Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

2nd June 2020

Agenda

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1. Introductions
2. Update on progress
   - Main recruitment
   - Second randomisation and convalescent plasma
3. Remdesivir
4. Hydroxychloroquine
5. Future plans
6. 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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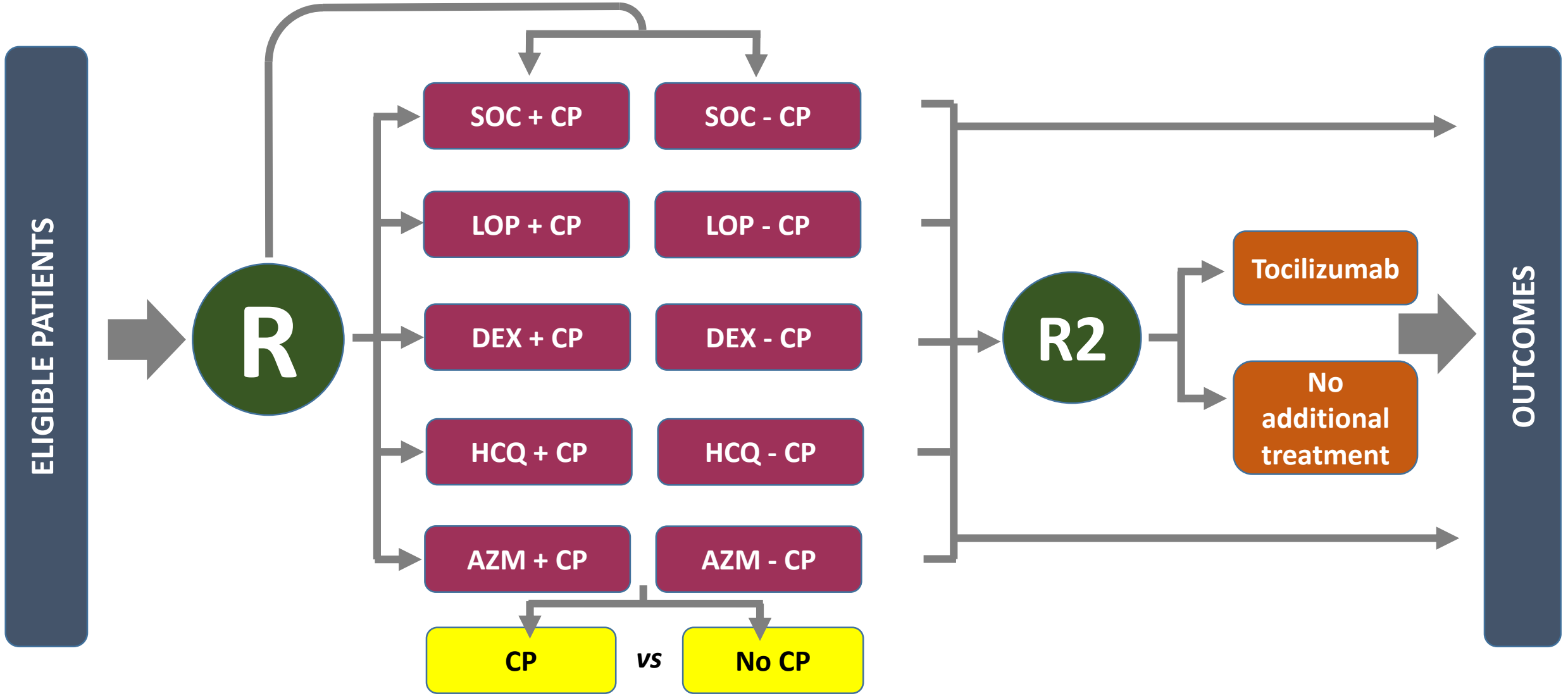

Recruitment by site

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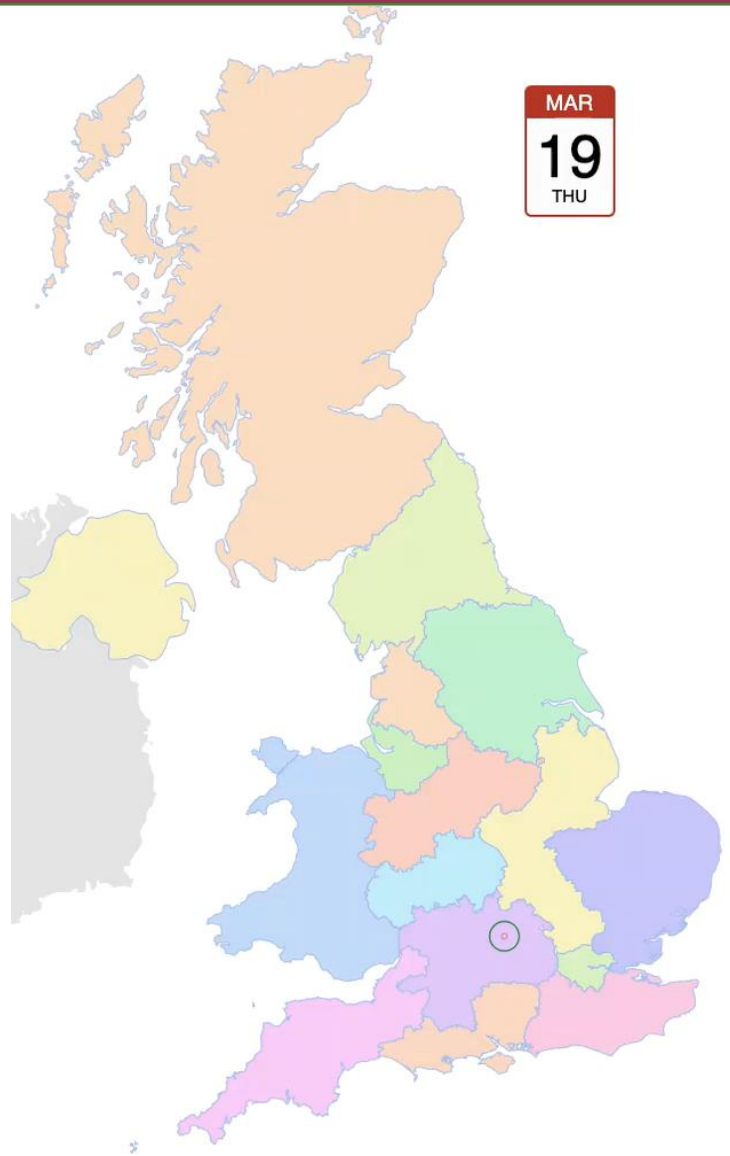

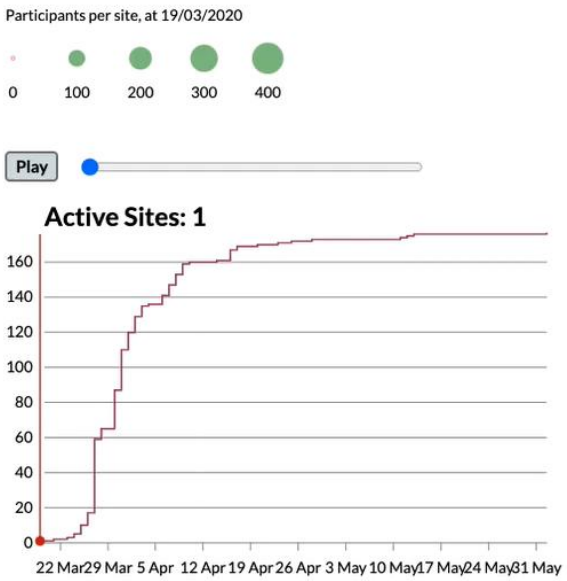

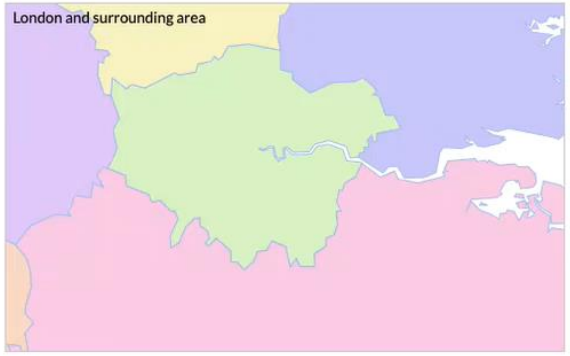

Recruitment progress

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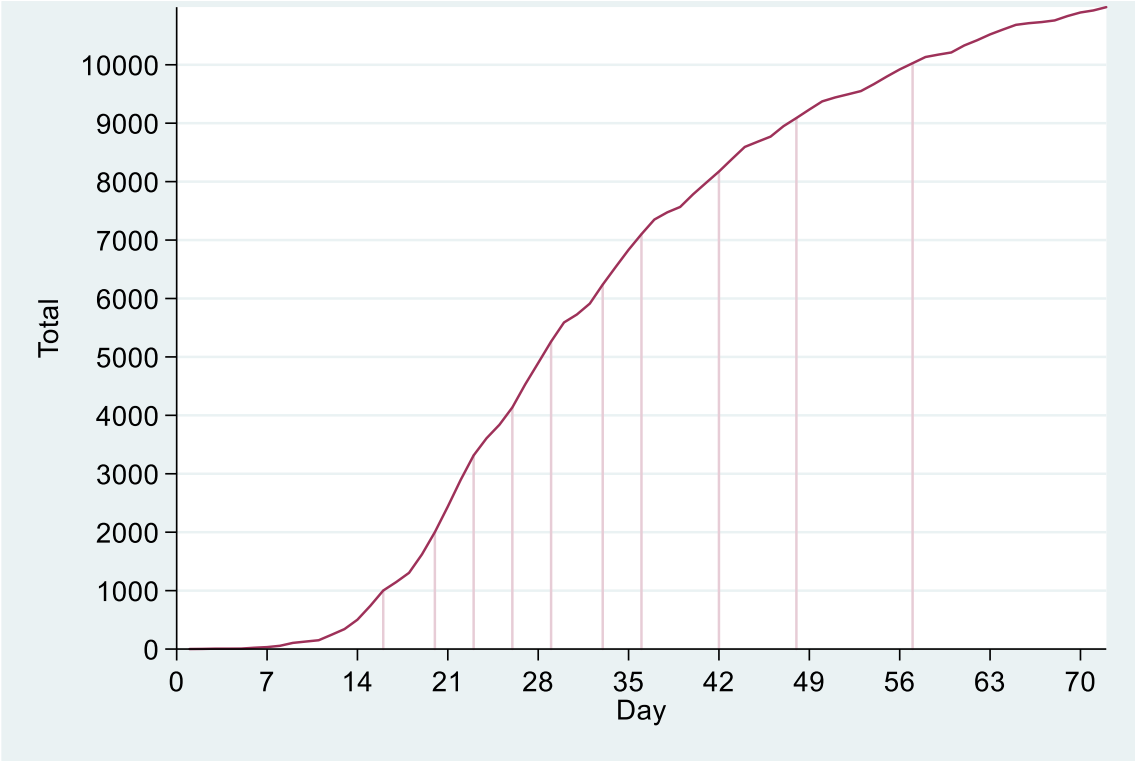
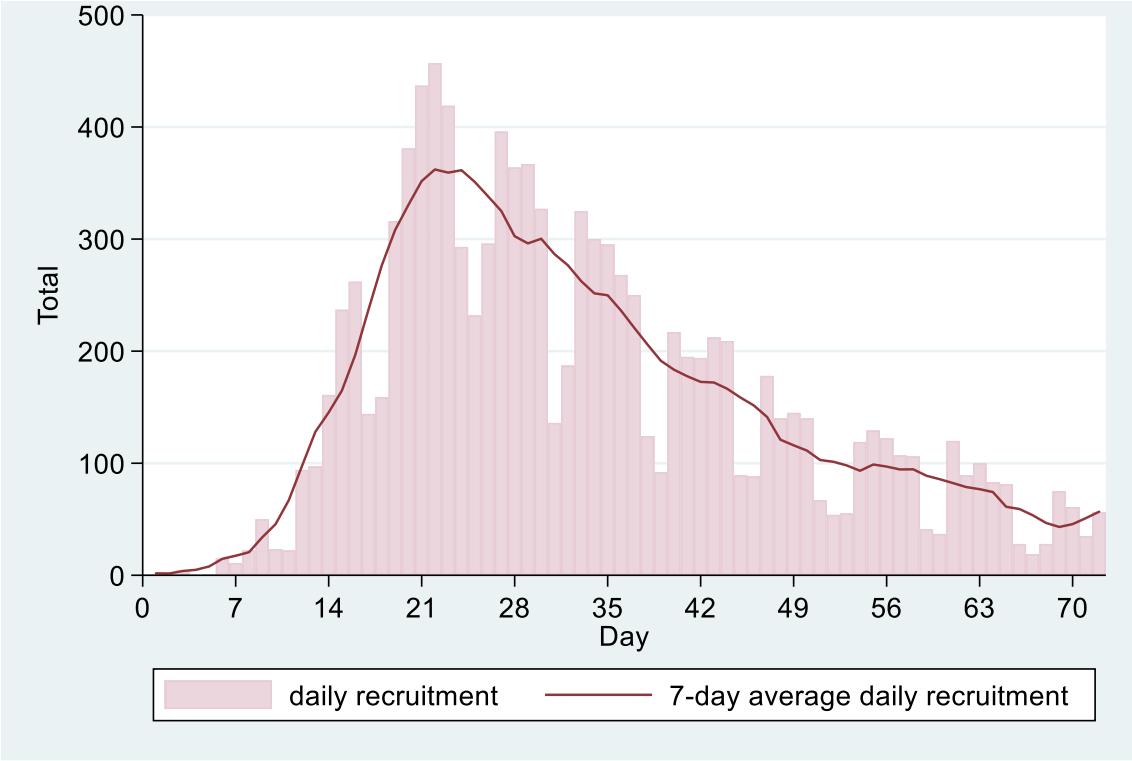
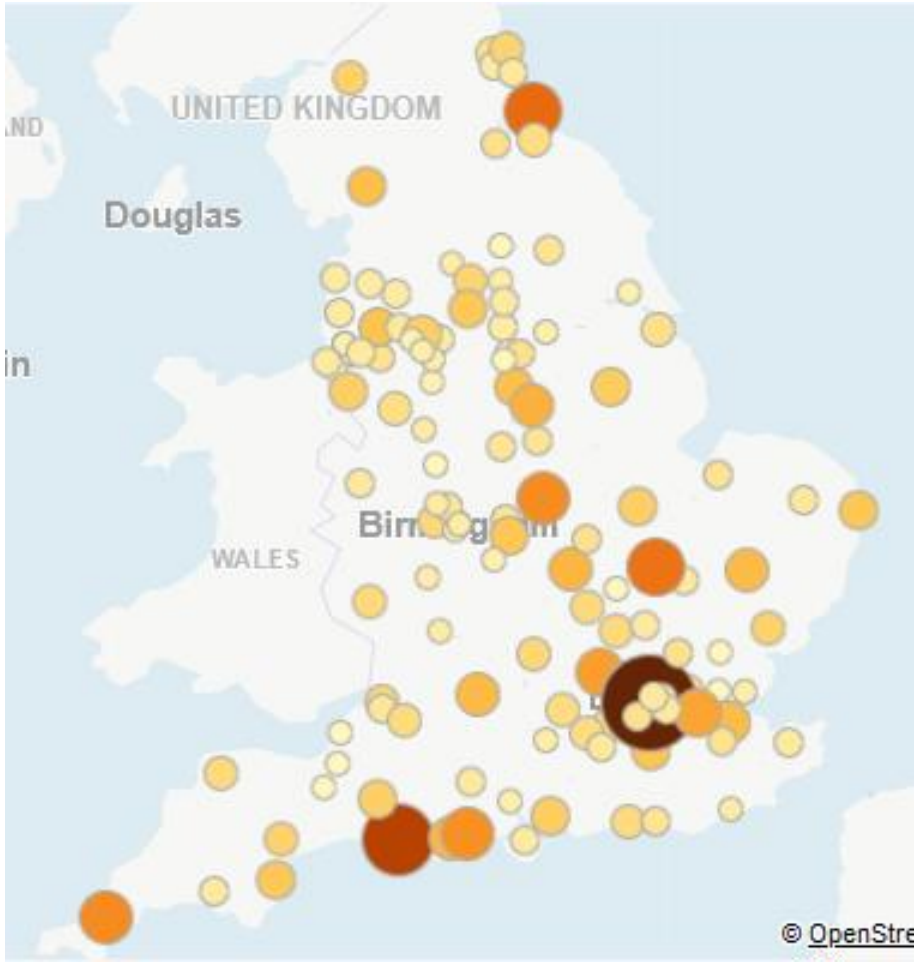
Total recruitment



Daily recruitment



Recruitment “efficiency”



- England-only data available from www.odp.nihr.ac.uk
- Larger darker circles indicate higher recruitment rate per 1000 admissions
- Varies from 1.5% to 64% (over 40 fold!)
- Average 101 per 1000

Characteristics at main randomisation (n=10,755)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		6786 (63%)
Age		66 (16)
Days since symptom onset		9 (5-13)
Days since hospitalisation		2 (1-5)
Severity of disease	No oxygen required	2622 (24%)
	Supplemental oxygen only	6633 (62%)
	Ventilation/ECMO	1502 (14%)
Prior disease	Diabetes	2896 (27%)
	Cardiovascular disease	2903 (27%)
	Chronic lung disease	2359 (22%)

What can we see in data?

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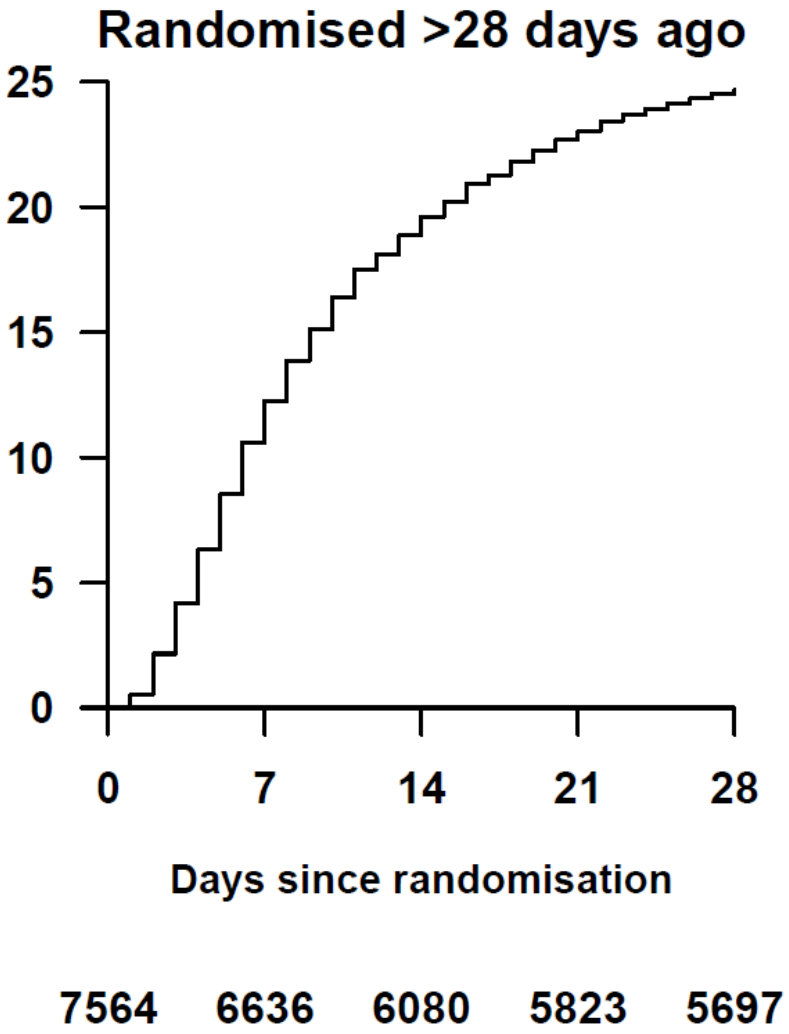

Characteristic		% dead at 28d
Age (years)		
	<50	7.7
	50-59	13.6
	60-69	23.6
	70-79	32.7
	80+	40.2
Sex		
	Female	19.1
	Male	25.7
Severity of disease		
	No oxygen	14.8
	Oxygen only	22.1
	Ventilation	35.0
Comorbidity		
	Diabetes	26.7
	Heart disease	33.1
	Chronic lung disease	31.1

When will we get some answers?

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- Although over 11,000 recruited now we still need 28 day follow-up
  - Please keep on top of the Follow-up forms!
- Due to design of trial, there are fewer than 2000 people on any one treatment (except standard of care)
  - Please keep recruiting!
- DMC review the data every two weeks (last review 28th May)

Second randomisation

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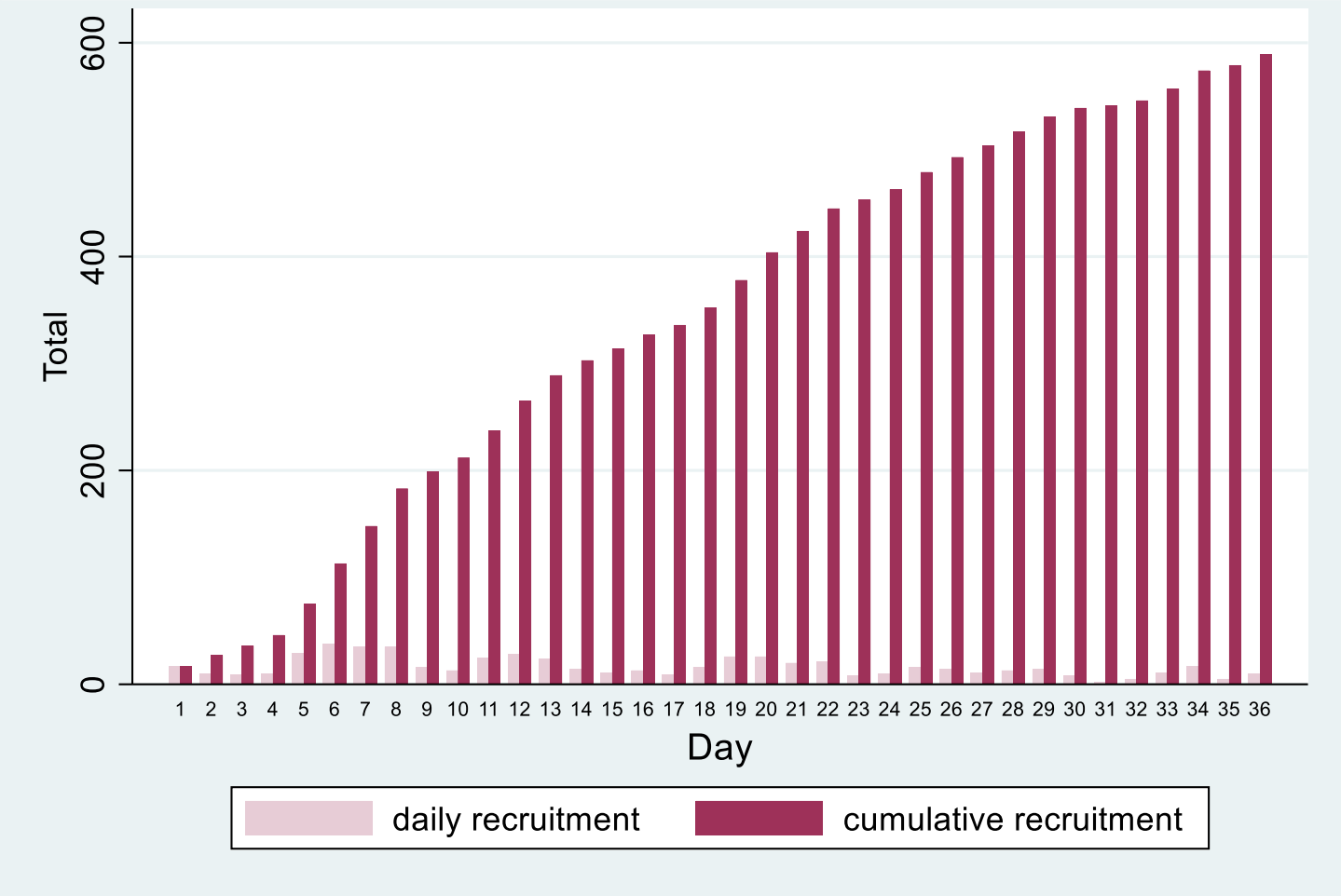

Convalescent plasma

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- First sites opened last week
- NHSBT are busy training transfusion laboratory staff and collecting plasma
- Aim is to open as many sites as possible, but rate will be determined by supply of convalescent plasma

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REMDESIVIR

ACTT-1 data

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- 1063 participants with laboratory proven COVID-19 and hypoxia
- Randomised between remdesivir (10 days) or placebo
- Primary outcome: time to recovery
  - Recovery = discharge alive or no longer requiring oxygen or medical care
- DMC stopped trial after 482 participants had recovered

ACTT-1 data (n=1063)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		684 (64%)
Age		58.9 (15)
Days since symptom onset		9 (6-12)
Severity of disease	No oxygen required	127 (12%)
	Supplemental oxygen only	618 (58%)
	Ventilation/ECMO	272 (26%)
	Missing	46 (4%)
Prior disease	Diabetes	275 (26%)
	Cardiovascular disease	2903 (27%)
	Chronic lung disease	2359 (22%)

ACTT-1 results

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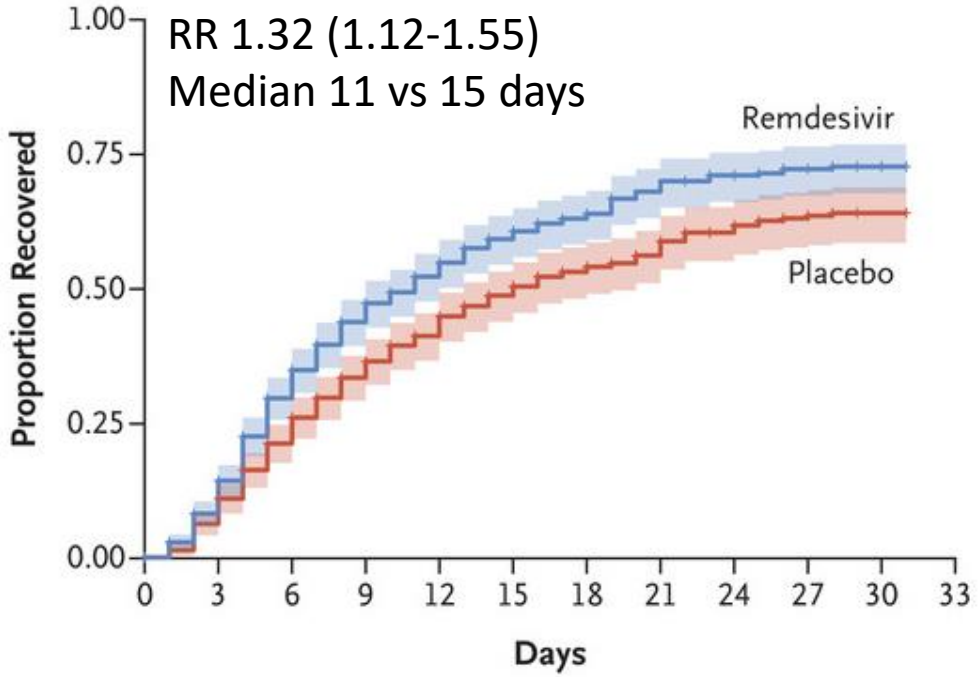
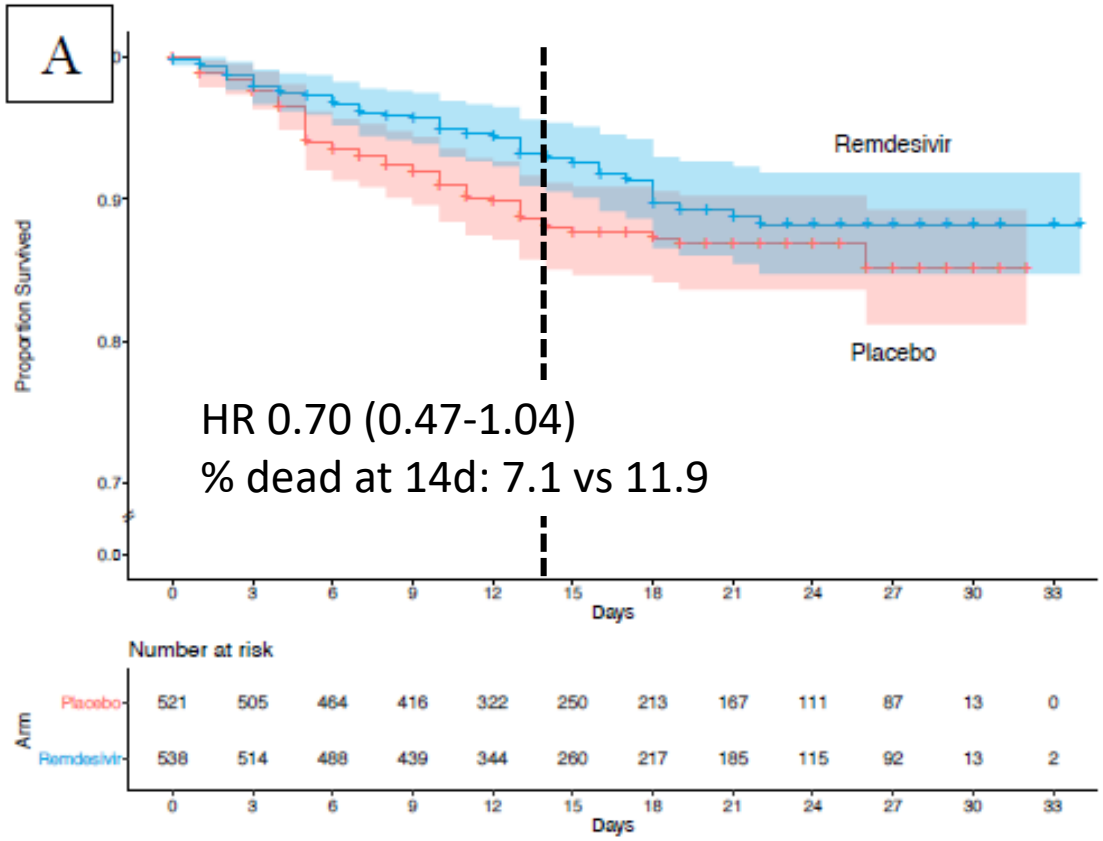
Recovery



No. at Risk

Remdesivir	538	481	363	274	183	142	121	98	78	65	3	0
Placebo	521	481	392	307	224	180	149	115	91	78	2	0

Survival



Remdesivir in RECOVERY

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- Remdesivir will be made available through Early Access to Medicines Scheme (EAMS) for selected patients with COVID-19

- **Patients on remdesivir can still be recruited into RECOVERY**

- **RECOVERY participants can be treated with remdesivir**

- Information on remdesivir use will be collected on Randomisation and Follow-up forms

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HYDROXYCHLOROQUINE

Hydroxychloroquine

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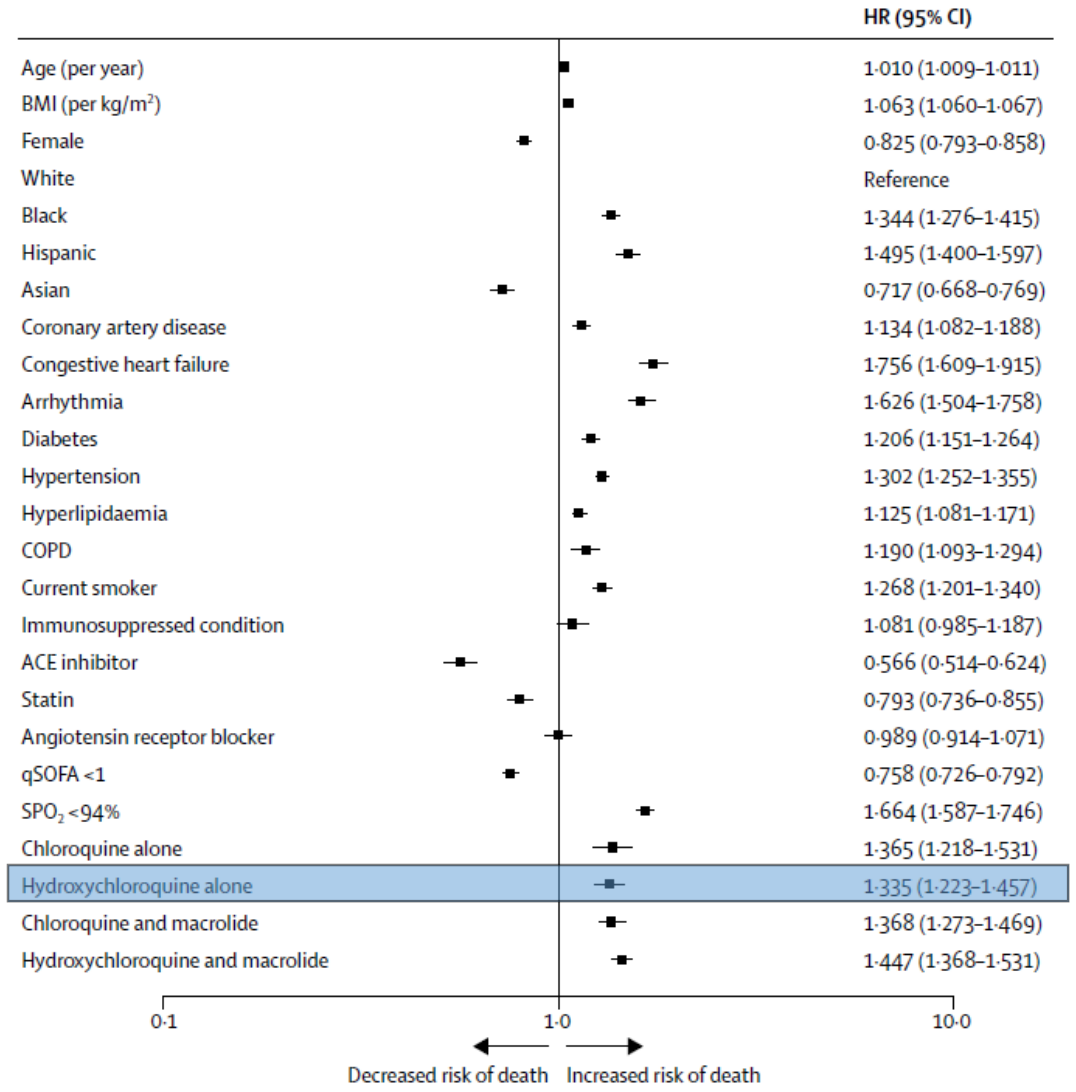

- **Non-randomised** analysis of factors associated with death
- Patients given HCQ will be different to those not given HCQ
- Non-randomised analyses cannot fully account for these differences so will be biased
- Authors acknowledged need for RCTs to test HCQ reliably

Discussions with MHRA

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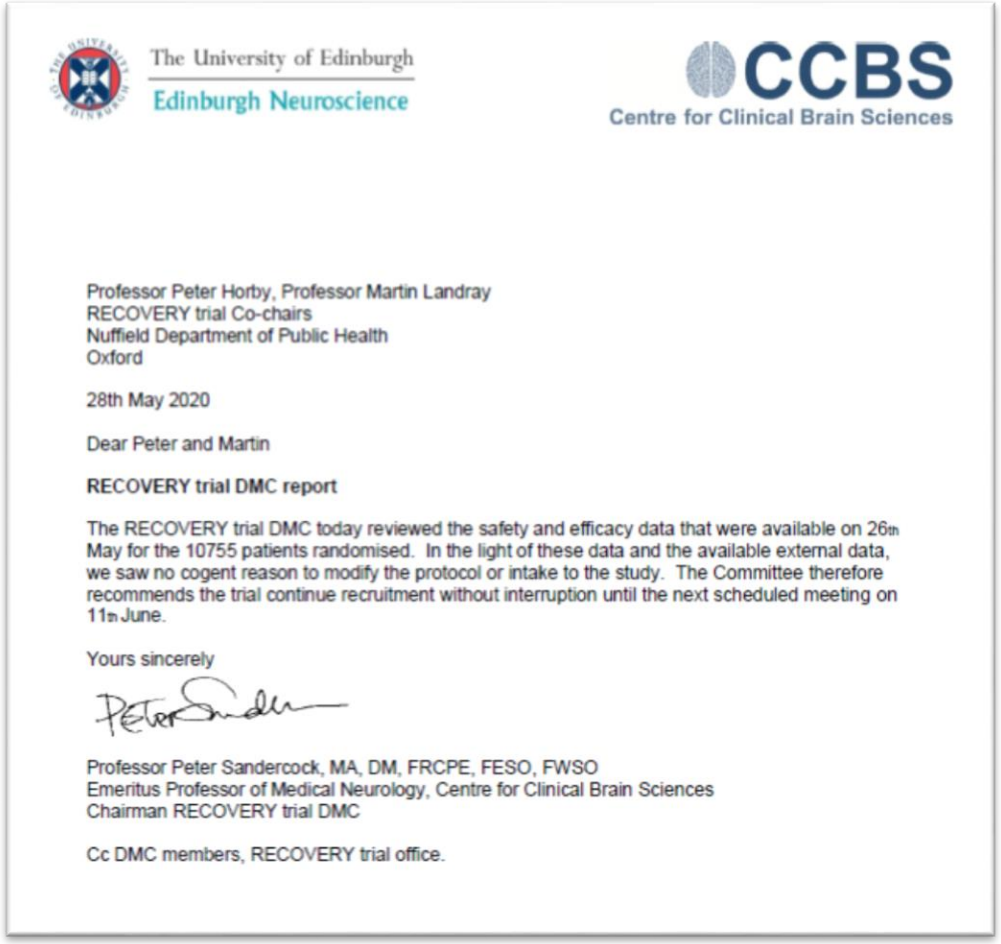
- MHRA wrote to all trials testing HCQ and requested the stop recruitment to HCQ arms on Friday 22nd May

- Updated data provided to RECOVERY DMC who met on 23rd May and concluded that no change to RECOVERY protocol was required

- RECOVERY Principal Investigators spoke to MHRA on 23rd May (before DMC meeting) and 24th May. MHRA agreed to allow RECOVERY to continue pending planned DMC review on 28th May

RECOVERY DMC



The University of Edinburgh
Edinburgh Neuroscience

CCBS
Centre for Clinical Brain Sciences

Professor Peter Horby, Professor Martin Landray
RECOVERY trial Co-chairs
Nuffield Department of Public Health
Oxford

28th May 2020

Dear Peter and Martin

RECOVERY trial DMC report

The RECOVERY trial DMC today reviewed the safety and efficacy data that were available on 26th May for the 10755 patients randomised. In the light of these data and the available external data, we saw no cogent reason to modify the protocol or intake to the study. The Committee therefore recommends the trial continue recruitment without interruption until the next scheduled meeting on 11th June.

Yours sincerely

Professor Peter Sandercock, MA, DM, FRCPE, FESO, FWSO
Emeritus Professor of Medical Neurology, Centre for Clinical Brain Sciences
Chairman RECOVERY trial DMC

Cc DMC members, RECOVERY trial office.

28th May

"…we saw no cogent reason to modify the protocol or intake to the study. The committee therefore recommends the trial continue recruitment without interruption until the next scheduled meeting on 11th June."

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FOLLOW-UP

Completeness is key

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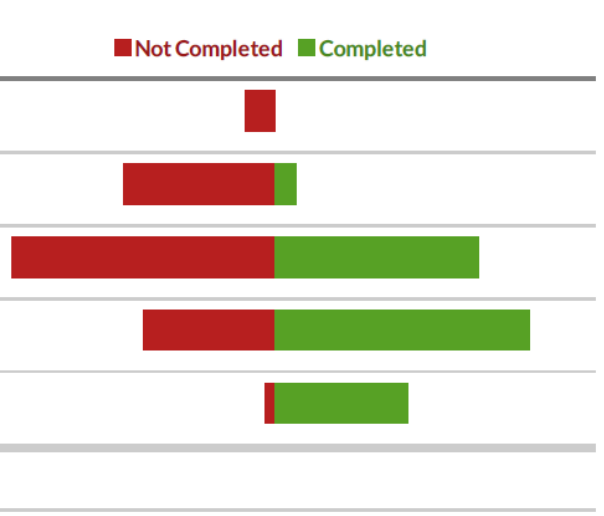
- Weekly reminders will be sent out by trial team to PI and staff with responsibility for completing Follow-up forms, highlighting participants randomised >28 days ago without complete form

- 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**



SAE reporting

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- Please remember that adverse events only need to be reported if they are **both**:
  - SERIOUS (e.g. prolong admission, require significant intervention to avoid life-threatening situation)

  AND
  - RELATED with reasonable probability to study treatment

- Please contact coordinating centre if such an event occurs.
- Please do not use “yellow card” system

Withdrawal of consent

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- Participants are free to withdraw consent for study procedures at any time

- It is **not** an "all or nothing" process. Withdrawal may be for:
  - Taking study treatment (e.g. they want to stop because of perceived side-effects)
  - Having hospital records reviewed for Follow-up form completion
  - Having linkage with NHS registries for long-term follow-up

- If participant wishes to withdraw, please find out which aspects they wish to withdraw from and inform coordinating centre

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FUTURE PLANS

Pharmaco-kinetic/-genomic substudy

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- Pharmacokinetics of hydroxychloroquine incompletely understood in COVID-19 population
- Predictors of QT prolongation (and other electrocardiographic changes) with HCQ (and AZM) unknown
- Plan to recruit patients allocated HCQ, AZM or control and measure:
  - ECG changes
  - HCQ concentrations at various time points
  - DNA sampling and other baseline characteristics
- Please contact coordinating centre if you are interested in participation

Carry on recruiting!

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- No additional arms currently being planned
- 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!