Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

5th May 2020

Agenda

RECOVERY
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1. Introductions
2. Update on progress
   - Main recruitment
   - Second randomisation
3. Follow-up
4. Future plans
5. 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

Trial design

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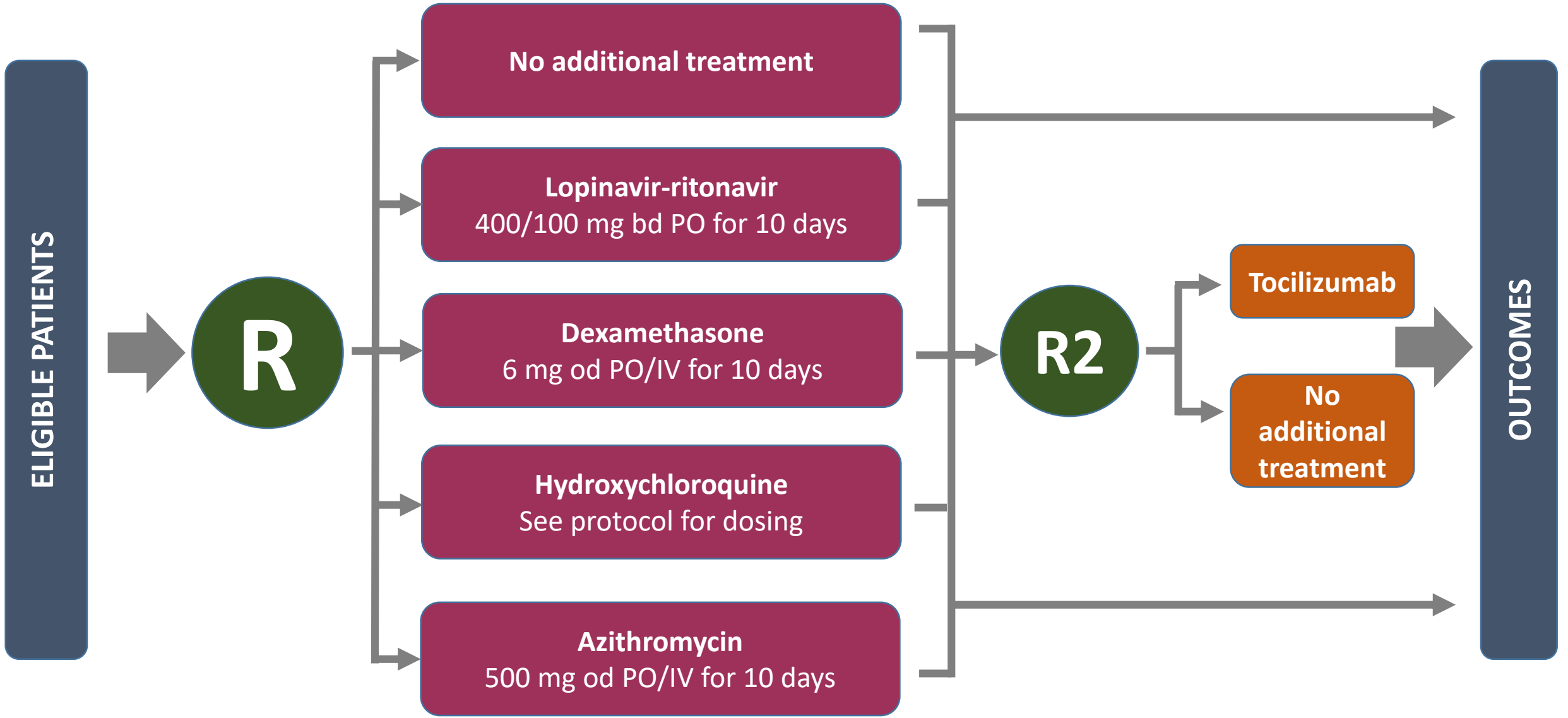

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PROGRESS UPDATE

Cases of COVID-19 across UK

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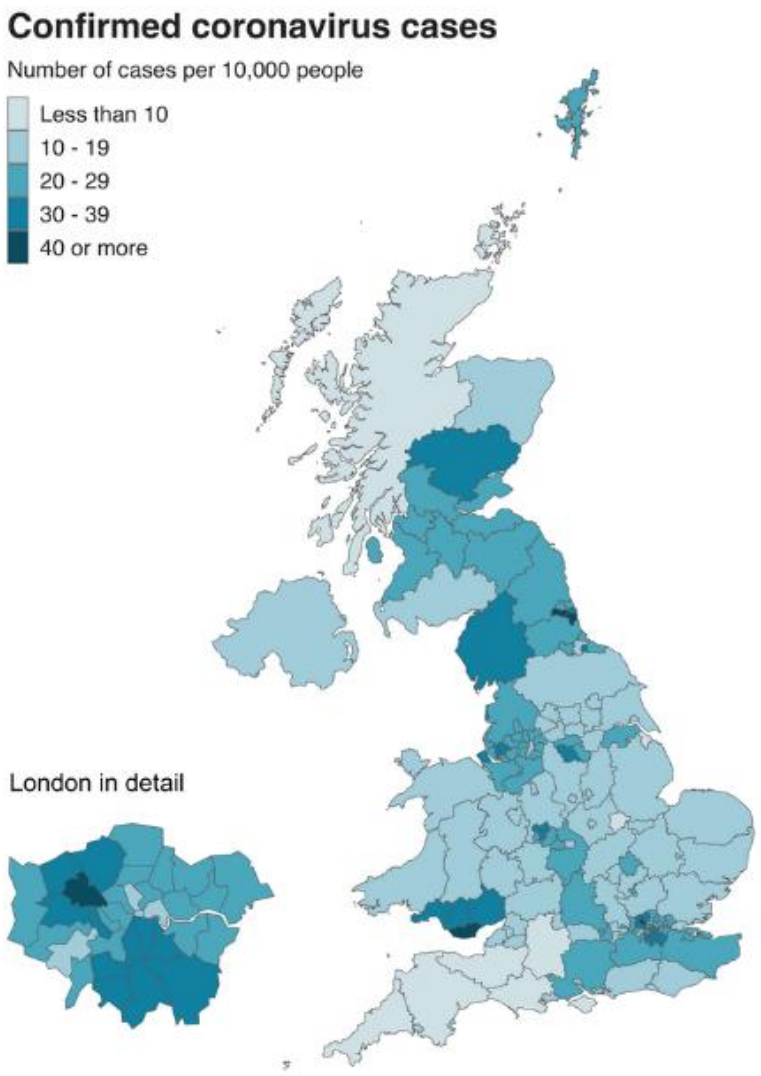
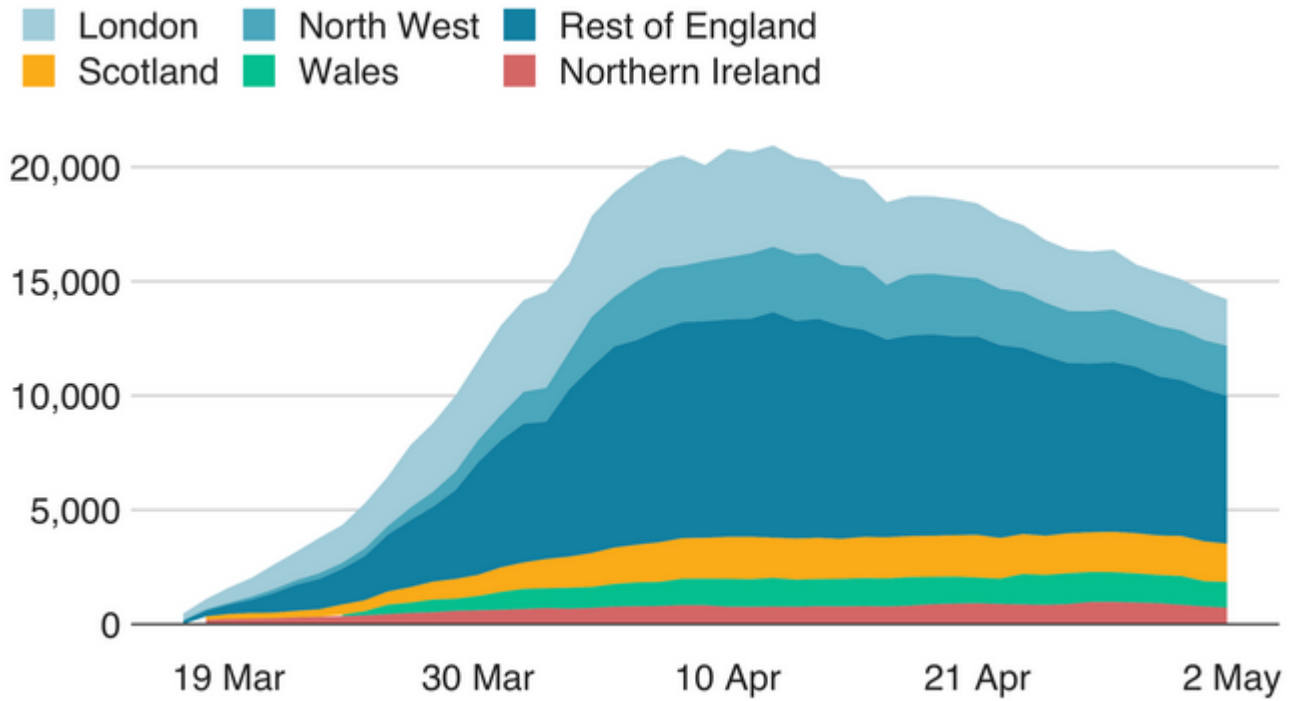
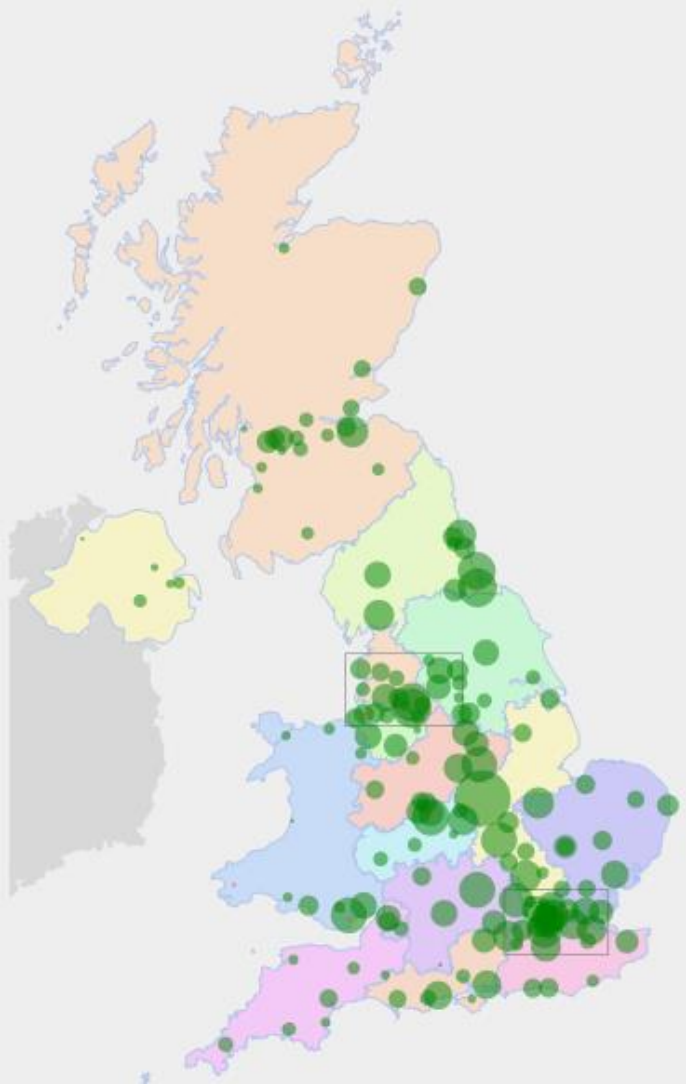




Recruitment by site



- One circle per site
- Size reflects recruitment which in turn depends on:
  - Admissions
  - Time since site activated
  - Availability of resources to recruit
  - Competing demands

Recruitment progress

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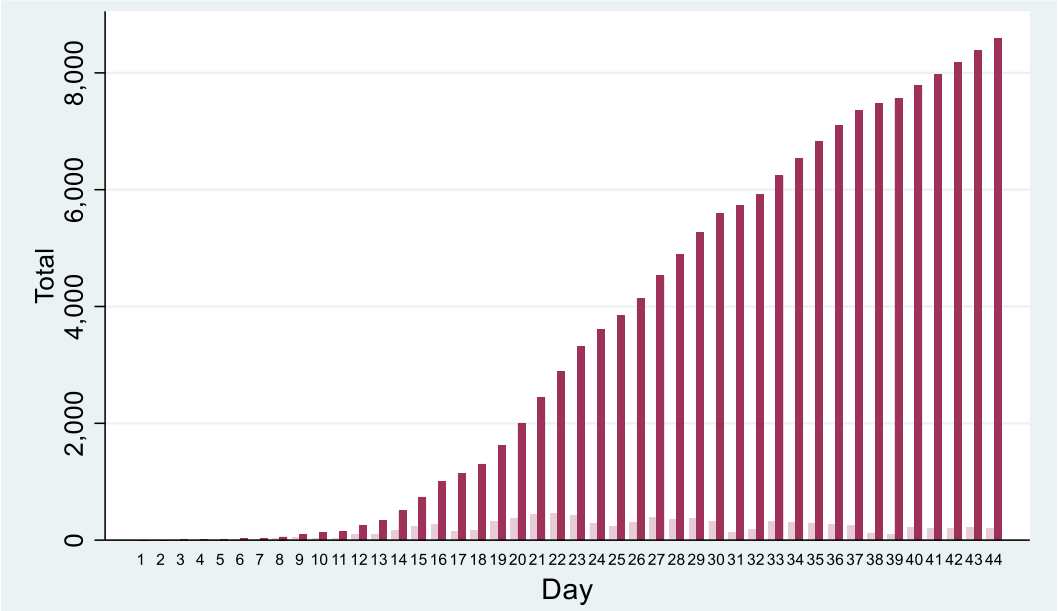
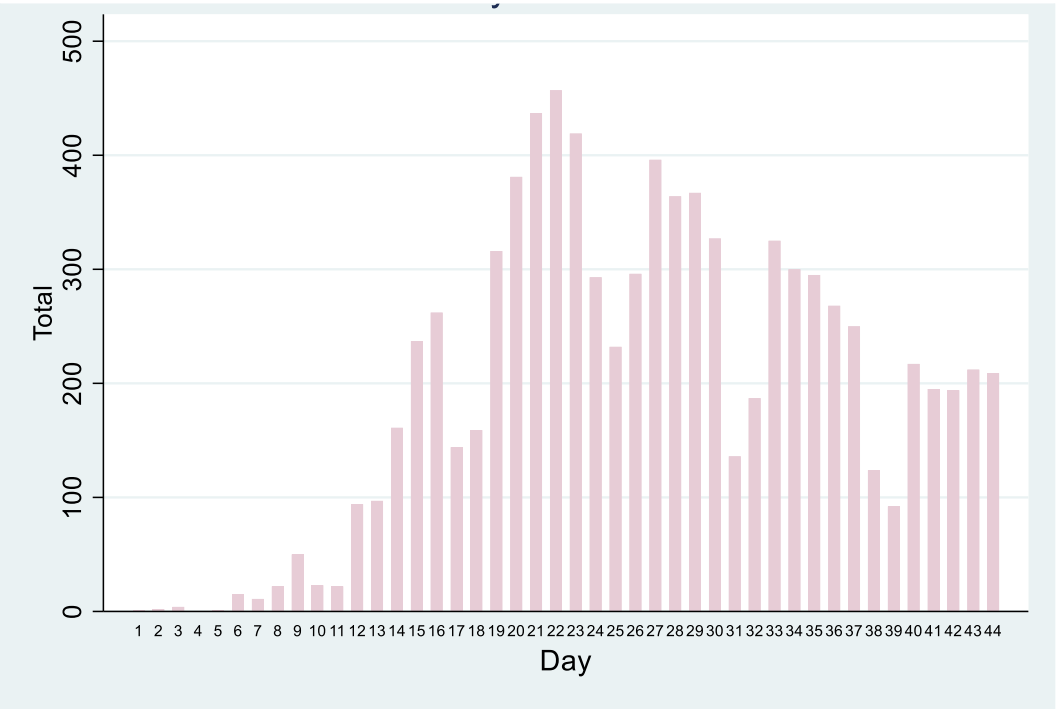
Total recruitment



Daily recruitment



Characteristics at main randomisation (n=7783)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		5010 (64%)
Age		65 (15)
Days since symptom onset		9 (6-14)
Days since hospitalisation		3 (1-5)
Severity of disease	No oxygen required	1635 (21%)
	Supplemental oxygen only	4811 (62%)
	Ventilation/ECMO	1339 (37%)
Prior disease	Diabetes	2079 (27%)
	Cardiovascular disease	1935 (25%)
	Chronic lung disease	1584 (20%)

Admissions with COVID-19 since activation, by trust (England only)

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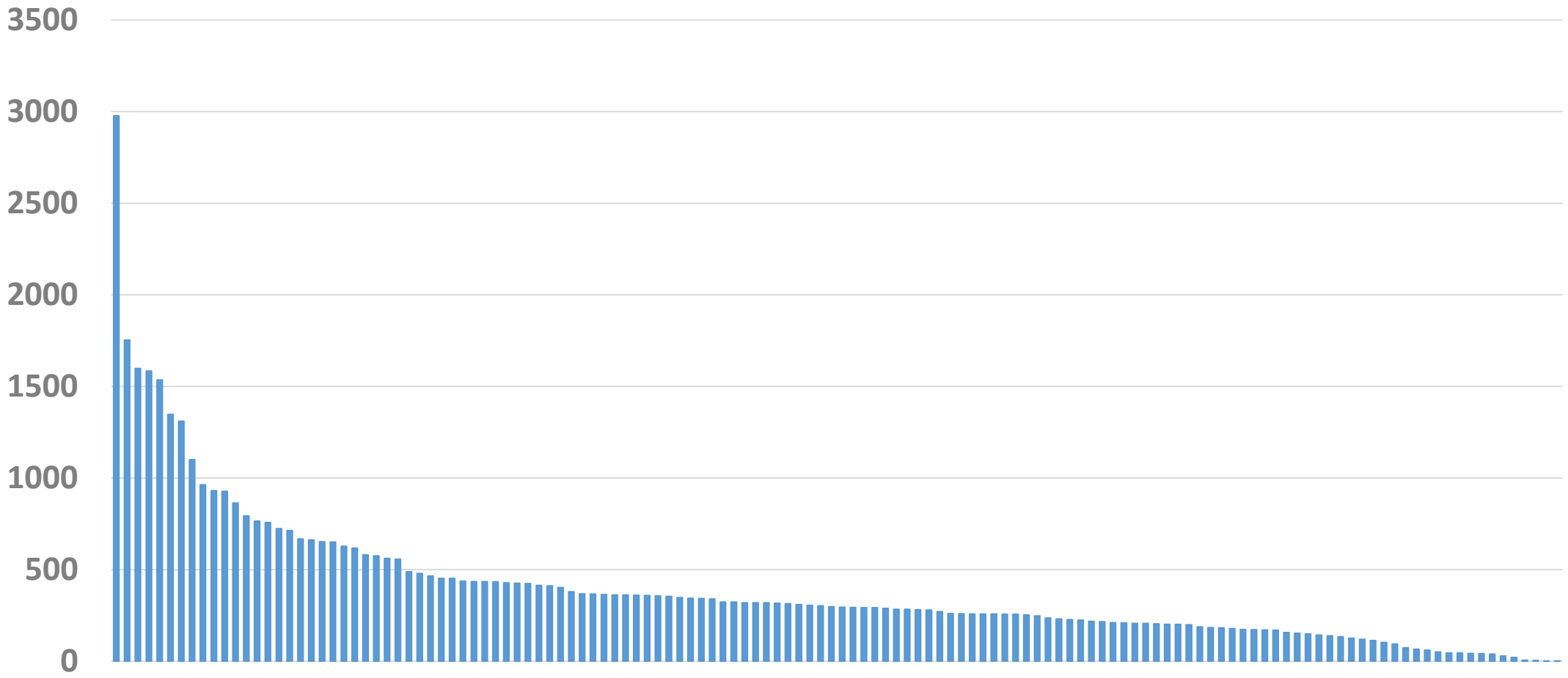

Recruitment into RECOVERY since activation

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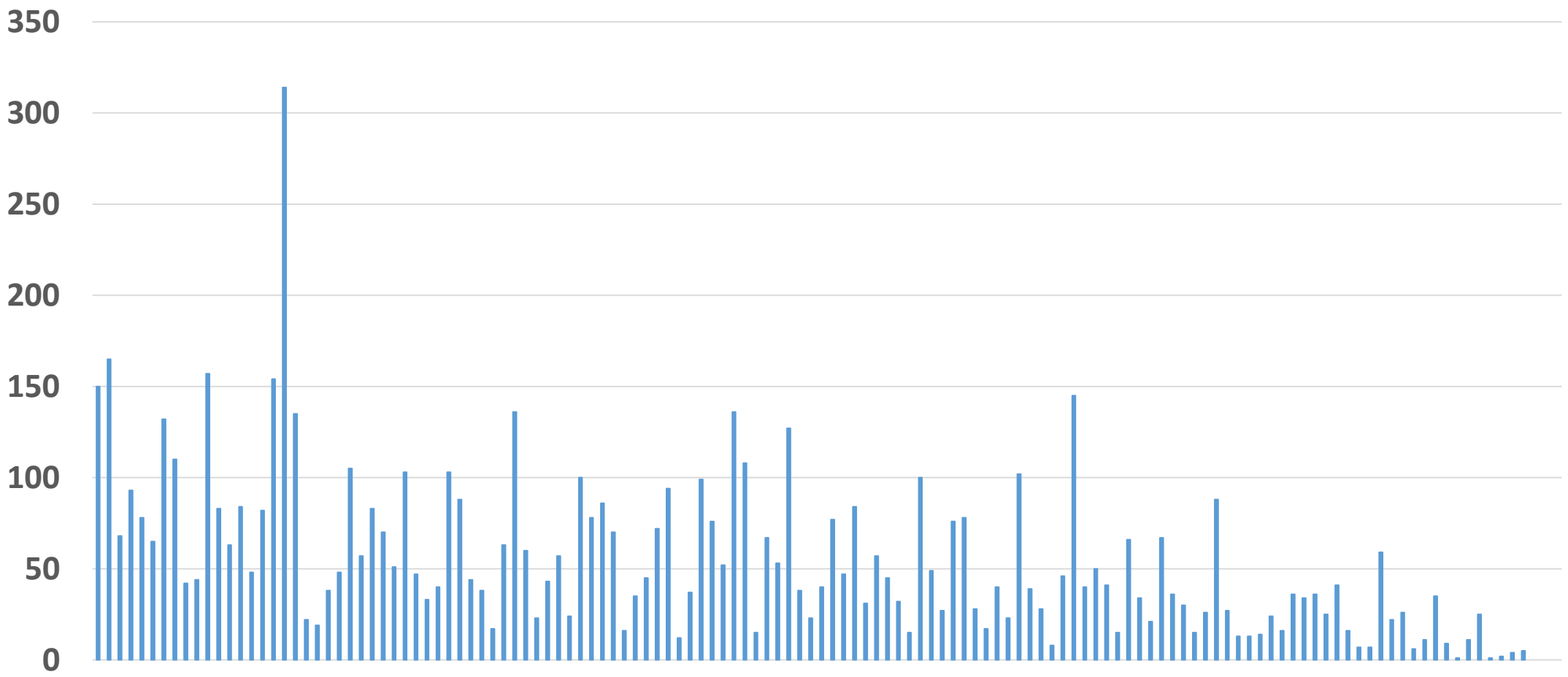

Recruitment and admissions since activation

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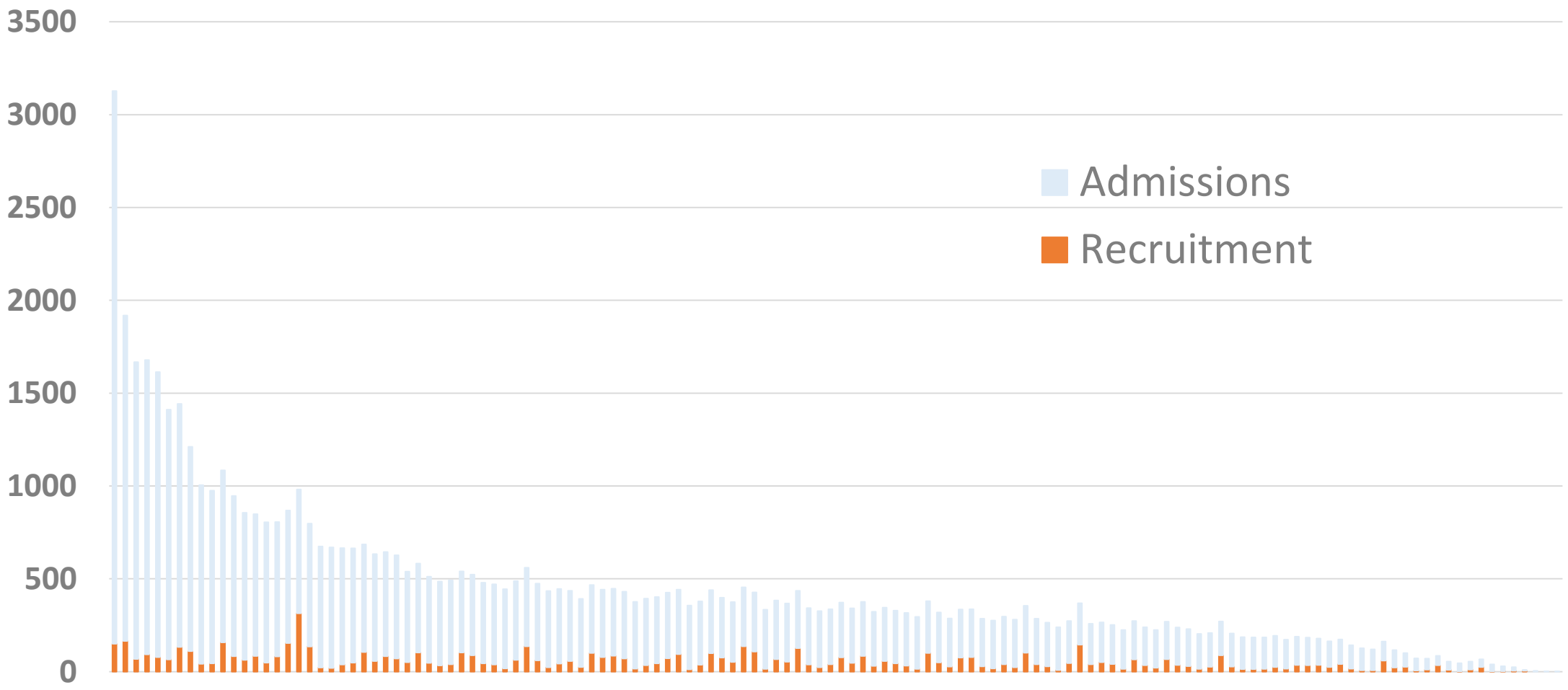

Recruitment proportion (ordered by total recruitment)

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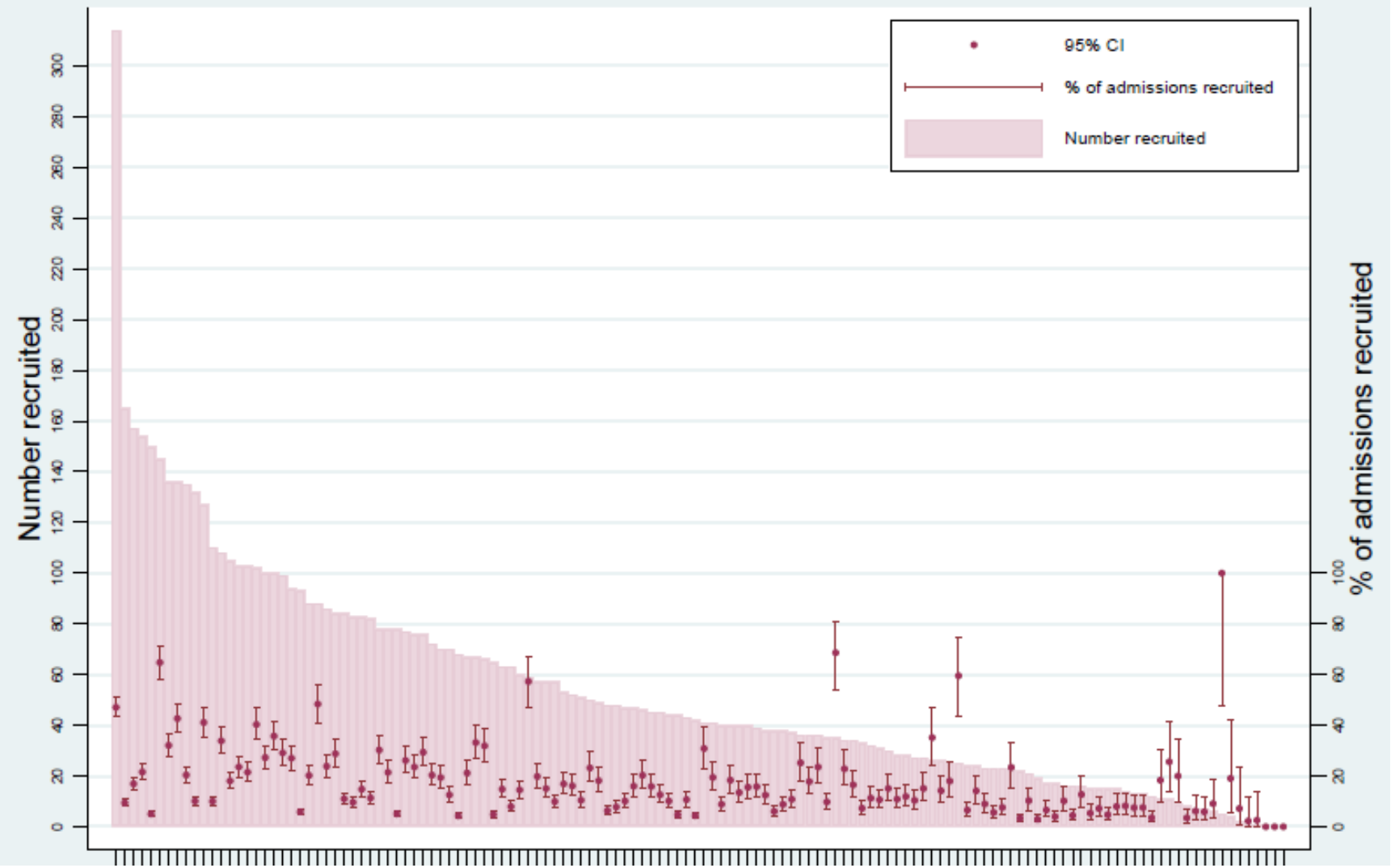

Recruitment proportion (ordered by proportion)

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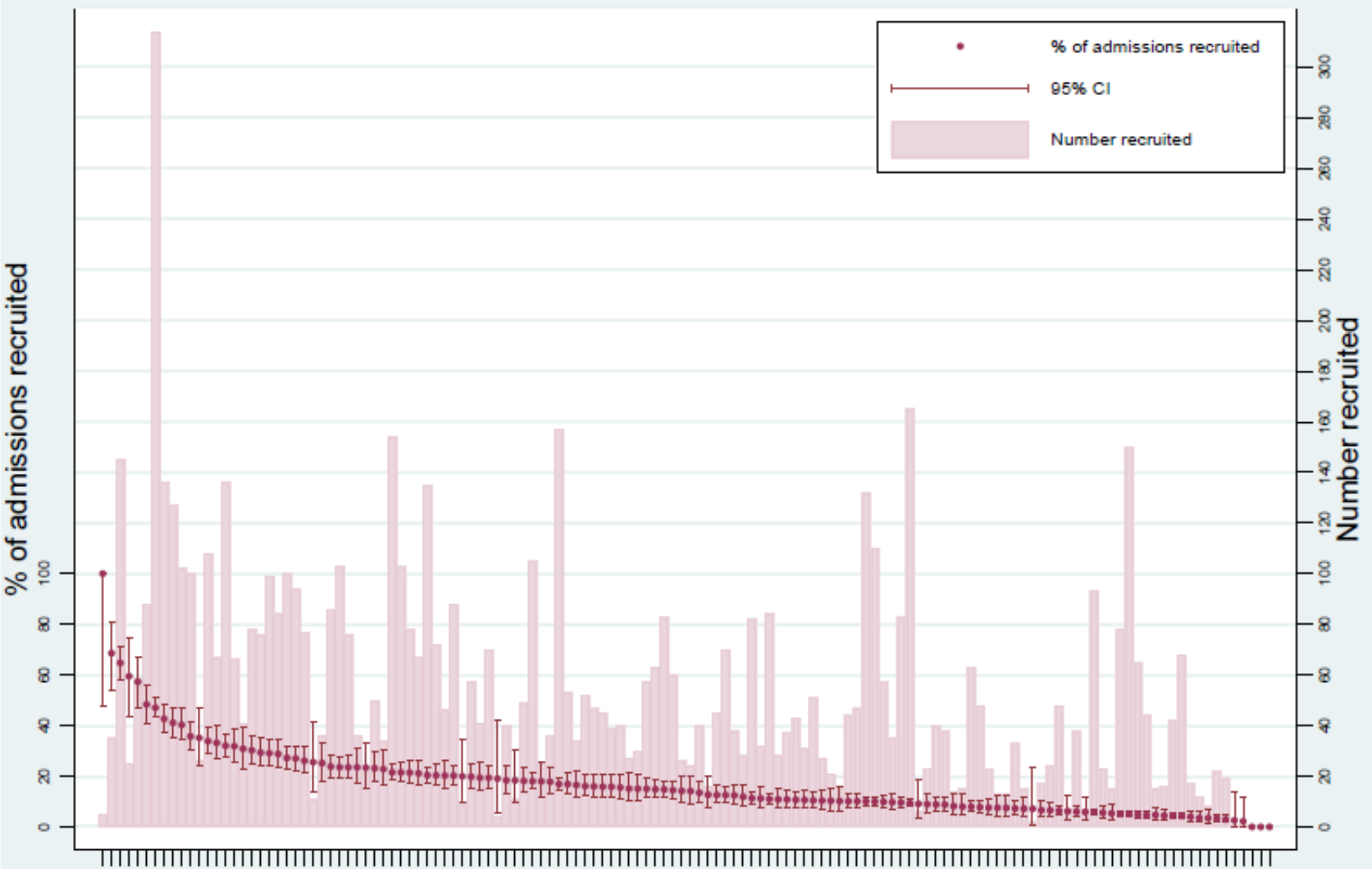

Recruitment proportion (ordered by proportion)

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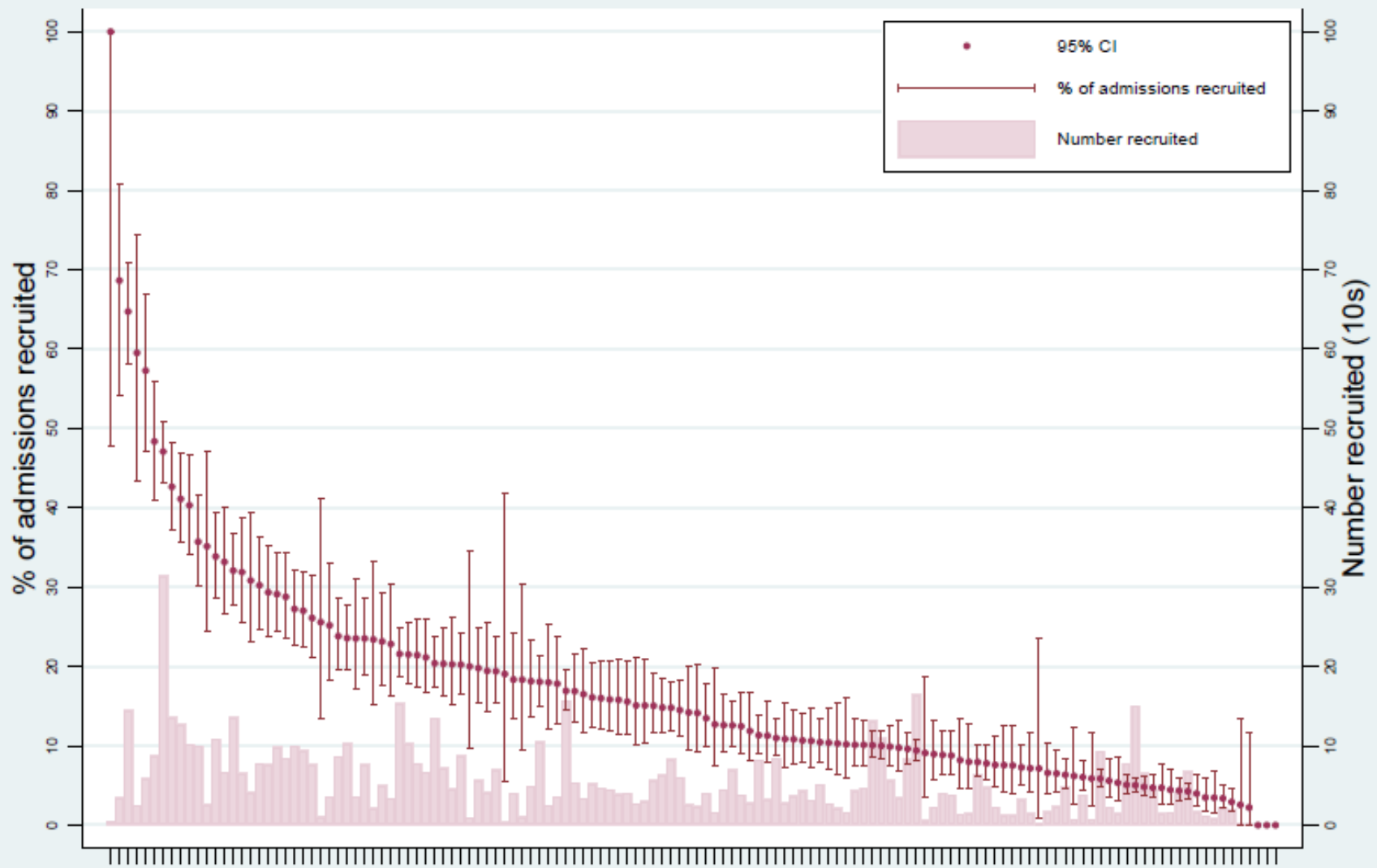

Aren't 9000 participants enough? No!

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- RECOVERY is the largest trial of COVID-19 therapies globally
  - But it's still not large enough!
- Designed to provide definitive evidence and change global practice
- Five arms in main randomisation means each treatment is in a trial of about 4500 people (1500 on treatment *vs* 3000 on control)
- Statistical 'power' of trial depends on:
  - Number randomised
  - Event rate (i.e. death rate in trial population)
  - Effect size: how much we reduce this event rate by
  - How confident we want to be in results (not missing an important benefit)

Aren't 9000 participants enough? No!

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- No treatment will be 'magic bullet' and we might hope for one-fifth reduction in death rate
  - 80 deaths instead of 100; or
  - 24,000 instead of 30,000 (current approximate number of deaths in UK)
- Trial needs **at least** 12,000 participants, just to answer the current questions
- And there are many other current and forthcoming treatments...

Second randomisation

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- So far 85 sites have been invited to participate, based on:
  - Recruitment
  - Recent recruitment rate
  - Geographical equity

- Further sites are likely to be included, but limited drug supply needs careful management

Second randomisation

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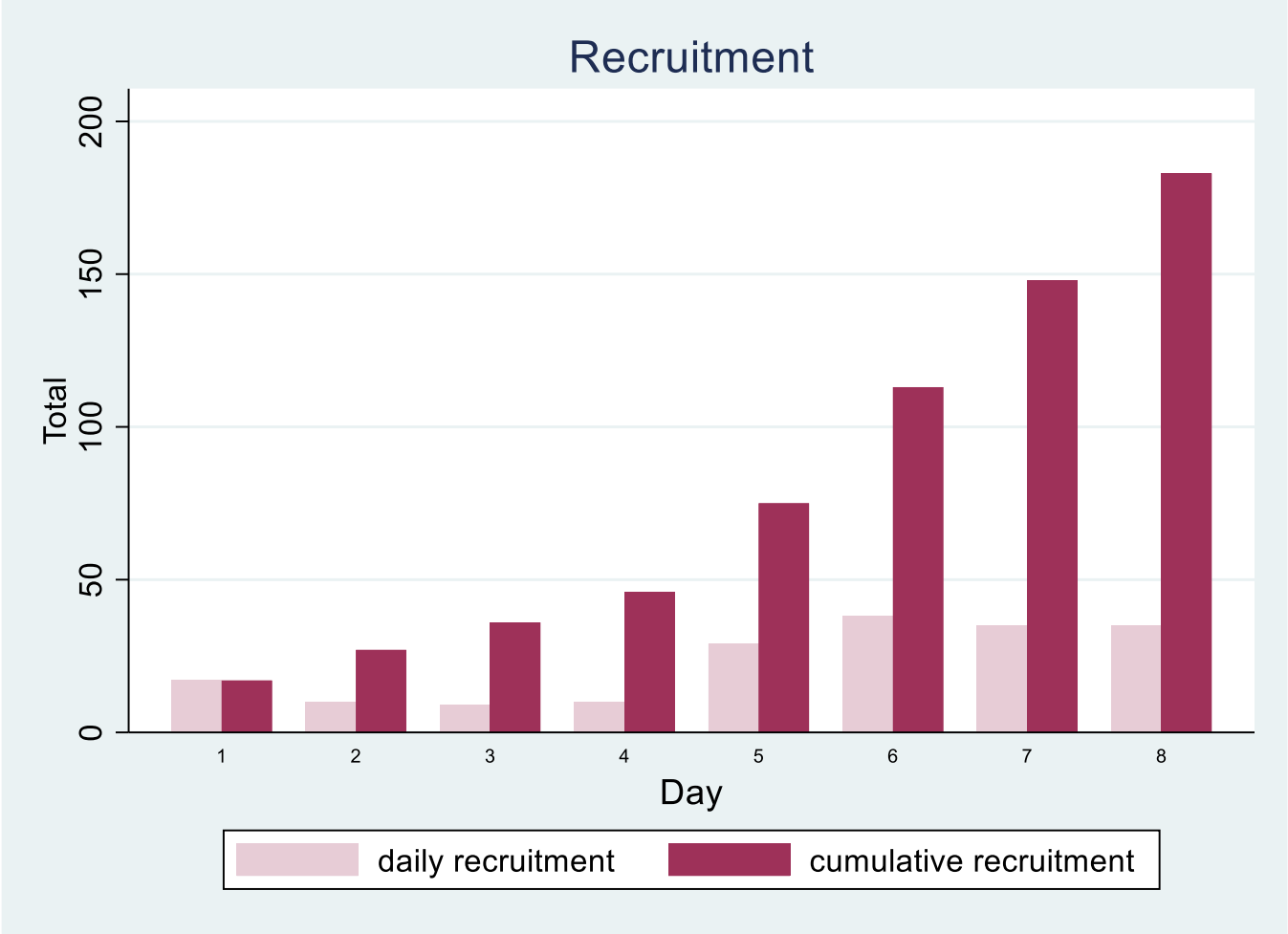

Characteristics at second randomisation (n=148)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		94 (64%)
Age		61 (14)
Days since symptom onset		14 (9-20)
Days since hospitalisation		6 (3-12)
Ventilation support	None	42 (28%)
	CPAP/NIV/HFNO	37 (25%)
	Ventilation/ECMO	69 (47%)
Biochemistry	CRP (mg/L)	180 (125-270)
	Ferritin (ng/mL)	1234 (497-2808)
	Creatinine (µmol/L)	77 (55-128)

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FOLLOW-UP

Completeness

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- Follow-up underway at all sites now
- 3194 Follow-up forms completed
  - 329 overdue (participant randomised >28 days ago)
- Follow-up supplemented by linkage with NHS Digital
- Coordinating team will be sending reminders

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FUTURE PLANS

Inclusion of children

- Working group led by Saul Faust (Southampton) have helped develop materials so children of all ages can be included into trial

- REC approval received; MHRA approval pending (as of 2 May)

- CRN has been helping to identify paediatric leads at sites
  - Please contact your CRN if you don't know who paediatric lead will be
  - They will assist with overseeing care of paediatric participants

Convalescent plasma

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- Plans developing to include this in RECOVERY
- Implementation requires NHSBT to have collected sufficient volume of plasma

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FREQUENTLY-ASKED QUESTIONS

Transfer of care

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- Significant minority of patients are moved between hospitals (including Nightingales) during care for COVID-19

- If acute care is ongoing then team will ensure receiving site is approved RECOVERY site so patients can remain on treatment under oversight of new PI
  - Communication is key
  - Follow-up remains responsibility of randomising hospital so links required

- If acute care over (e.g. transfer for rehabilitation) then transfer should be considered discharge

Summary

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- **THANK YOU** for all your help with RECOVERY to date
- Although RECOVERY is the largest trial, it is not yet large enough to provide robust answers so please keep recruiting!
- If you are involved in care of pregnant women (Monday) or children (Tuesday) please stay “on the line” for specific update

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RECOVERY FOR CHILDREN

Background

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- The majority of children who develop COVID-19 present with mild symptoms or are asymptomatic
- For the few children that develop severe or life-threatening disease, a robust evidence base is essential to guide the use of effective treatments and to avoid potential harm
- There are currently no proven treatments for COVID-19 for either adults or children
- 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
- RCPCH treatment criteria should be used to guide the decision about treatment and therefore enrolment into RECOVERY. (RCPCH guidelines are constantly being updated please make sure you are aware of the latest version).
- It is anticipated that any child with COVID-19 being considered for treatment (over and above supportive care), should be enrolled in RECOVERY
- Overall, and considering the new KD/toxic shock syndrome consideration, if the treating clinician feels none of the first line randomisation drugs are should be offered to the patient then randomisation should not occur. If antiviral treatment is indicated then the first (and second) randomisation could be considered.

Patient information leaflets and Consent

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- Children <10 years of age should be provided with the 'younger' children information leaflet and this should be read along with their parent (s). The parent / guardian should sign the consent form.
- Children aged 10-15 years of age should be provided with the relevant information sheet and the child given the opportunity to sign the information sheet to indicate their assent if they are well enough and signature is possible. The parent / guardian should sign the consent form (or witnessed consent used).
- Young people aged >16 years should be provided with the 'adult' information sheet and they should sign the consent form (or witnessed consent used).
- 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.

Paediatric specific dosing of trial medication

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- All five of the first stage interventions are open to children, including specific corticosteroid options for children.
- Drugs/ages not open to young neonates and infants:
  - Lopinavir-Ritonavir (<42 weeks or neonates with postnatal age of < 14 days)
  - hydroxychloroquine (postnatal age of < 180 days)
- Children over 1 year old may be randomised to the 2nd stage intervention at any time after the first randomisation
- **A specific paediatric guidance document gives specific guidance for drug dosing and administration in neonates and children**
- This document also answers frequently asked questions

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RECOVERY FOR NEONATES

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 the majority of babies who develop COVID-19 present with mild symptoms or are asymptomatic.
- Symptomatic babies can present days to weeks after birth.
- In the neonatal period, 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 …..

- 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 either adults or children.
- 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 (RCPCH guidelines are constantly being updated please make sure you are aware of the latest version).
- 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 starting babies less than or equal to 28 days old on the study treatments may include:
    - 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.

Patient information leaflets and Consent

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Randomised Evaluation of COVID-19 Therapy

- Parents of babies, 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.

Paediatric specific dosing of trial medication

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- All five of the first stage interventions are open to children, however there are specific corticosteroid options for children.
- Drugs/ages 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 or infants less than 1 year of age.
- **A specific paediatric guidance document outlines drug dosing and administration in babies and children**
- This document also addresses frequently asked questions