Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

7th & 8th December 2020

Agenda

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1. Introductions
2. Update on progress
3. Tocilizumab
4. Colchicine
5. Convalescent plasma
6. Trial procedures
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

Design

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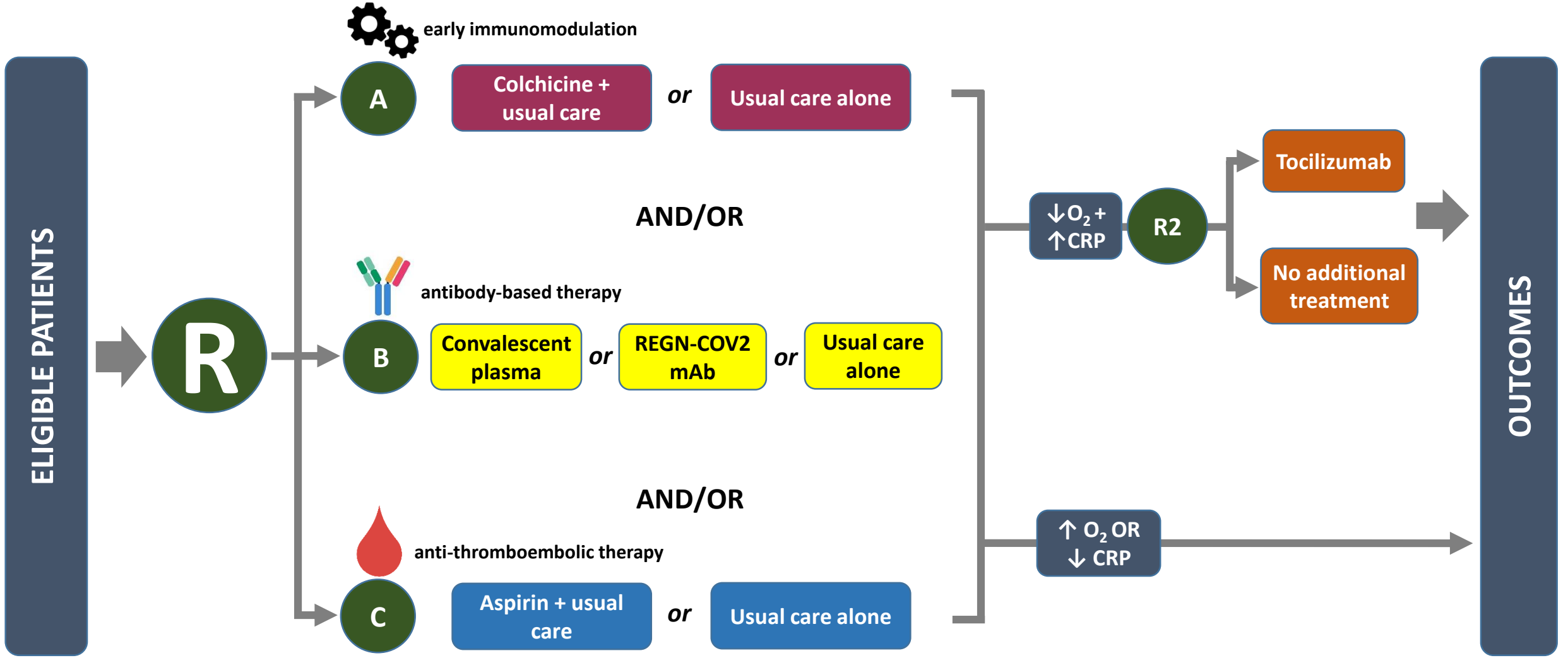

Recruitment by site and by time

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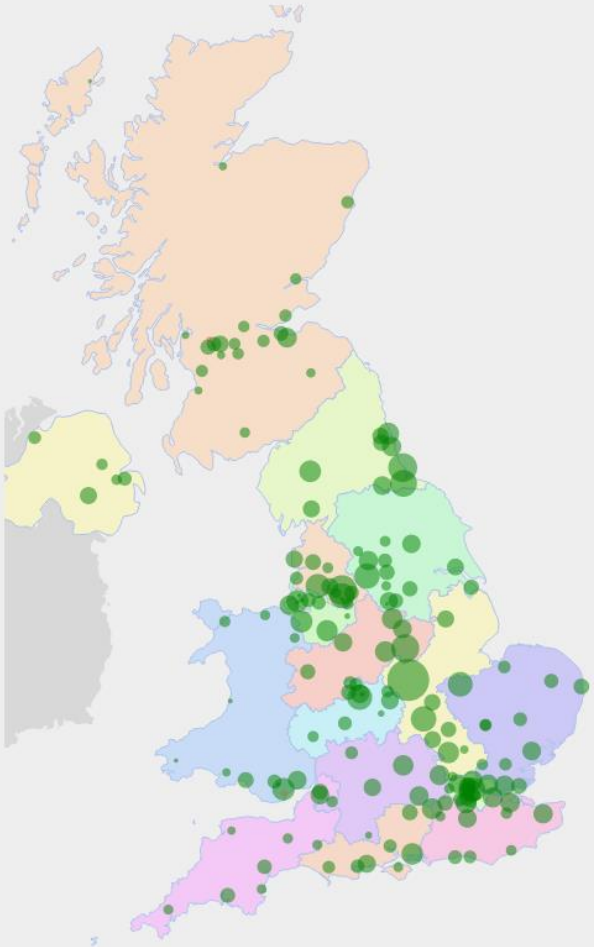
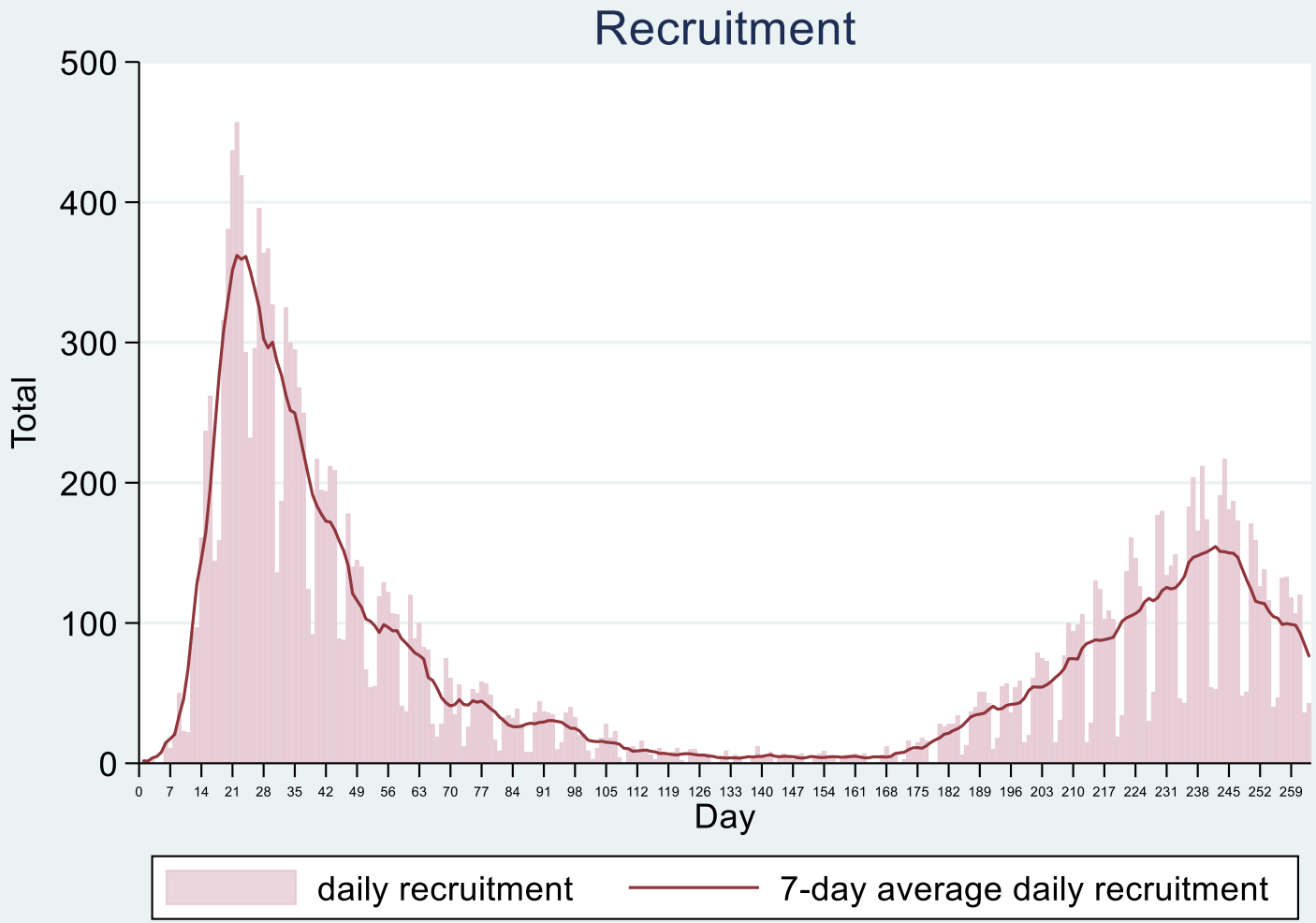
Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.
176	174	19948	2164	6756	1986





Recruitment

- Please continue to prioritise RECOVERY in accordance with its Urgent Public Health Priority 1A status (same as vaccine trials)

- Average recruitment remains at about 10% of all COVID-19 admissions, but with significant variation between regions and sites

- Please let us know how we could support recruitment at your site

Recruitment

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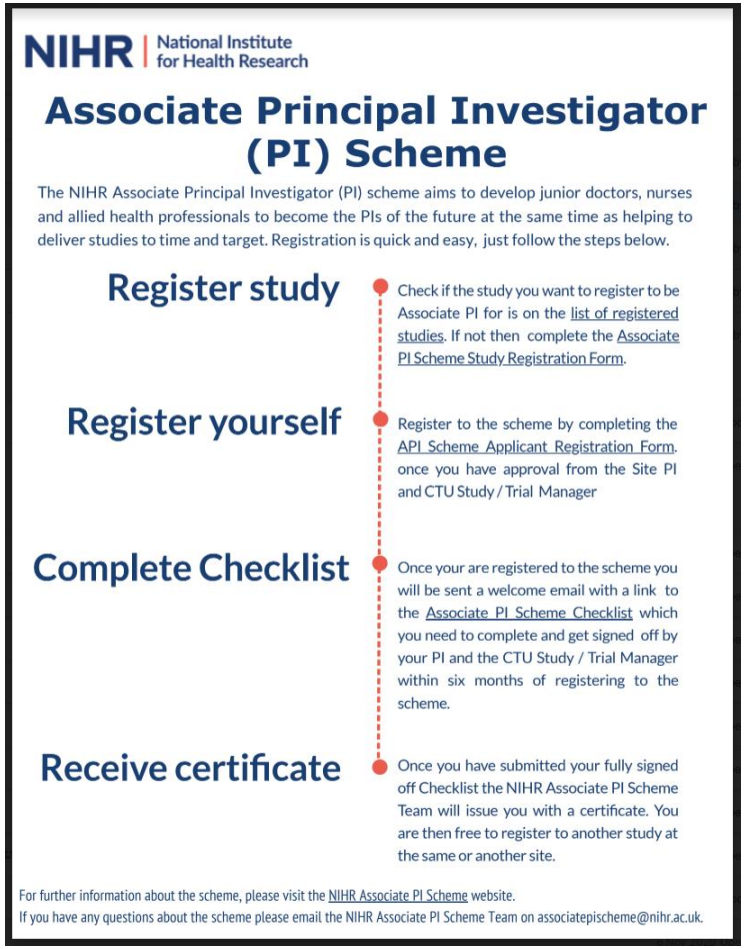
- RECOVERY now active on Associate PI scheme
- Many applications now in process
- Further details available (including recorded webinar) at:

https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040



NIHR | National Institute for Health Research

Associate Principal Investigator (PI) Scheme

The NIHR Associate Principal Investigator (PI) scheme aims to develop junior doctors, nurses and allied health professionals to become the PIs of the future at the same time as helping to deliver studies to time and target. Registration is quick and easy, just follow the steps below.

Register study
Check if the study you want to register to be Associate PI for is on the list of registered studies. If not then complete the Associate PI Scheme Study Registration Form.

Register yourself
Register to the scheme by completing the API Scheme Applicant Registration Form. once you have approval from the Site PI and CTU Study / Trial Manager

Complete Checklist
Once your are registered to the scheme you will be sent a welcome email with a link to the Associate PI Scheme Checklist which you need to complete and get signed off by your PI and the CTU Study / Trial Manager within six months of registering to the scheme.

Receive certificate
Once you have submitted your fully signed off Checklist the NIHR Associate PI Scheme Team will issue you with a certificate. You are then free to register to another study at the same or another site.

For further information about the scheme, please visit the NIHR Associate PI Scheme website.
If you have any questions about the scheme please email the NIHR Associate PI Scheme Team on associatepischeme@nihr.ac.uk.

How long until the next result?

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- Azithromycin recruitment now halted

- Please complete Follow-up forms as promptly as possible

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TOCILIZUMAB

Tocilizumab in REMAP-CAP

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- REMAP-CAP released preliminary results on 19 November
- Based on 303 participants randomised between usual care, tocilizumab, sarilumab, anakinra or interferon
- Estimated odds ratio of 1.87 for a better outcome with tocilizumab with high degree of statistical certainty (99.75% probability)
- Subsequent CAS alert from DHSC was not a directive to treat, but to ensure tocilizumab was available for licensed indications and gave permission to use it for patients who met REMAP-CAP criteria
- Randomisation into trials remains DHSC priority
  - NB REMAP-CAP are still randomising between tocilizumab and other immunomodulators (but have ceased usual care arm)

Tocilizumab in RECOVERY

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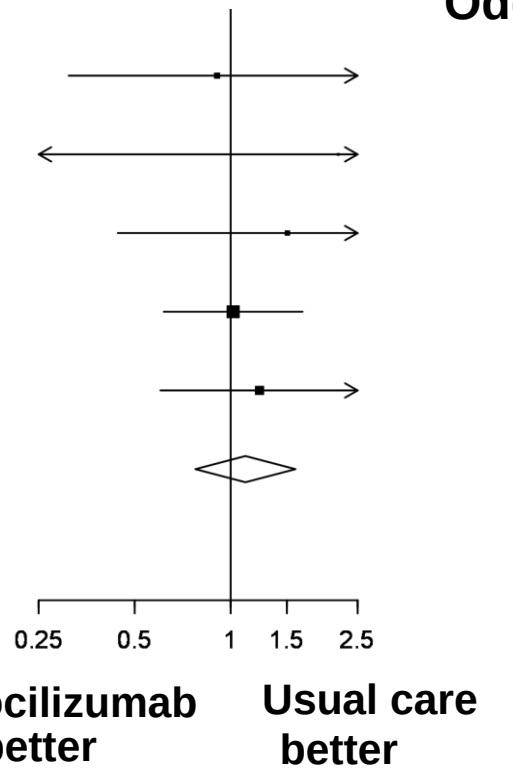
- Substantial uncertainty remains, at least until details of REMAP-CAP results are released

	Events/Participants (%)		
Trial	**Tocilizumab**	**Usual care**	**Odds Ratio (95% CI)**
CORIMUNO-TOCI	7/64 (11%)	8/67 (12%)	0.91 (0.31-2.65)
RCT-TCZ-COVID-19*	2/60 (3%)	1/66 (2%)	2.17 (0.22-21.33)
BACC Bay	9/161 (6%)	3/82 (4%)	1.51 (0.44-5.13)
COVACTA	58/294 (20%)	28/144 (19%)	1.02 (0.62-1.68)
EMPACTA	26/249 (10%)	11/128 (9%)	1.23 (0.60-2.52)
Overall	**102/828 (12%)**	**51/487 (10%)**	**1.11 (0.77-1.60)** **p=0.56**



Tocilizumab in RECOVERY

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- 2150 randomised
- Sufficient tocilizumab supply for 4000 randomised.
  - Agreement from NHS England that NHS stock can be used where trial stock unavailable
- Please ensure you consider this randomisation for appropriate participants:
  - On oxygen (or sats <92%)
  - CRP ≥75 mg/L

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COLCHICINE

Colchicine

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- Well-known anti-inflammatory agent

- Commonly used in:
  - Gout
  - Familial periodic fever syndromes
  - Pericarditis

- Well-recognised side-effects e.g. diarrhoea

Colchicine

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- **Contraindicated** if:
  - Women <55 years old (or older women with child-bearing potential)
  - Severe hepatic impairment
  - Significant cytopaenia (neutrophil count <1; platelet count <50; reticulocyte count <20)
  - Concomitant use of strong CYP3A4 inhibitor (macrolide antibiotics; systemic azole antifungals) or P-gp inhibitors (ciclosporin, verapamil)
  - Hypersensitivity to lactose

Colchicine

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- **Caution** if:
  - Concomitant use of moderate CYP3A4 inhibitor (diltiazem)
  - eGFR <30 mL/min/1.73m^2
  - Estimated body weight <70 kg

- In such patients use a reduced maintenance dose:
  - 1 mg at randomisation; 500 mcg 12 h later
  - 500 mcg **once** daily thereafter

- If a patient has >1 of these factors, responsible clinician should consider marking colchicine as “unsuitable”

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CONVALESCENT PLASMA

Convalescent plasma

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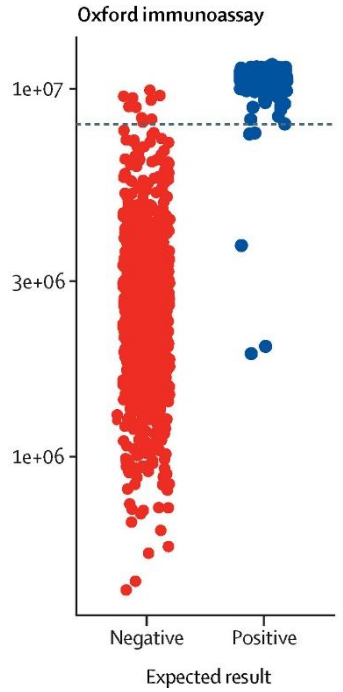
- Over 5500 participants in this comparison now
- Recent ‘negative’ trial from Argentina only included 300 participants
- Baseline serum samples now being analysed using Oxford immunoassay
  - Cut-off at 8 million for diagnosis



Antibody levels from 3668 participants

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Characteristic		Median [IQR] ($x10^6$)	Proportion >8 $x10^6$
All participants		9.1 [4.6-10.0]	59%
Age	<70	9.3 [6.0-10.0]	64%
	≥70 <80	8.9 [3.7-10.0]	57%
	≥80	5.9 [2.1-9.7]	41%
Respiratory support	No oxygen	5.1 [1.8-9.5]	37%
	Oxygen only	9.1 [5.0-10.0]	60%
	Ventilated	10.0 [8.8-10.2]	79%
Days since symptoms	≤7	6.7 [2.5-9.6]	42%
	>7	9.7 [7.4-10.1]	71%

Antibody levels from 3668 participants

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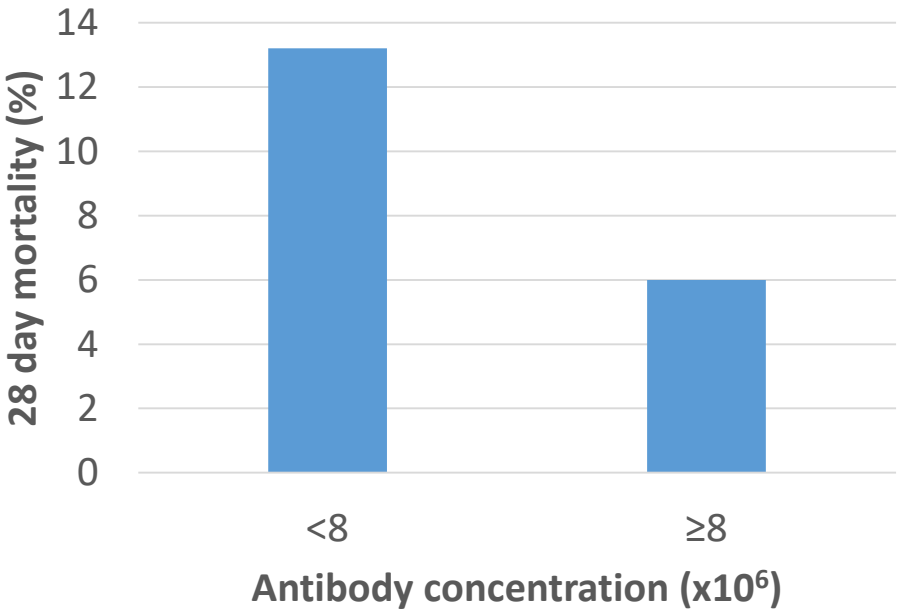
Baseline antibody level and risk of death



Baseline antibody level by arm

Recipient concentration	Convalescent plasma	Usual care
Available	73%	66%
Missing	27%	34%

Serum samples

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- **All** participants entering antibody comparison (CP vs mAb vs control) need to have serum sample collected prior to randomisation

- Must be taken for all participants in that comparison (regardless of allocation)

- **Please check whether any samples have not been returned to the central lab**

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TRIAL PROCEDURES

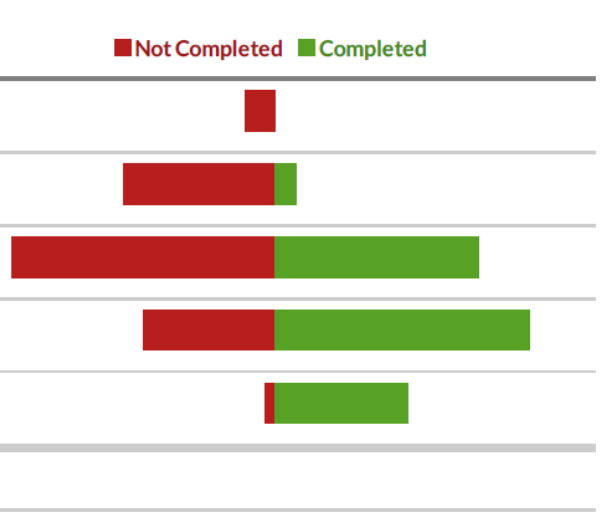
Completeness of follow-up

- Weekly reminders highlighting participants randomised >28 days ago without complete form **and also** those needing an Antibody Comparison 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**



Christmas dates

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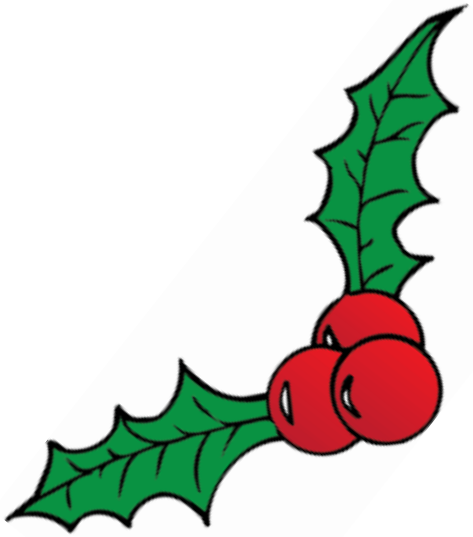
- Trial inbox will be monitored on working days
- Urgent clinical enquiries: **0800 138 5451**

- Last orders for postage kits for serum samples: **18th December**
- Please post serum samples on days in green, not those in red:

December	21	22	23	24	25	26	27
	28	29	30	31			
					01	02	03
January	04	05	06	…			



Carry on recruiting!

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- RECOVERY remains the largest global trial in COVID-19 and is an exemplar of what trials can do (both in and after pandemic)
- Current therapies are exciting, but need reliable data before they should be used routinely
- Thank you for your support!

RECOVERY trial for children

- **RCPCH treatment** criteria have been update to include signposting to RECOVERY

Options for Randomisation >=44 we

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- **1st stage interventions:**
  - (PIMS-TS)

    No additional treatment

    IVIg (PIMS-TS ONLY)

    Methylprednisolone(PIMS-TS ONLY)

  - Optional (Respiratory COVID – per protocol can be done with or instead of above interventions – advice is NOT to randomize in PIMS-TS)

    No additional treatment

    Convalescent plasma

    Synthetic neutralizing antibodies (>12years of age and ≥40kg only, who have not received IVIG)

2nd stage interventions: only open to children > 1 year of age

No additional treatment vs Tocilizumab (can use NHS stock as per adult NHSE instructions)

Infants: <44 weeks corrected GA

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- For neonates and infants with a corrected gestational age of < 44 weeks with respiratory COVID phenotype, options for RECOVERY randomisation include
  - Hydrocortisone
  - No additional treatment
  - Convalescent plasma

What next for RECOVERY for children

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PIMS-TS where children have already received IVIG and MP

- R1 bypass being programmed – next amendment

Consideration of new therapies – paediatric working group discussion with CIs and TSC

- new biological arm and possible randomisation ratio for PIMS-TS

Please keep recruiting!