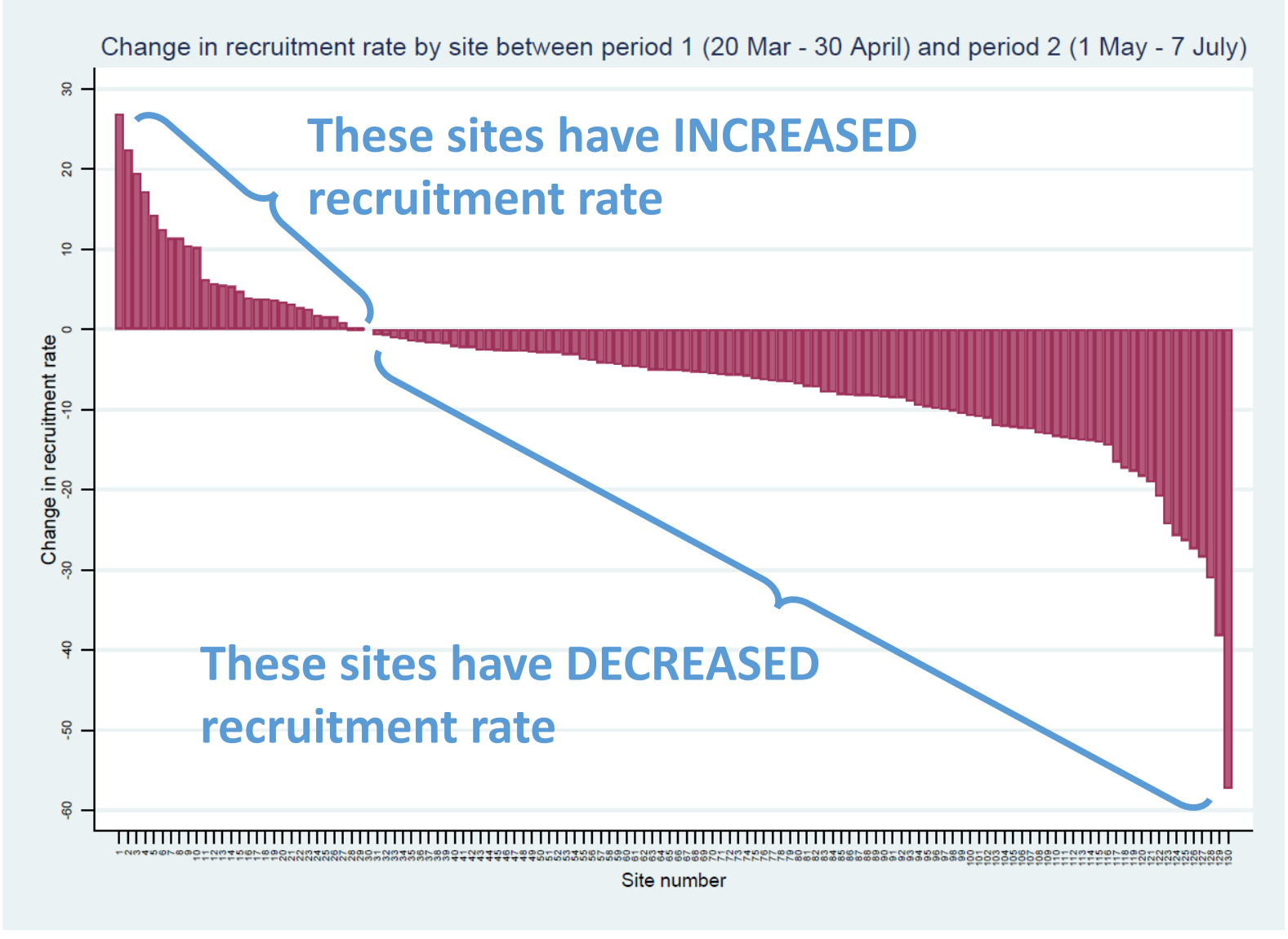

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TOCILIZUMAB

Tocilizumab

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- Added to protocol on 14 April as a second randomisation for deteriorating participants
  - Hypoxia (or significant systemic disease with persistent pyrexia in children)
  - Inflammation (CRP ≥75 mg/L)

- Two other tocilizumab trials due to present results at the end of July
  - COVACTA: Roche's own trial of 450 participants
  - BACC study: 243 participants

- If your site is not included yet but would like to be, please e-mail recoverytrial@ndph.ox.ac.uk

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FOLLOW-UP

Completeness is key

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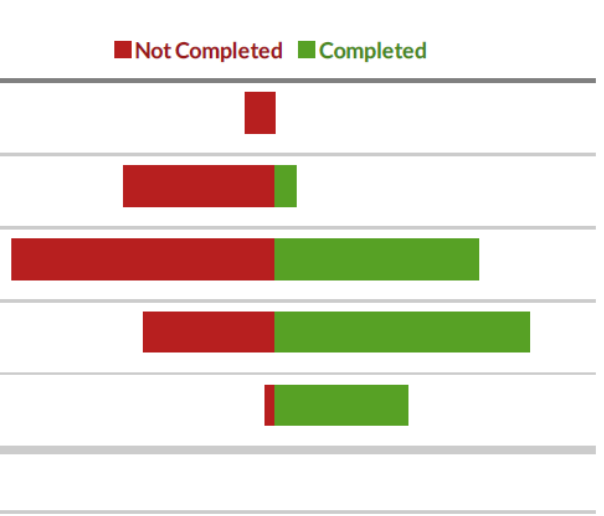
- Weekly reminders highlighting participants randomised >28 days ago without complete form **and also** those needing a Convalescent Plasma 72h safety form

- 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**



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FUTURE PLANS

Current trial design

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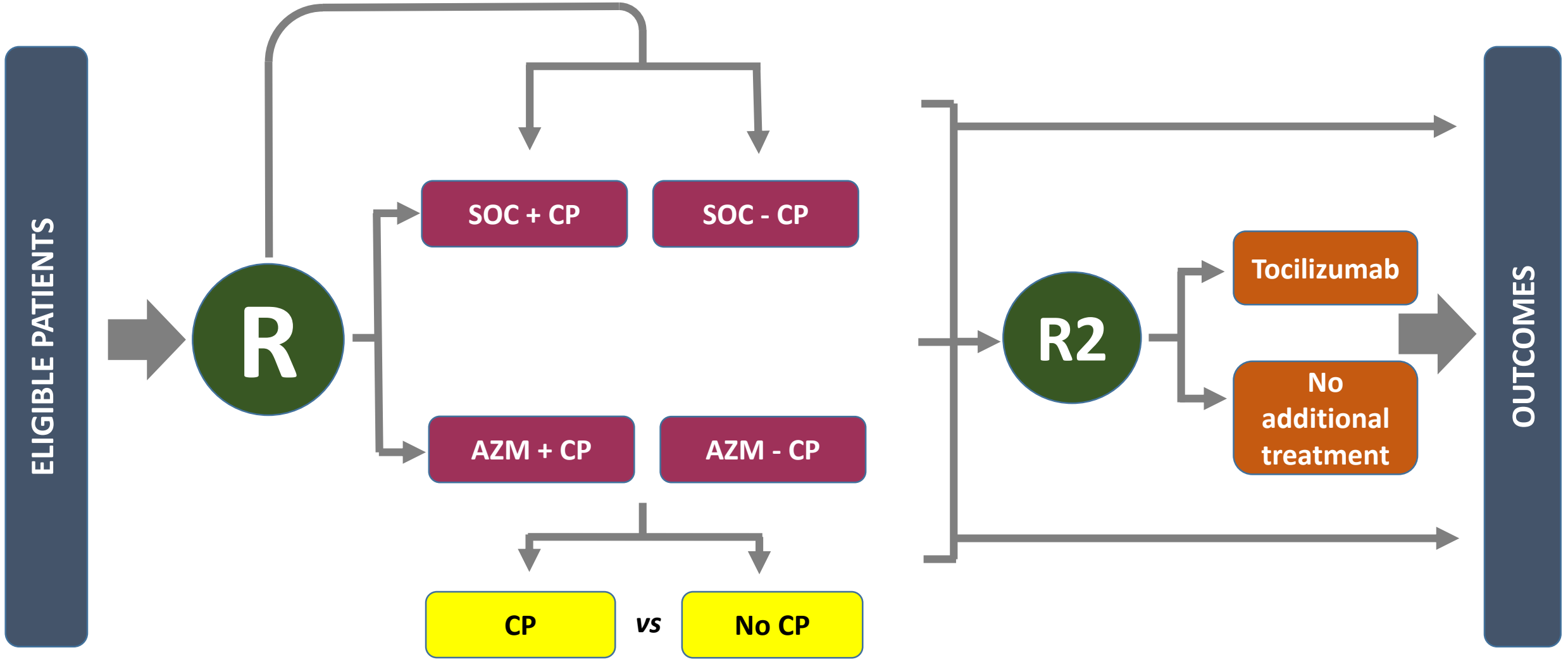

Protocol V8.0

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- Adds collection of serum sample at baseline for patients entering convalescent plasma comparison

- Standard serum sample (often ‘red top’) to be sent to transfusion laboratory **before** patient is randomised
- Will allow measurement of coronavirus and antibodies against it, to help assessment of effect of convalescent plasma

Protocol V8.0

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- Introduces treatments for PIMS-TS (Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19)
  - High-dose methylprednisolone *vs*
  - intravenous immunoglobulin *vs*
  - usual care

Carry on recruiting!

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- 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!

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Paediatric Collaborators' Meeting

14th July2020

Agenda

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1. Current trial design
2. Protocol 8.0: Introduces treatments for PIMS-TS (Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19) for children over 44 weeks corrected gestational age – 18 years
3. Neonates and infants under 44 weeks corrected GA

Current trial design >18 years

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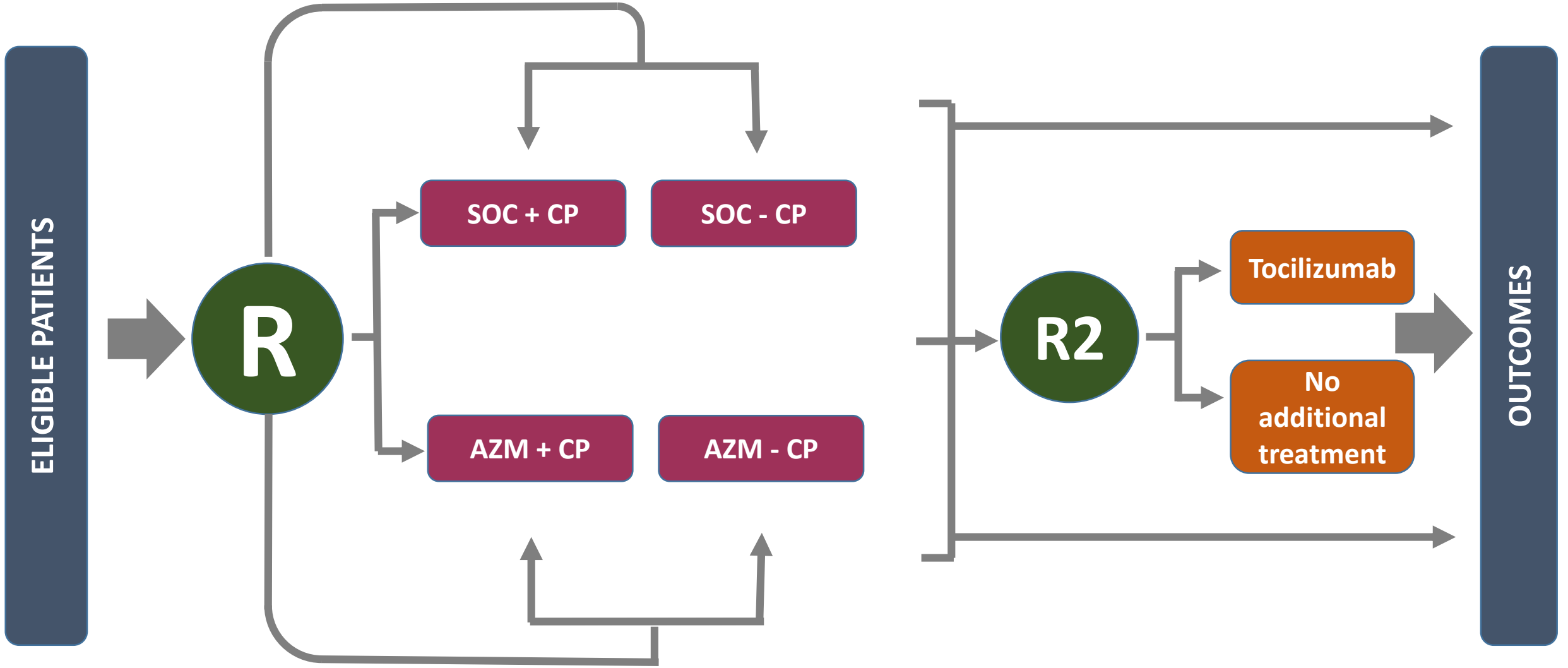

PIMS-TS Delphi and RECOVERY

- **A national consensus management pathway for Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS): The results of a national Delphi process**

- Submitted to ADC

- Rachel Harwood, Benjamin Allin, Simon Kenny

Box 4: Research for children with PIMS-TS

RECOVERY trial

RECOVERY is an adaptive trial and based on this Delphi process, the Trial Steering Committee are considering a PIMS-TS specific first randomisation protocol amendment.

1. All children who meet the criteria for inclusion in the RECOVERY trial should be offered the opportunity to enter and be randomised in the first stage.
2. For a future amendment in RECOVERY or a future research trial there is equipoise for children with both phenotypes of PIMS to receive methylprednisolone OR IVIg as a first line treatment within a research study.
3. Children enrolled in the RECOVERY trial should be offered the opportunity to enter the 2nd stage intervetions arm (Tocilizumab vs standard of care) if they have been discussed by a MDT and the decision made to commence biological therapy.
4. For a future research trial there is equipoise between tocilizumab, anakinra and infliximab for patients with a non-specific phenotype.
5. Infliximab is the preferred biologic for children with Kawasaki-like Disease.
6. All families should be approached for inclusion in research studies including DiAMONDS and ISARIC/CCP-UK. All children should be enrolled to the national BPSU PIMS-TS registry.

RECOVERY for PIMS-TS

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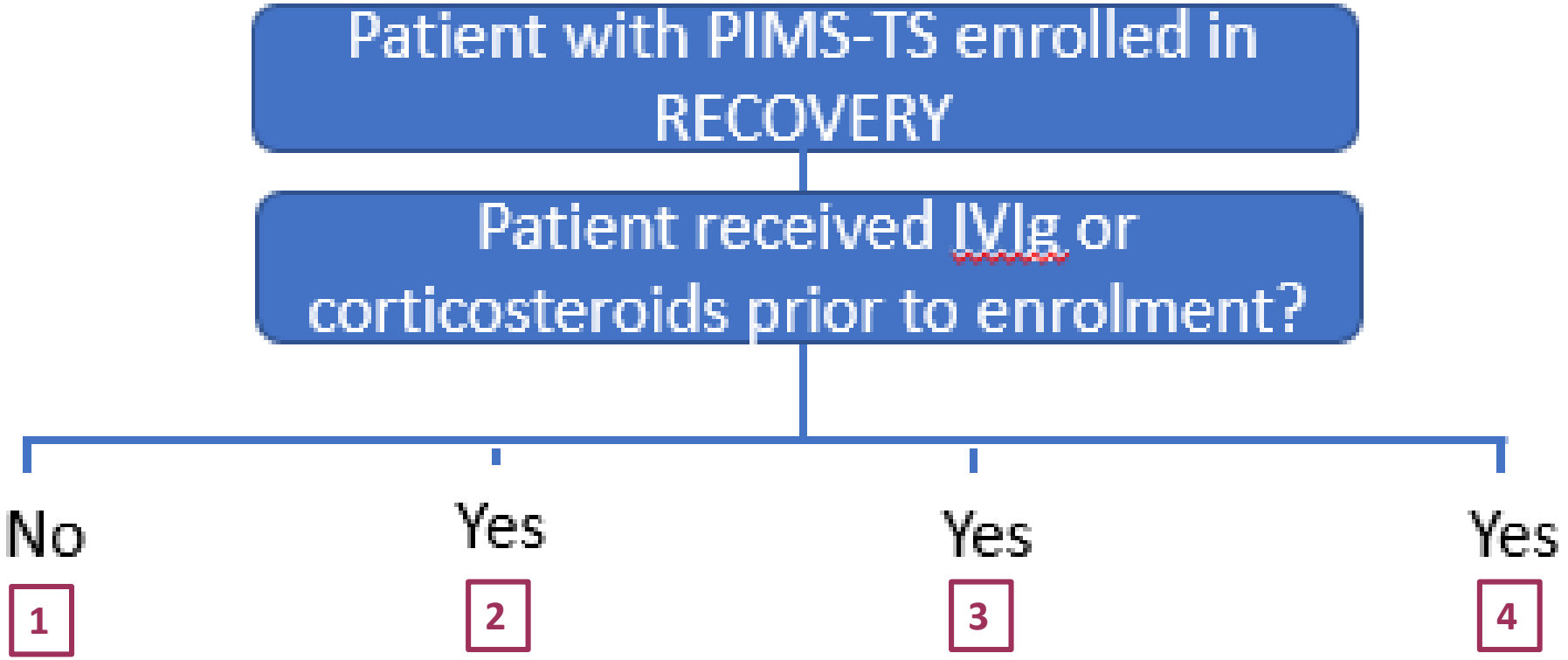
Aim: compare steroids vs SOC (in presence and absence of IVIg) and IVIg vs SOC (in presence and absence of steroids).

Design being reviewed by REC will:

- Allow investigators to use no treatment, IVIg or steroids or as standard care if deemed necessary
- Allow effects of steroids and IVIg to be compared with SOC separately (in presence and absence of other drug)
- Allow wide spectrum of severity to be recruited because some treatment can be guaranteed but not absolutely required
- Second randomisation to tocilizumab is still available.
- Also collects baseline use of steroids/IVIg at second randomisation (although not recommended this is in case clinicians go off-protocol in-between two randomisations)

Scenarios


Patient with PIMS-TS enrolled in RECOVERY
Patient received IVIg or corticosteroids prior to enrolment?
No
1
Yes
2
Yes
3
Yes
4

Scenario 1: Patient with PIMS-TS who has not received treatment* prior to enrolment

*IVIg, methylprednisolone or equivalent to ≥ 2mg/kg prednisolone

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Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to IVIg vs methylprednisolone vs no additional treatment

↓

Scenario 1: Patient with PIMS-TS who has not received treatment* prior to enrolment

*IVIg, methylprednisolone or equivalent to ≥ 2mg/kg prednisolone

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to IVIg vs methylprednisolone vs no additional treatment

↓

Evidence of ongoing fever and inflammation or clinical deterioration?

Yes ↓

Randomise to 2nd stage interventions:
Tocilizumab no additional treatment

Can transfer to tertiary centre if clinically necessary

No ↓

Do not proceed to 2nd stage interventions

Scenario 2: Patient with PIMS-TS who has already received IVIg prior to enrolment

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Select **IVIg as unsuitable** for 1st stage intervention

↓

Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to methylprednisolone vs no additional treatment

↓

Scenario 2: Patient with PIMS-TS who has already received IVIg prior to enrolment

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Select **IVIg as unsuitable** for 1st stage intervention

↓

Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to methylprednisolone vs no additional treatment

↓

Evidence of ongoing fever and inflammation or clinical deterioration?

Yes

Can transfer to tertiary centre if clinically necessary

No

↓

Randomise to 2nd stage interventions:
Tocilizumab no additional treatment

↓

Do not proceed to 2nd stage interventions

Scenario 3: Patient with PIMS-TS who has already received methylprednisolone* prior to enrolment

*** (or equivalent to ≥ 2mg/kg prednisolone)**

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Select **methylprednisolone as unsuitable** for 1st stage intervention

↓

Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to IVIg vs no additional treatment

↓

Scenario 3: Patient with PIMS-TS who has already received methylprednisolone* prior to enrolment

*** (or equivalent to ≥ 2mg/kg prednisolone)**

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Select **methylprednisolone as unsuitable** for 1st stage intervention

↓

Azithromycin should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to IVIg vs no additional treatment

↓

Evidence of ongoing fever and inflammation or clinical deterioration?

Yes

Can transfer to tertiary centre if clinically necessary

No

Randomise to 2nd stage interventions:
Tocilizumab no additional treatment

Do not proceed to 2nd stage interventions

Scenario 4: Patient with PIMS-TS who has already received IVIg AND methylprednisolone* prior to enrolment * (or equivalent to ≥ 2mg/kg prednisolone)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

IVIg and methylprednisolone should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to no additional treatment vs azithromycin (if no contraindications) or consider randomisation 1B (See FAQ 12)

↓

Scenario 4: Patient with PIMS-TS who has already received IVIg AND methylprednisolone* prior to enrolment * (or equivalent to ≥ 2mg/kg prednisolone)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

IVIg and methylprednisolone should be marked as **unsuitable** for 1st stage intervention

↓

Randomise to no additional treatment vs azithromycin (if no contraindications) or consider randomisation 1B (See FAQ 12)

↓

Evidence of ongoing fever and inflammation or clinical deterioration?

Yes ↓

Randomise to 2nd stage interventions:
Tocilizumab no additional treatment

No ↓

Do not proceed to 2nd stage interventions

Scenarios 1-4: ongoing inflammation

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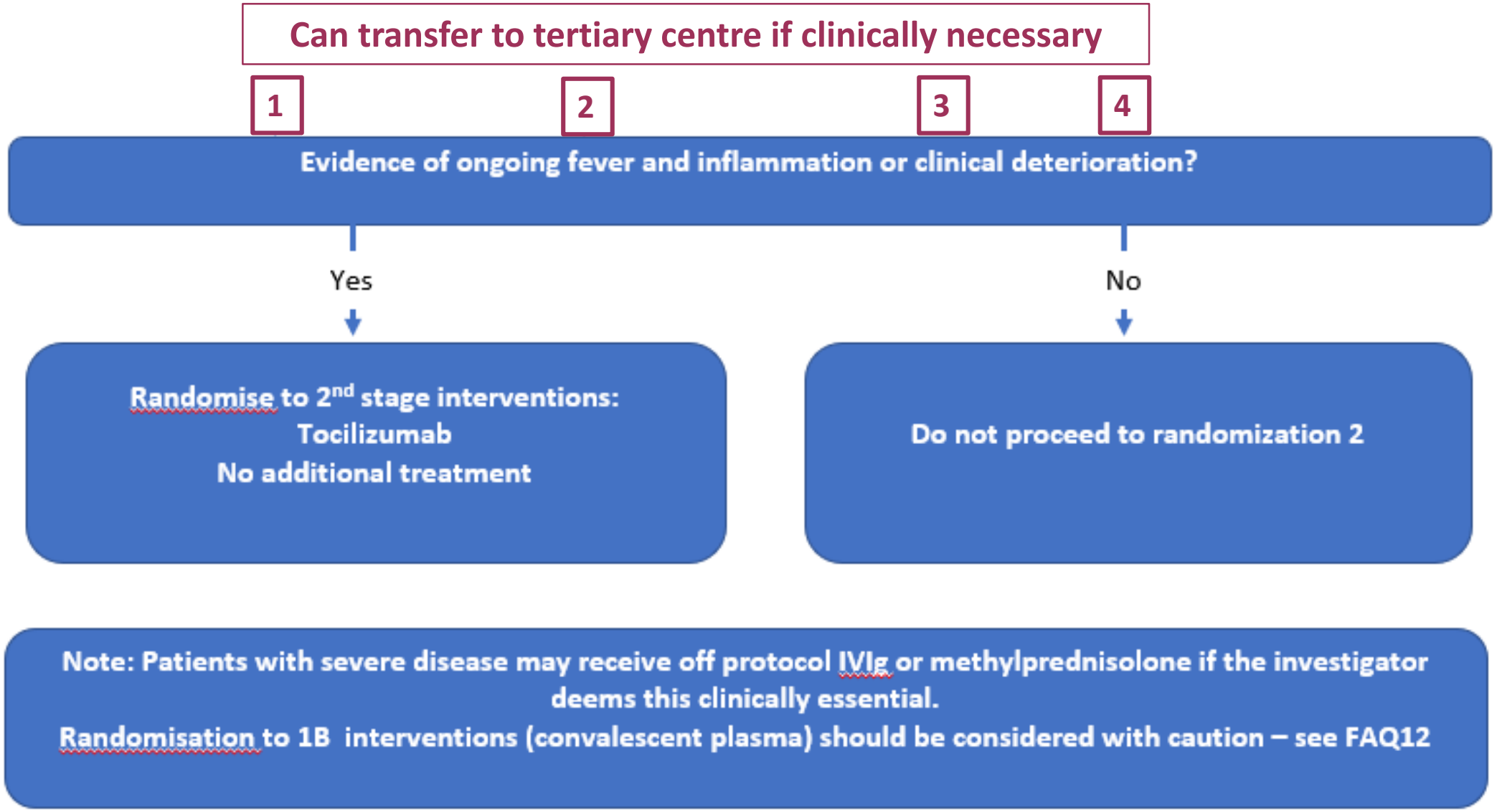

Summary

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- Allows investigators to use no treatment, IVIg or steroids or as standard care if deemed necessary
- Allows effects of steroids and IVIg to be compared with SOC separately (in presence and absence of other drug)
- Allows wide spectrum of severity to be recruited because some treatment can be guaranteed but not absolutely required
- Second randomisation to tocilizumab is still available.
- Also collects baseline use of steroids/IVIg at second randomisation (although not recommended this is in case clinicians go off-protocol in-between two randomisations)

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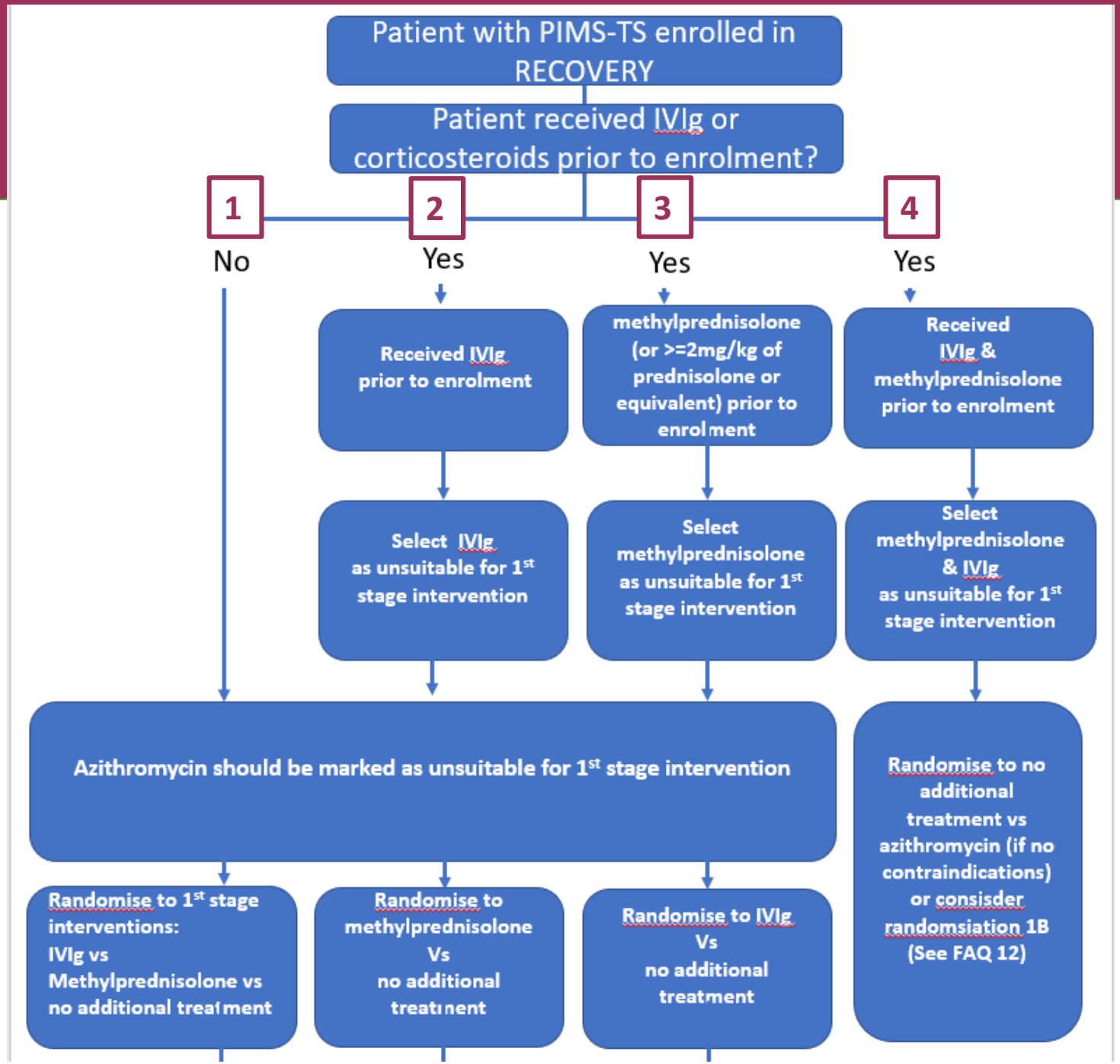

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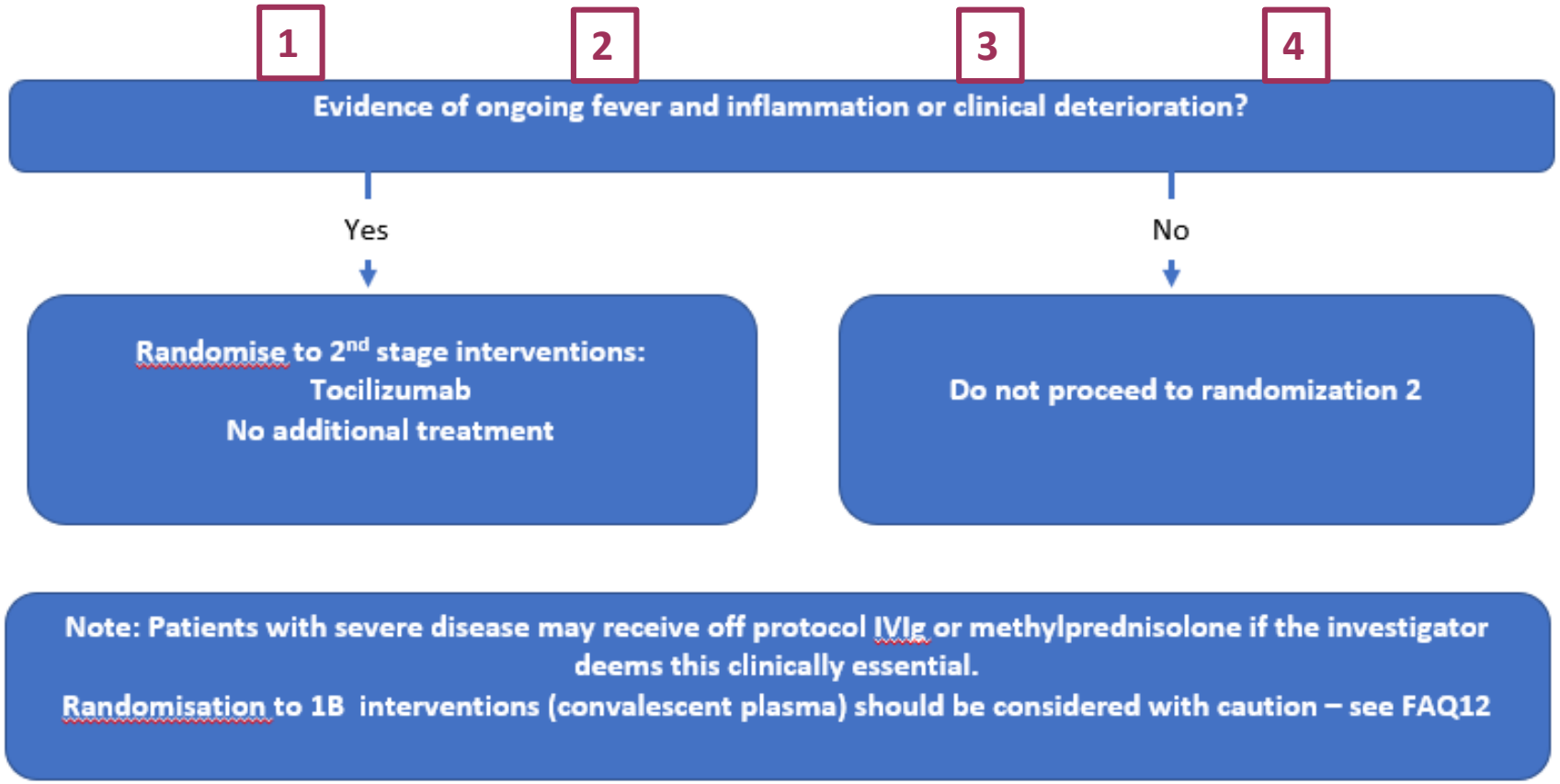

IVIg

- Use routine hospital stock (any brands with MA)
- Prior approval not required (as per Kawasaki disease)
- NHSE has been informed that Trusts usage may increase (Note: overall usage of IVIg is likely to be reduced due to randomisation)

Pharmacists:

- Complete MDASA database (PIMS-TS diagnosis has been added to the database)
- Reimbursement by NHSE (via normal route)

Convalescent plasma

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- Individual investigators may choose to randomise neonates, infants and children to convalescent plasma, where it is available in a specific research site and local investigators consider this appropriate for that child.
  - ***Acute respiratory presentation of COVID-19 – likely to be appropriate for randomisation where available***
  - ***PIMS-TS:*** Convalescent plasma may be used as potential entry to RECOVERY for those children who have received both IVIg and high dose methylprednisolone as treatment prior to consideration of entry to RECOVERY
- In the FAQ, the scenario table notes 'caution'. This is because of the potential, but as yet unproven, antibody-mediated contribution to the pathogenesis of PIMS-TS.
- No safety concerns have been noted in adult patients received CP to date, however enhanced safety monitoring is in place in adults and children.

<44 weeks corrected GA

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- Neonates and infants with a corrected gestational age of < 44 weeks
  - not yet established steroid as SOC
  - not known to develop inflammatory syndrome

- For neonates and infants with a corrected gestational age of < 44 weeks with respiratory COVID phenotype, options for RECOVERY randomisation include
  - Hydrocortisone
  - Azithromycin
  - SOC

Carry on recruiting!

RECOVERY
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- The current protocol can be used for PIMS-TS as per the current guidance document (will be updated later this week to v6.0 to incorporate changes discussed today).

- Potential amendment has been reviewed by MHRA, awaiting REC.

- Planning for second wave / local spikes or waves

- Thank you!