Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

4th May 2020

Agenda

RECOVERY
Randomised Evaluation of COVID-19 Therapy

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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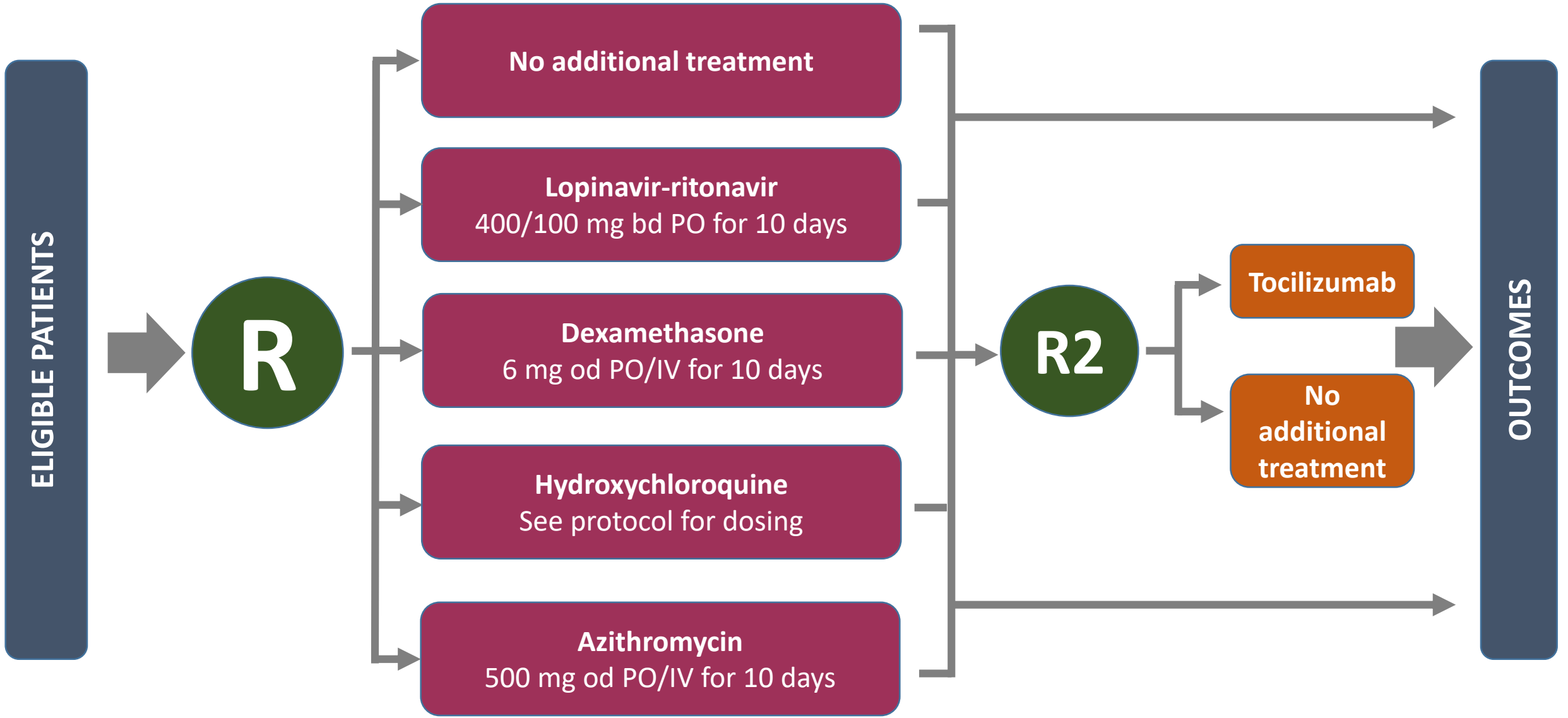
Randomised Evaluation of COVID-19 Therapy



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PROGRESS UPDATE

Cases of COVID-19 across UK

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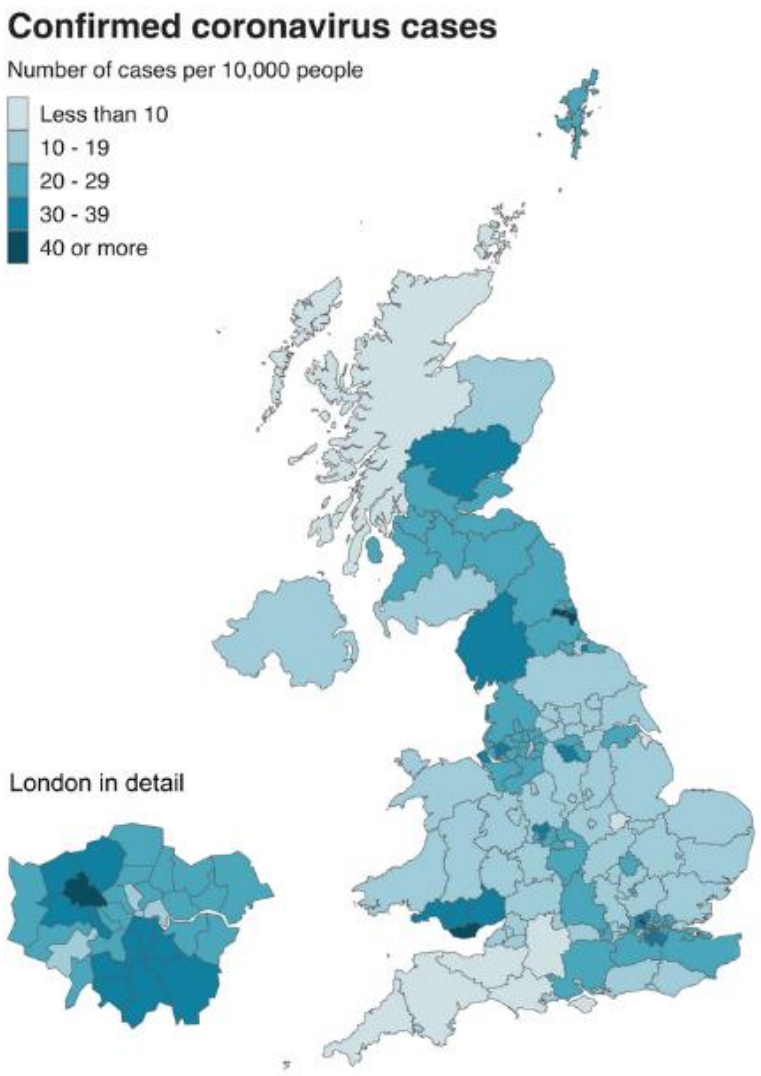
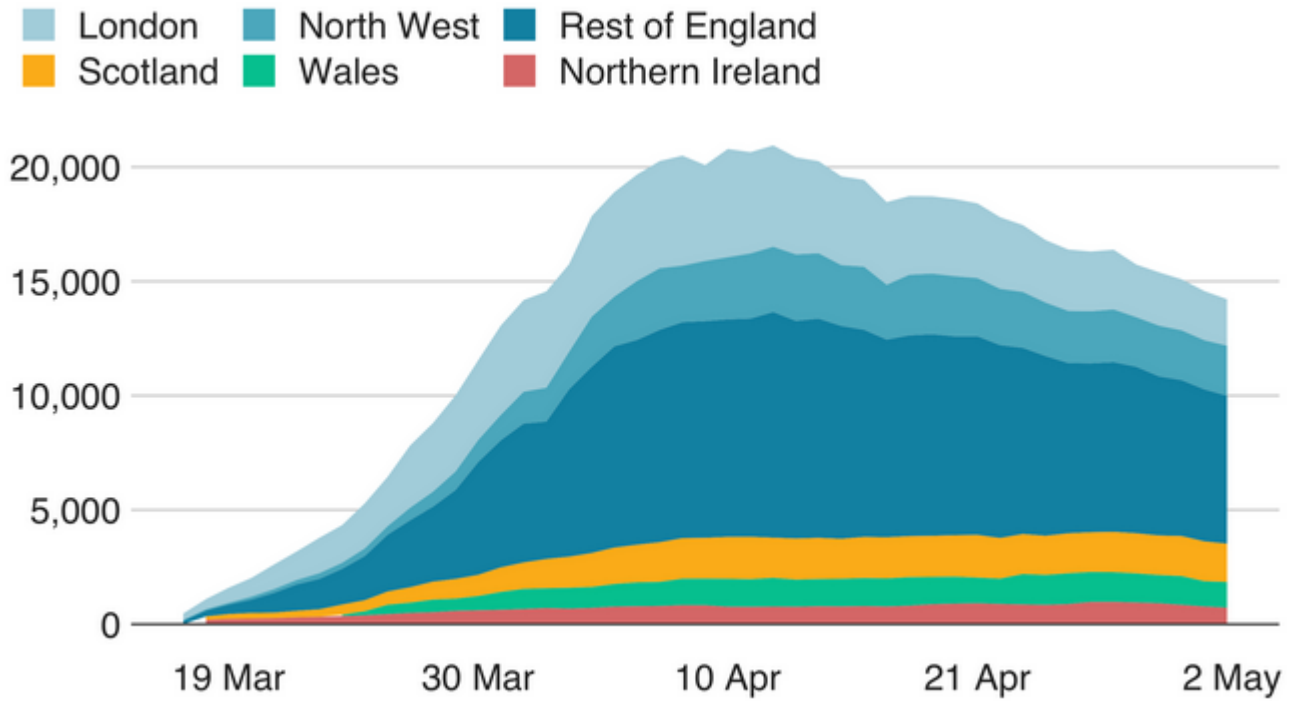
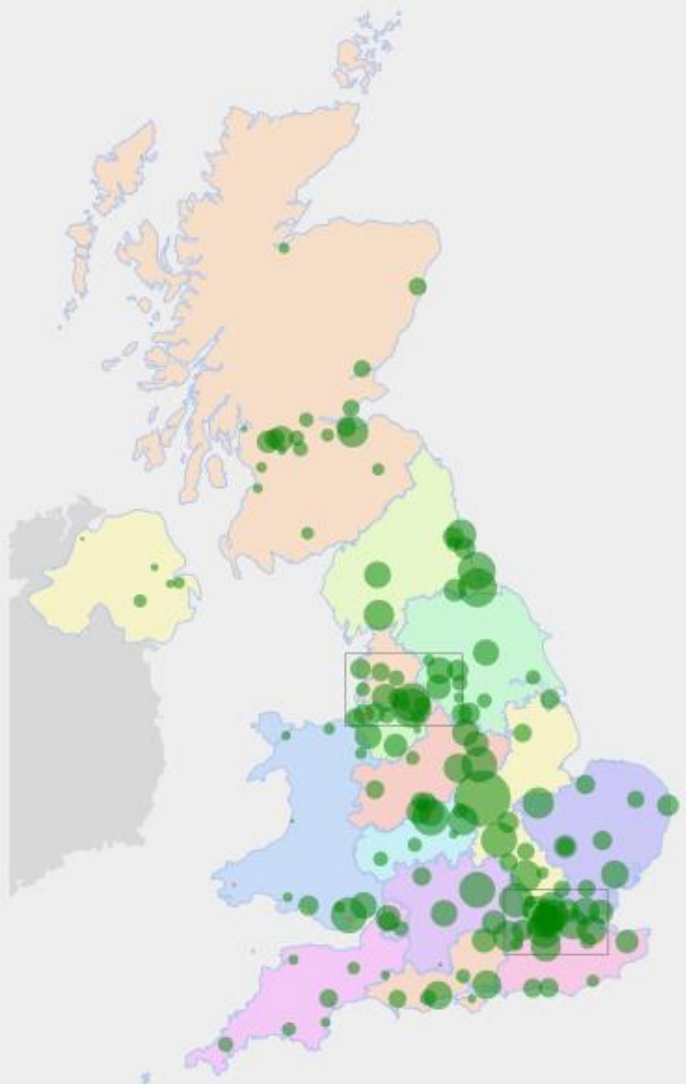




Recruitment by site



- 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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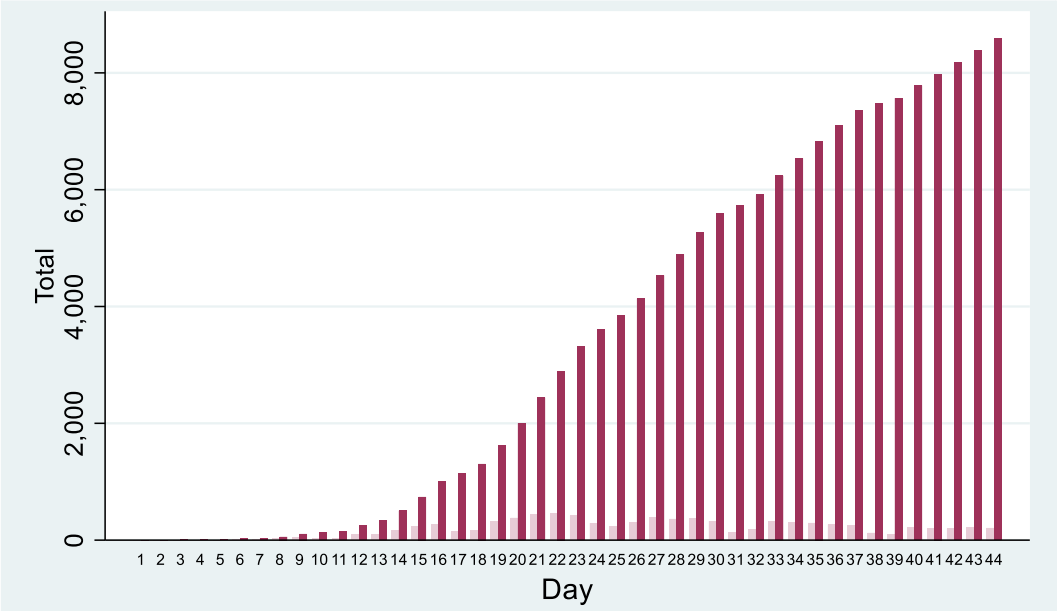
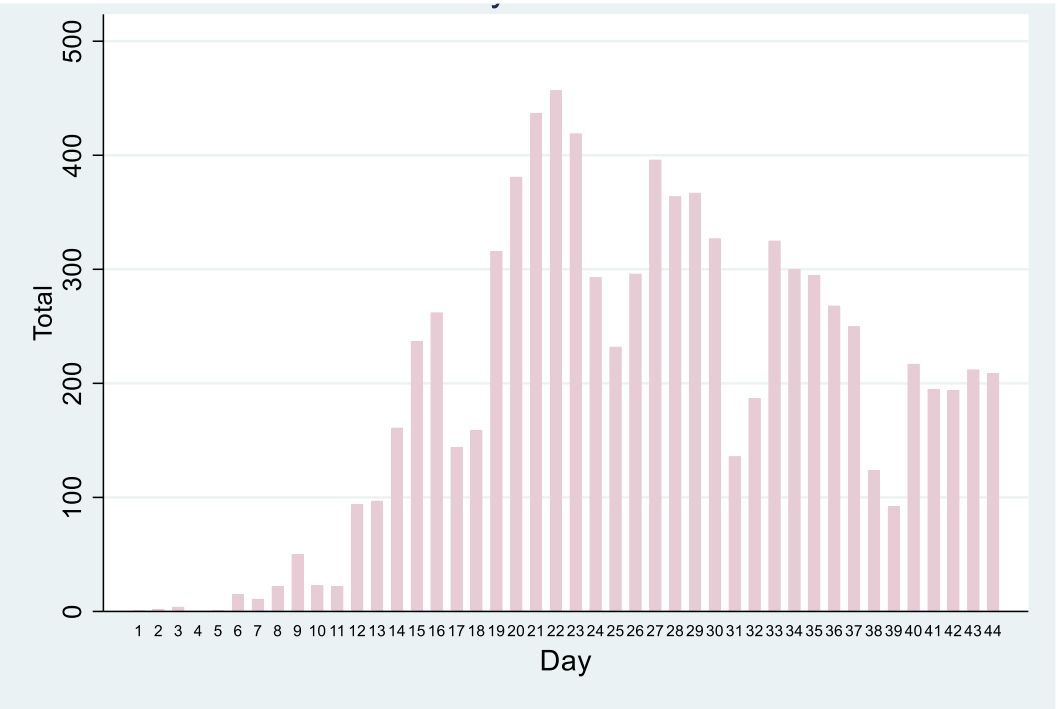
Total recruitment



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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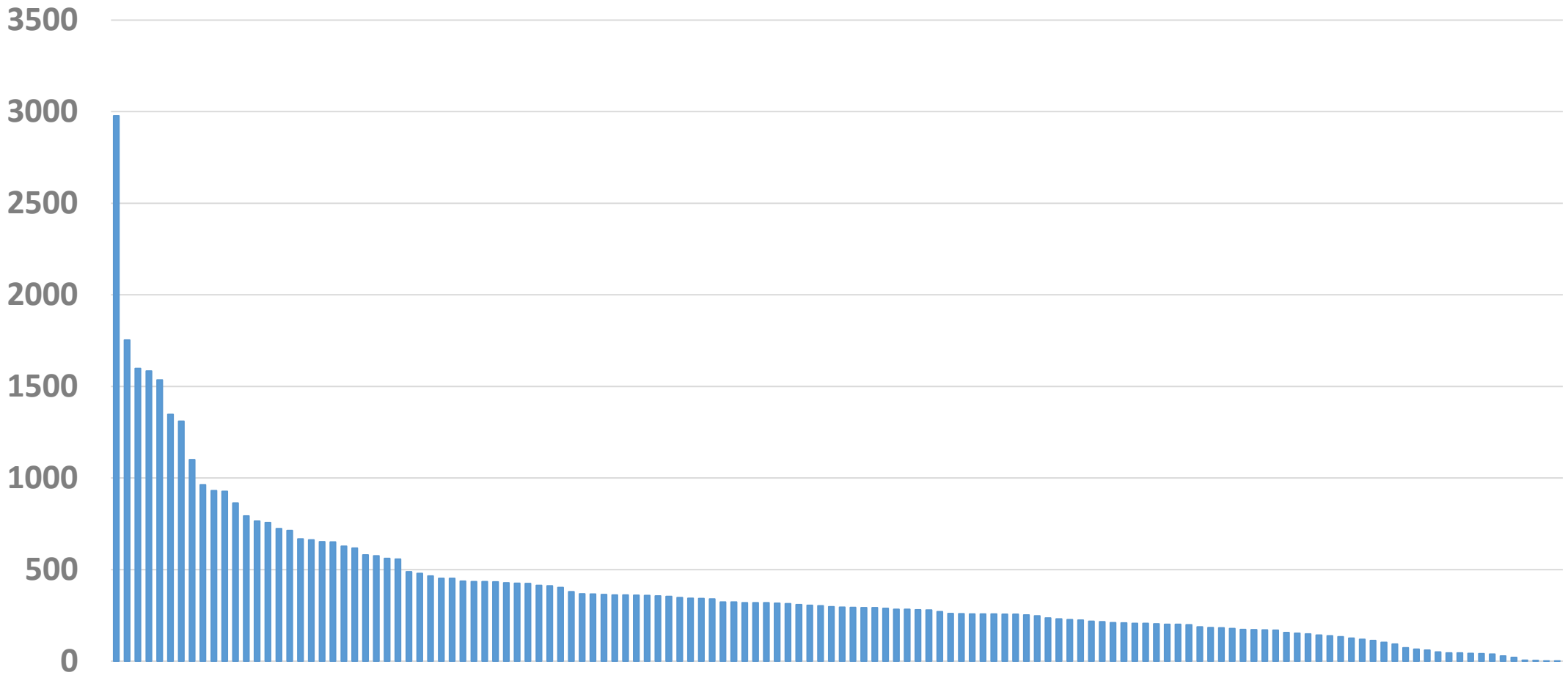

Recruitment into RECOVERY since activation

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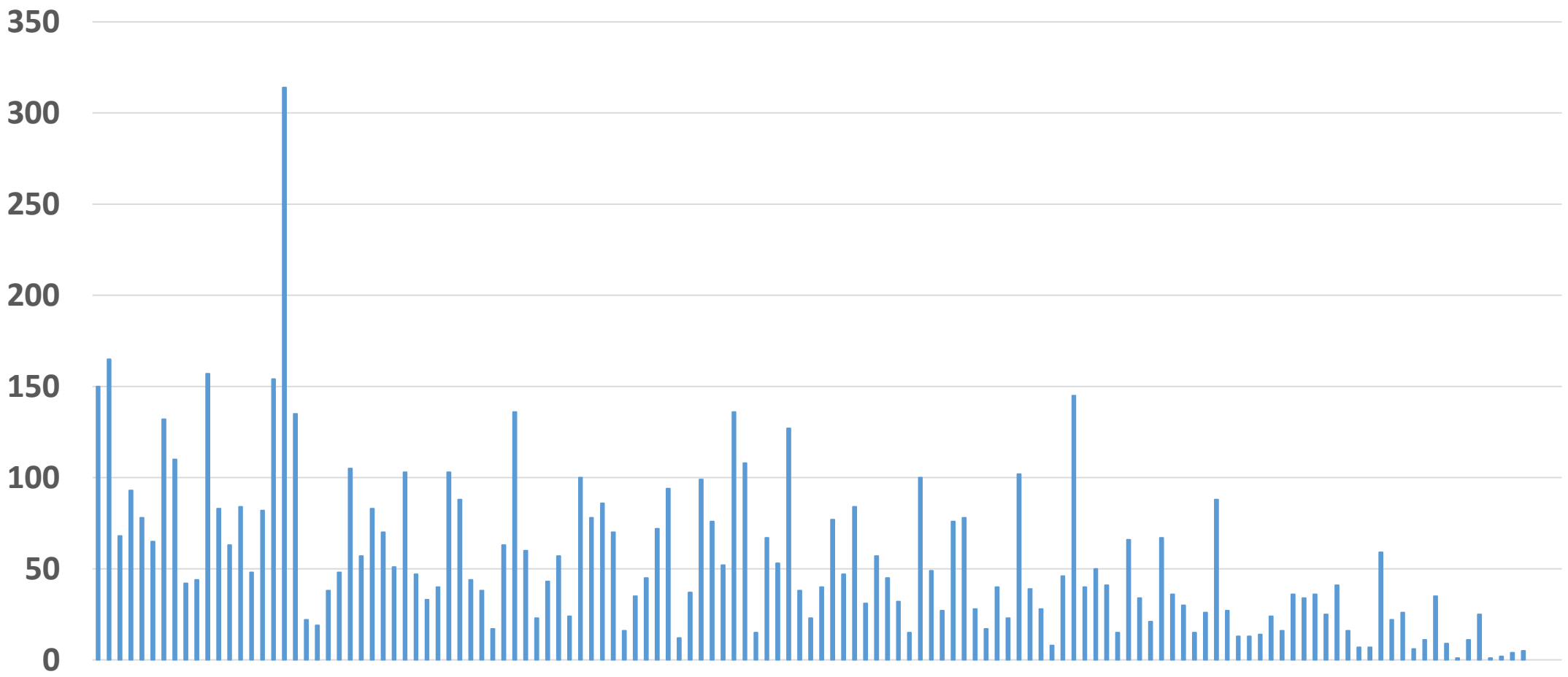

Recruitment and admissions since activation

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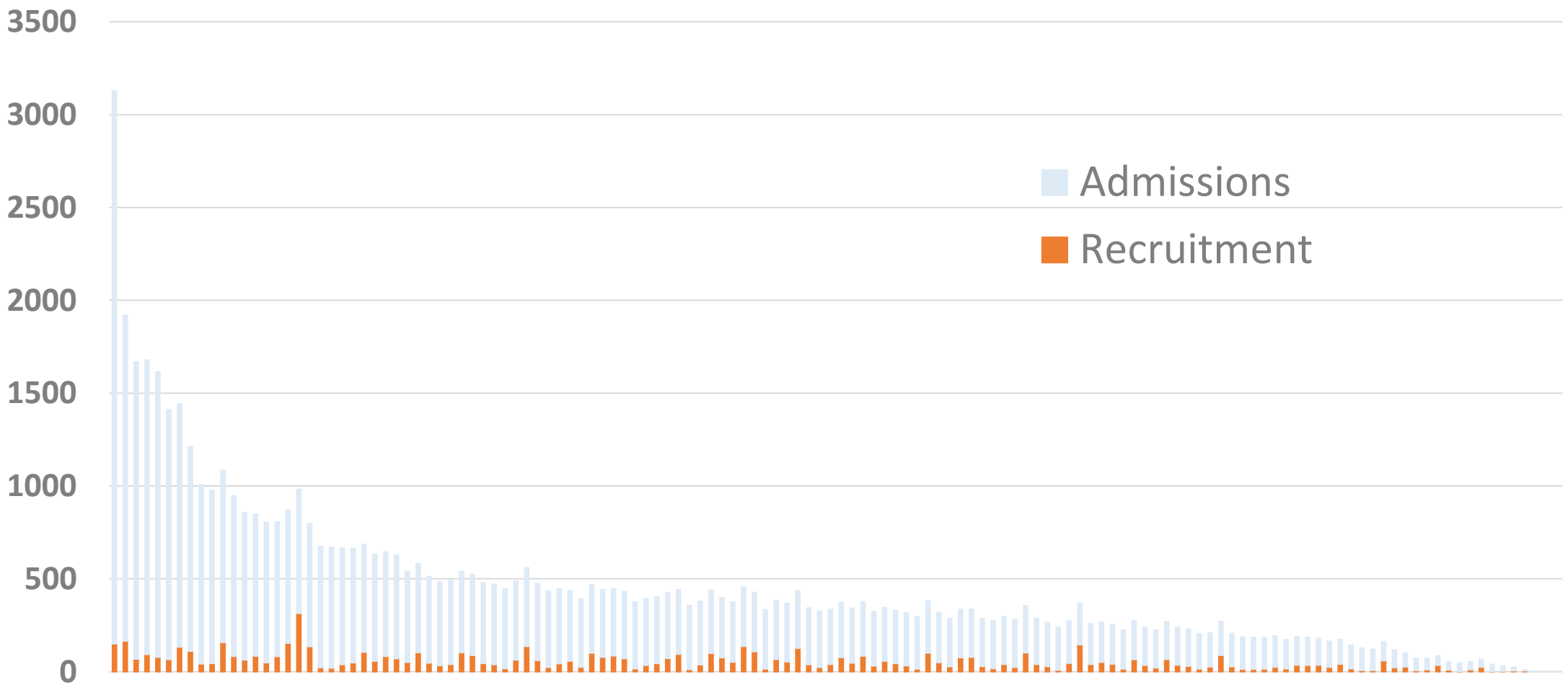

Recruitment proportion (ordered by total recruitment)

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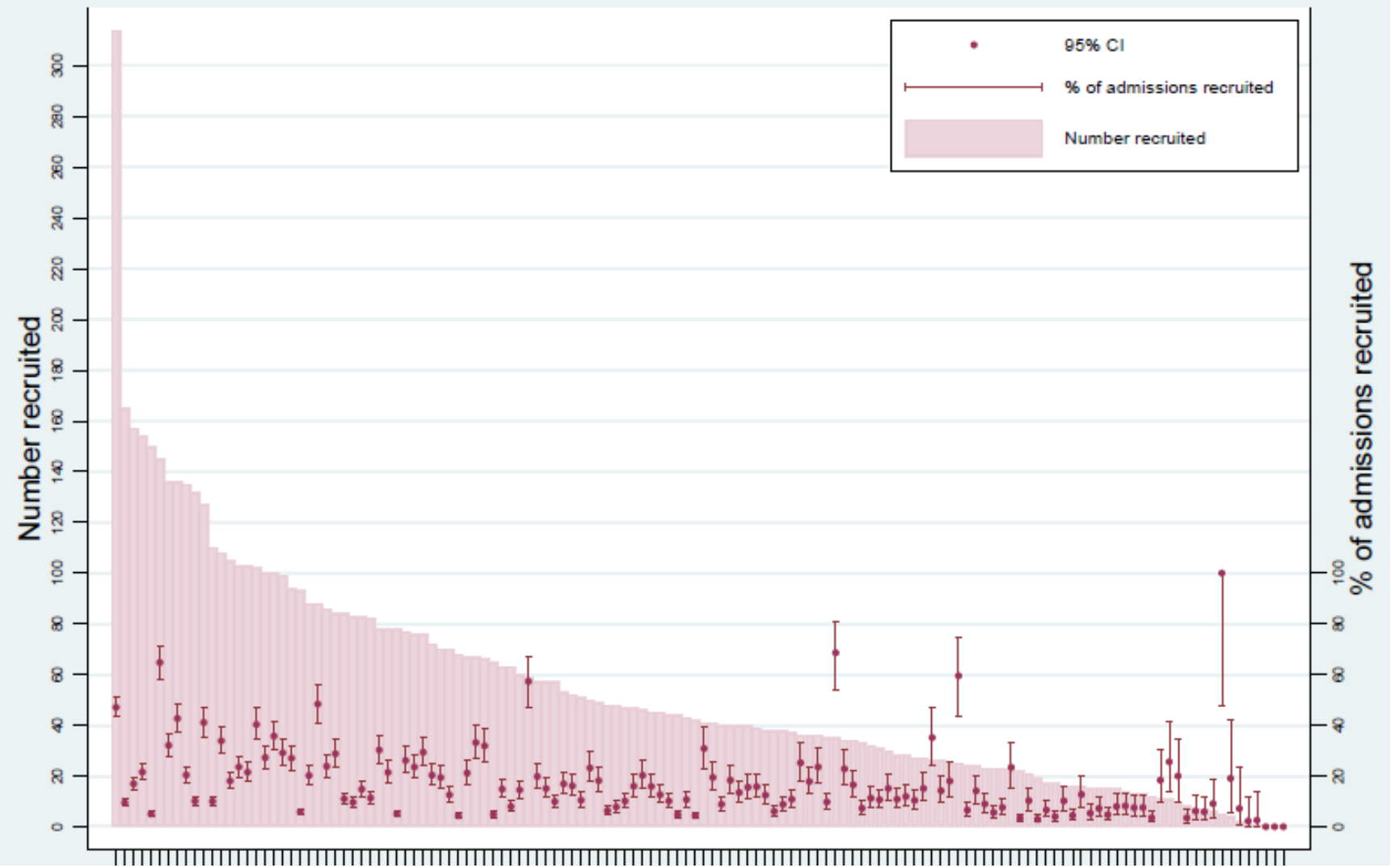

Recruitment proportion (ordered by proportion)

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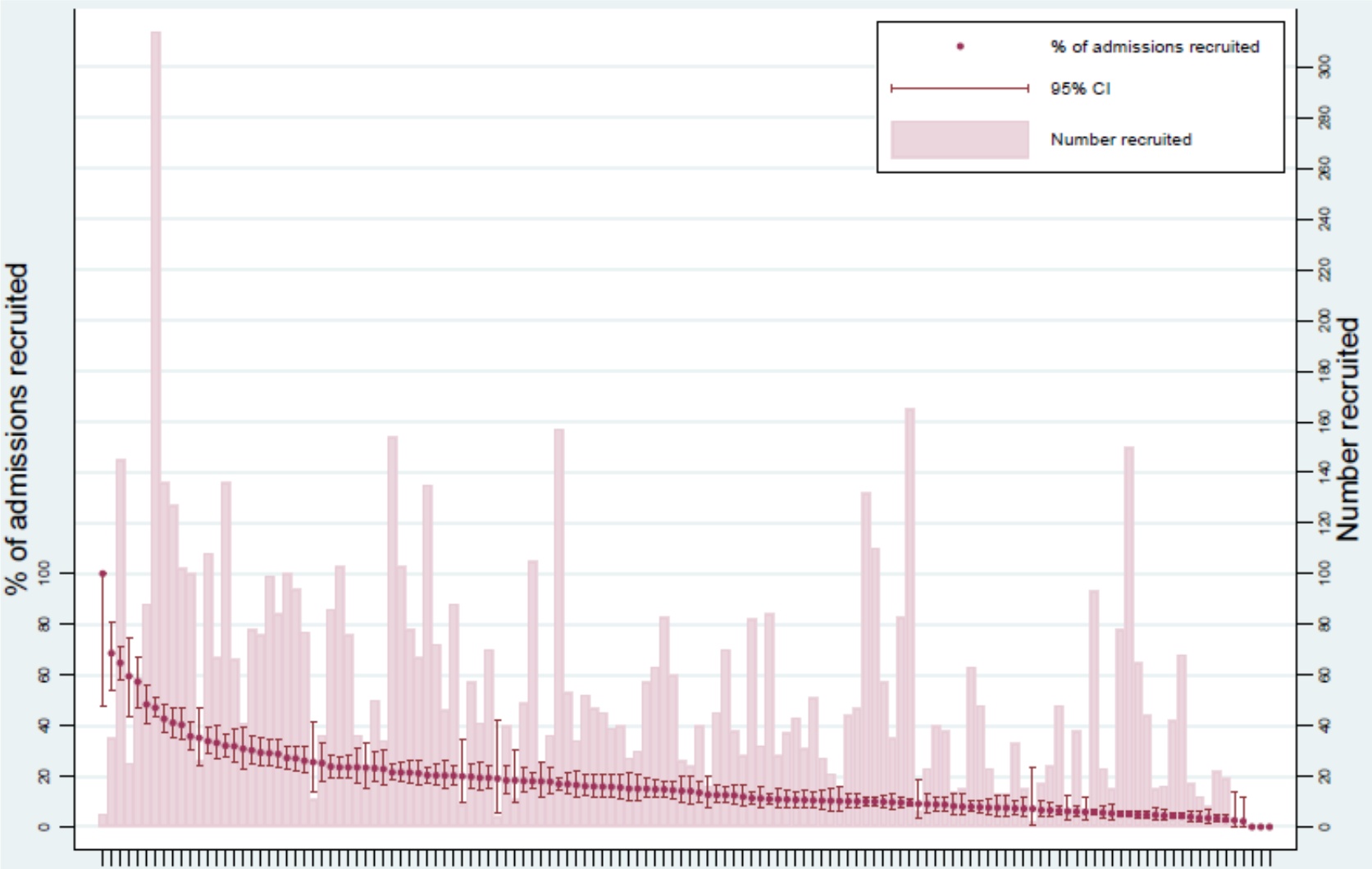

Recruitment proportion (ordered by proportion)

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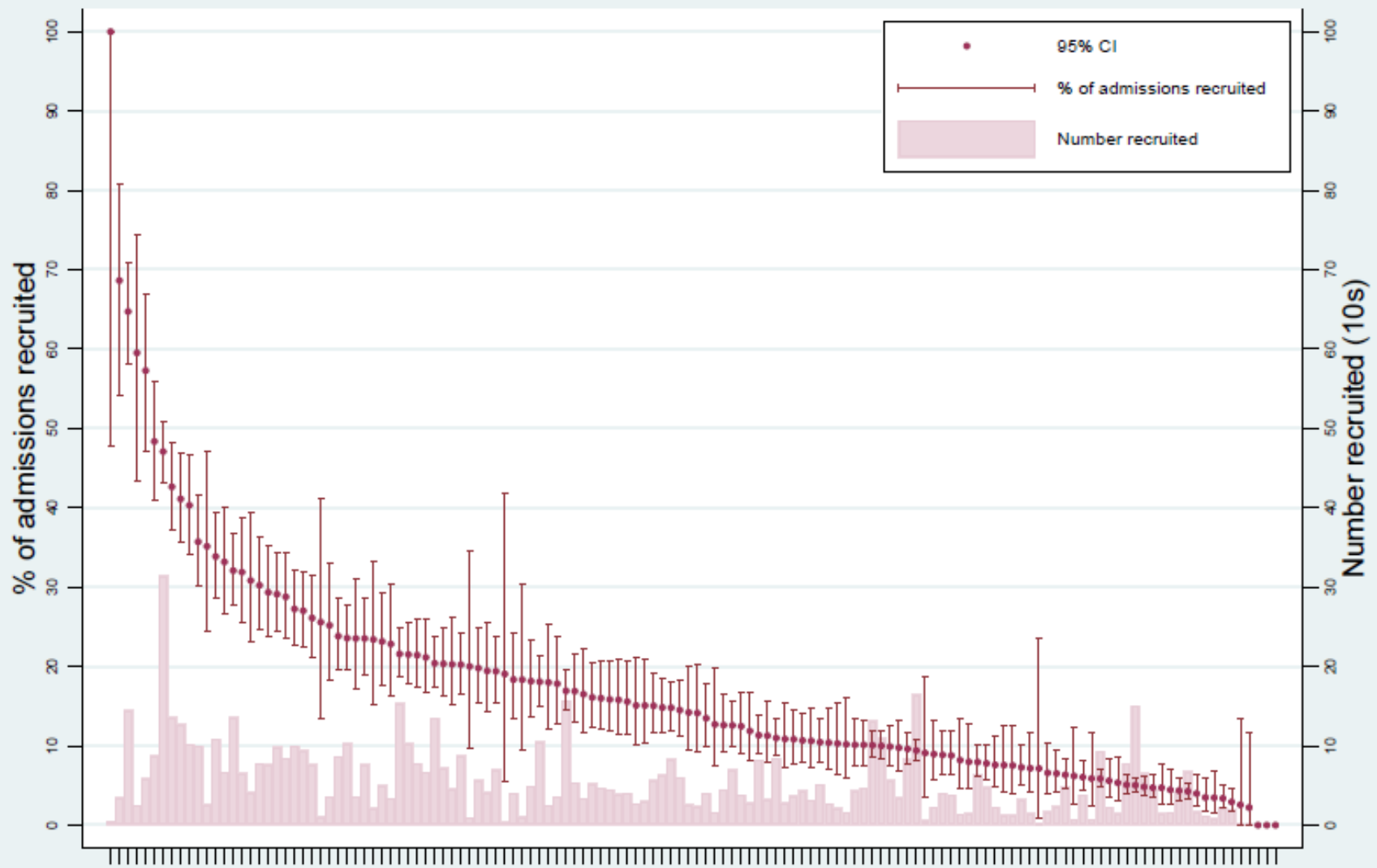

Aren't 9000 participants enough? No!

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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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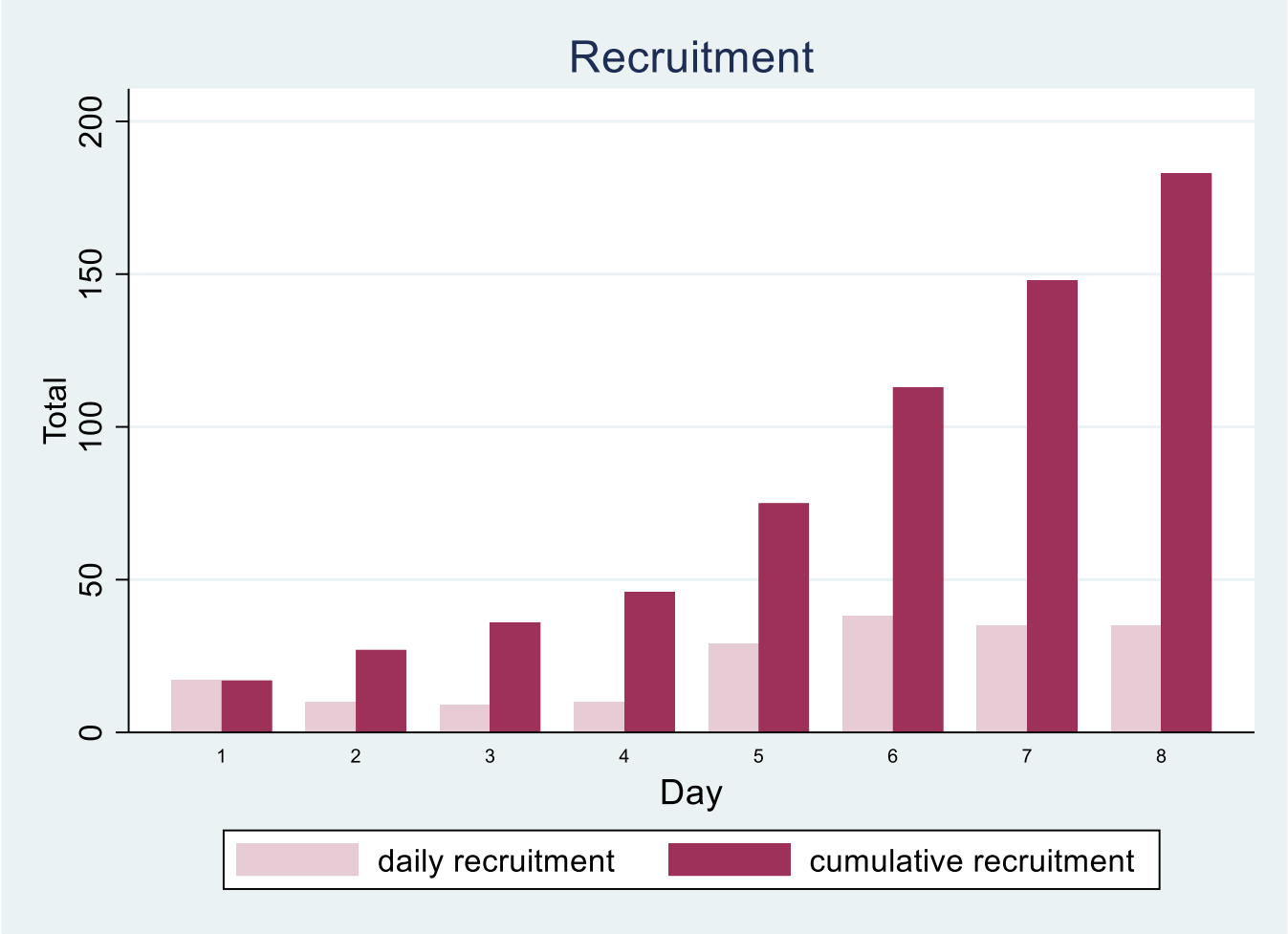

Characteristics at second randomisation (n=148)

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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

RECOVERY
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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 PREGNANT WOMEN

RECOVERY for pregnant women

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. Overview of adaptions
2. Follow-up
3. Update on progress
4. Future plans
5. Q&A

RECOVERY for pregnant women

RECOVERY
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For Site Staff / site teams

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.

INTERVENTION INFORMATION

RECOVERY intervention sheet - lopinavir-ritonavir

RECOVERY intervention sheet - hydroxychloroquine

RECOVERY intervention sheet - dexamethasone

RECOVERY intervention sheet - azithromycin

RECOVERY intervention sheet - tocilizumab

GUIDES FOR SPECIFIC PATIENT GROUPS

RECOVERY for pregnant and postpartum women

RECOVERY for patients with chronic kidney disease

RECOVERY Privacy Notice for Trial Staff

COLLABORATORS' MEETING

Slides presented at the collaborators' meeting on 20 & 21 April 2020

Slides presented at the collaborators' meetings on 6 & 7 April 2020

RECOVERY for pregnant women

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Randomised Evaluation of COVID-19 Therapy

RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)

for pregnant and postpartum women

Pregnancy leads: Prof Lucy Chappell, Prof Catherine Williamson, Prof Marian Knight

	RECOVERY trial protocol	Adaption for pregnancy
Eligibility	Patients are eligible if all of the following are true: i. Aged at least 18 years ii. Hospitalised iii. SARS-CoV-2 infection iv. 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	Same eligibility (To be eligible women should be hospitalised for management of SARS-CoV-2 infection (rather than women with SARS-CoV2 who are admitted for other reasons)
Interventions	• Arm 1: No additional treatment • Arm 2: Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) • Arm 3: Corticosteroid in the form of dexamethasone by oral or intravenous preparation 6 mg • Arm 4: Hydroxychloroquine • Arm 5: Azithromycin	Same option of 5 arms, but substitution of corticosteroid (arm 3): iv hydrocortisone 80mg bd/ oral prednisolone 40mg od (in place of iv dexamethasone)
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ 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
		Adaptions for breastfeeding women
		The same interventions should be used as for pregnant women. UKOSS COVID-19 case number added if available.

Eligibility = same

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2.1 Eligibility

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

(i) Aged at least 18 years
(ii) Hospitalised
(iii) SARS-CoV-2 infection (clinically suspected[1] or laboratory confirmed)
(iv) 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

What about women with a positive covid-19 swab result but admitted for a pregnancy reason…?

Interventions = almost the same

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Trial design

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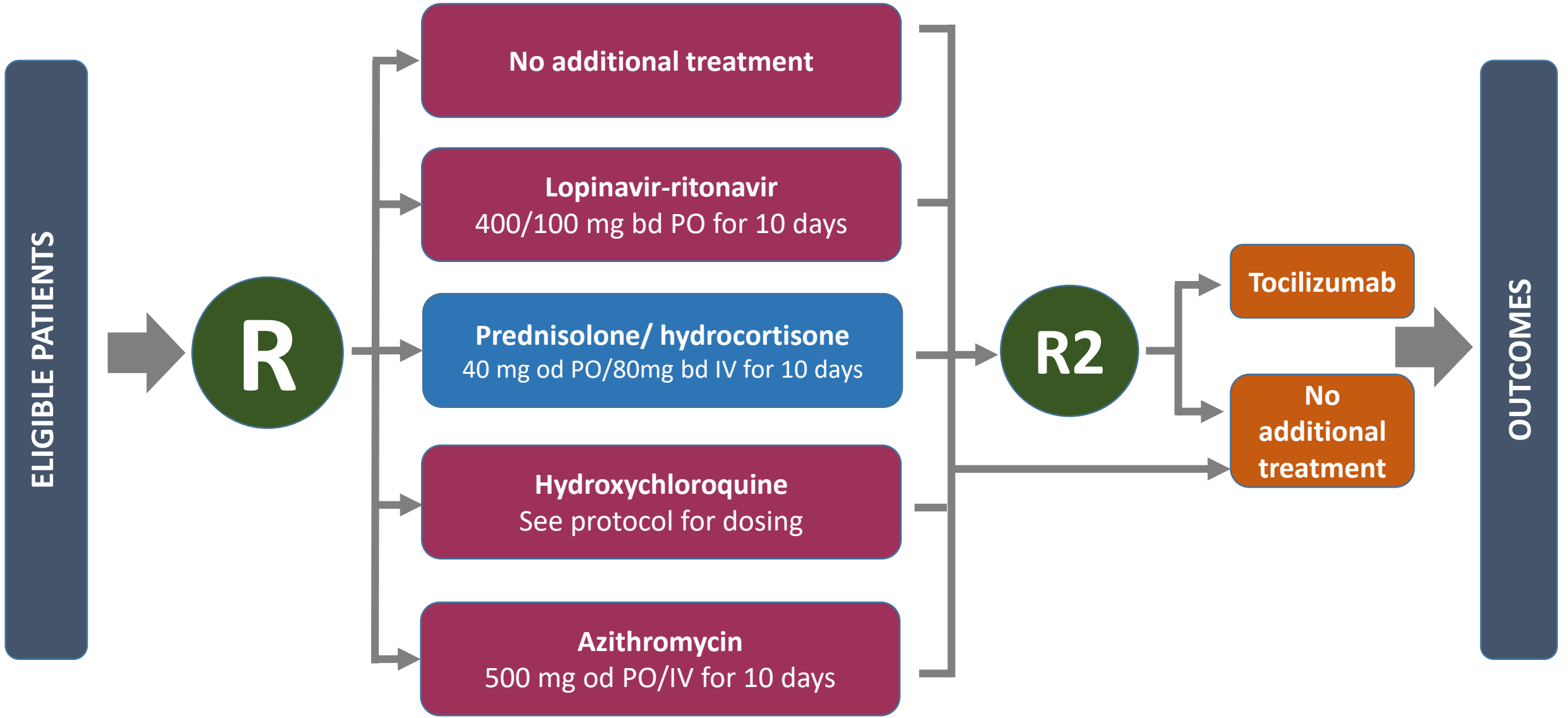

Use of drugs in pregnancy

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Annex A: Trial drugs in pregnancy and during lactation

All trial drugs have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The existing data related to each drug is summarized below.

Annex A: Trial drugs in pregnancy and during lactation
All trial drugs have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The existing data related to each drug is summarized below.

Lopinavir-Ritonavir
Lopinavir-ritonavir (400/100mg) treatment is used throughout pregnancy to treat HIV, with treatment reducing viral load and vertical transmission.[1] Elevated liver transaminases and impaired glucose tolerance should be screened for, but are not commonly seen in pregnancy. Some studies reported increased rates of late preterm birth in lopinavir-ritonavir-treated women compared to other protease inhibitors .[2] However, a systematic review that included nine studies (2,675 lopinavir/ritonavir-treated pregnant women with HIV) and considered preterm birth, low birth weight and stillbirth did not suggest any safety concerns.[3] Ergometrine should be avoided in women receiving lopinavir-ritonavir. Lopinavir and ritonavir are detected in breast milk, but the levels are considerably lower than maternal blood levels, and most studies have reported very low infant blood concentrations,[4] as reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501550/).

Hydrocortisone/ prednisolone
Prednisolone 40 mg PO od or, in women unable to take oral medicine, hydrocortisone 80mg IV BD are recommended instead of dexamethasone treatment in light of accumulating evidence that repeated doses of dexamethasone have deleterious effects on long-term neurodevelopment of the fetus.[5-7] While 90% dexamethasone is transferred transplacentally to the fetus, both hydrocortisone and prednisolone are converted by 11β-hydroxysteroid dehydrogenase to inactive glucocorticoids and considerably less drug is transferred to the fetus. Glucocorticoids can worsen maternal glycaemic control, so blood glucose should be checked and managed appropriately. Otherwise there is no convincing evidence that prednisolone use is associated with increased rates of adverse pregnancy outcomes when taken in the first trimester or later pregnancy.[8] Very low concentrations of prednisolone enter breastmilk. There is a paucity of data about pharmacological use of hydrocortisone, but it is likely that this is also safe when breastfeeding,[8] as also reviewed in the Lactmed database (www.ncbi.nlm.nih.gov/books/NBK501076/). Prednisolone (or hydrocortisone) should be used in breastfeeding women, in preference to dexamethasone.

Hydroxychloroquine
Several studies have provided reassuring safety data for the use of hydroxychloroquine (HCQ) in the first trimester, later pregnancy and when breastfeeding.[8, 9] The doses used in the RECOVERY trial are higher, but acceptable given the good safety profile of HCQ. Reports of retinopathy, nephrotoxicity, myopathy and cardiomyopathy have all been reported after long-term (more than 6 months) treatment, rather than the short course proposed here.

Azithromycin
Azithromycin is used in pregnancy to treat genital Chlamydia trachomatis infection, with a Cochrane systematic review and meta-analysis reporting fewer gastrointestinal side-effects compared to erythromycin, and inconsistent results on risk of preterm birth, preterm rupture of membranes, perinatal mortality and low birthweight, confounded by the indication for treatment.[10] A recent systematic review and meta-analysis of all macrolide antibiotics acknowledges potential bias in child outcome reports due to treatment indication.[11] The UK Teratology Information Service monograph concludes that there is no definitive evidence linking azithromycin with increased risk of miscarriage or congenital malformations (https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-MACROLIDES-IN-PREGNANCY/). Azithromycin is detected in only low levels in breastmilk and is not expected to cause adverse events in breastfed infants (reviewed in Lactmed database: www.ncbi.nlm.nih.gov/books/NBK501200/) .Azithromycin has also been used in several trials in preterm infants as a prophylactic treatment to prevent bronchopulmonary dysplasia.[12]

Second randomisation intervention: Tocilizumab
Two pharmaceutical global safety registry database studies have reported on tocilizumab use in pregnancy, including outcomes from 288 pregnancies [13] and 61 pregnancies,[14] typically for rheumatoid or other arthritides, and with the majority having received the drug in the first trimester. These data suggest that the rates of congenital abnormality, spontaneous pregnancy loss and other adverse outcomes were not higher than in the general population.[14] Small studies have shown that tocilizumab is transferred to the fetus with serum concentrations approximately 7-fold lower than those observed in maternal serum at the time of birth.[15] Very low concentrations of tocilizumab are identified in

Follow-up = the same, + extra

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You are here: UKOSS / Current Surveillance / COVID-19 in Pregnancy

COVID-19 in Pregnancy

UKOSS
UK Obstetric Surveillance System

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

Update on progress

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- 138 pregnancy leads identified, supported by research midwives
- Midwife champions on board
- 7 pregnant women recruited

Future plans

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Health

Coronavirus: Thousands signal interest in plasma trial

Q&A

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