Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

5th January 2021

Agenda

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1. Introductions
2. Update on progress
3. Tocilizumab
4. Colchicine
5. Convalescent plasma
6. Recent trial results
7. Future amendments to the protocol
8. Trial procedures
9. Paediatric update
10. 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 design

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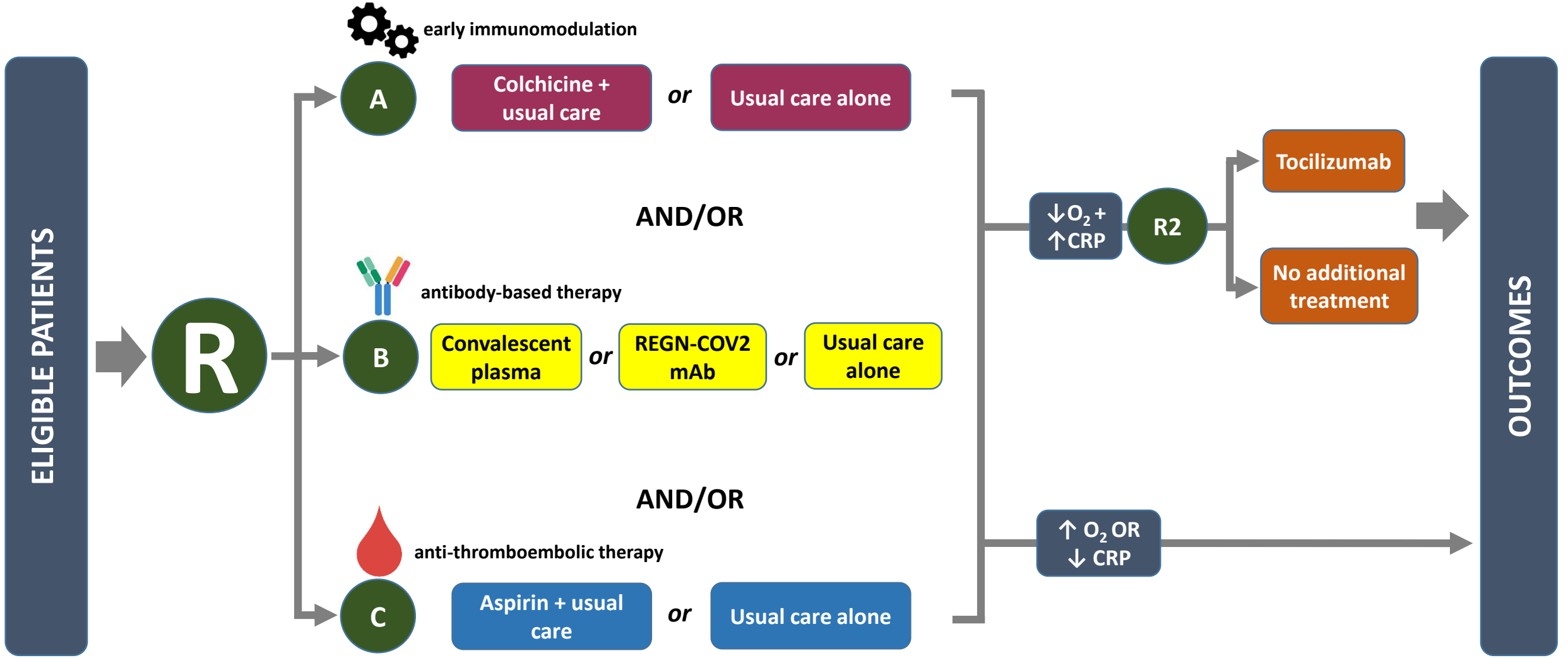

Recruitment by site and by time

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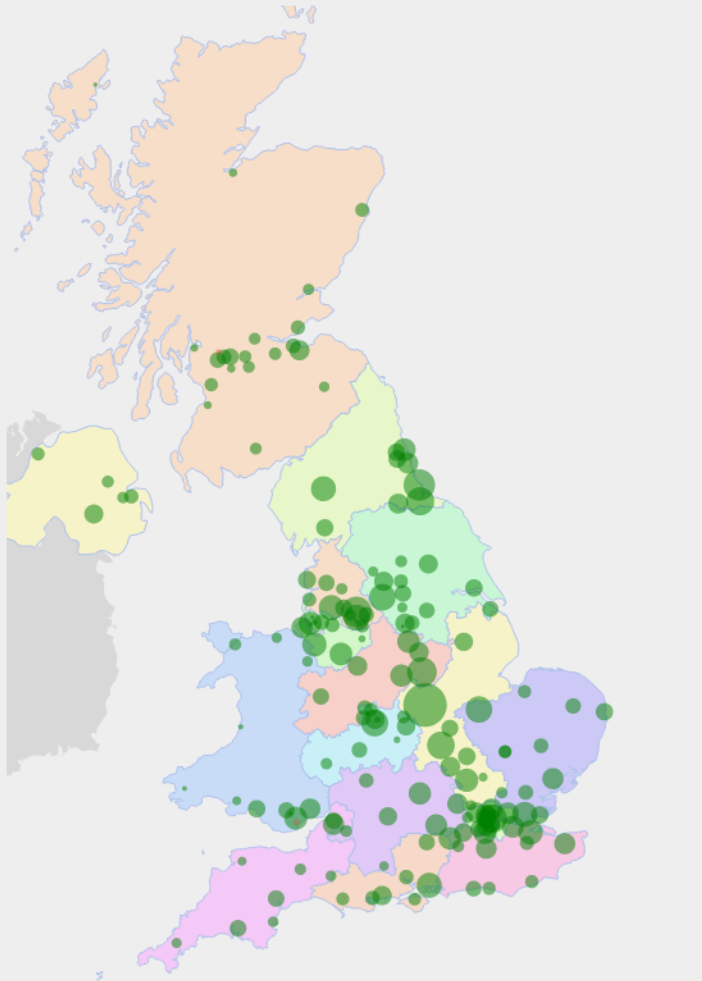
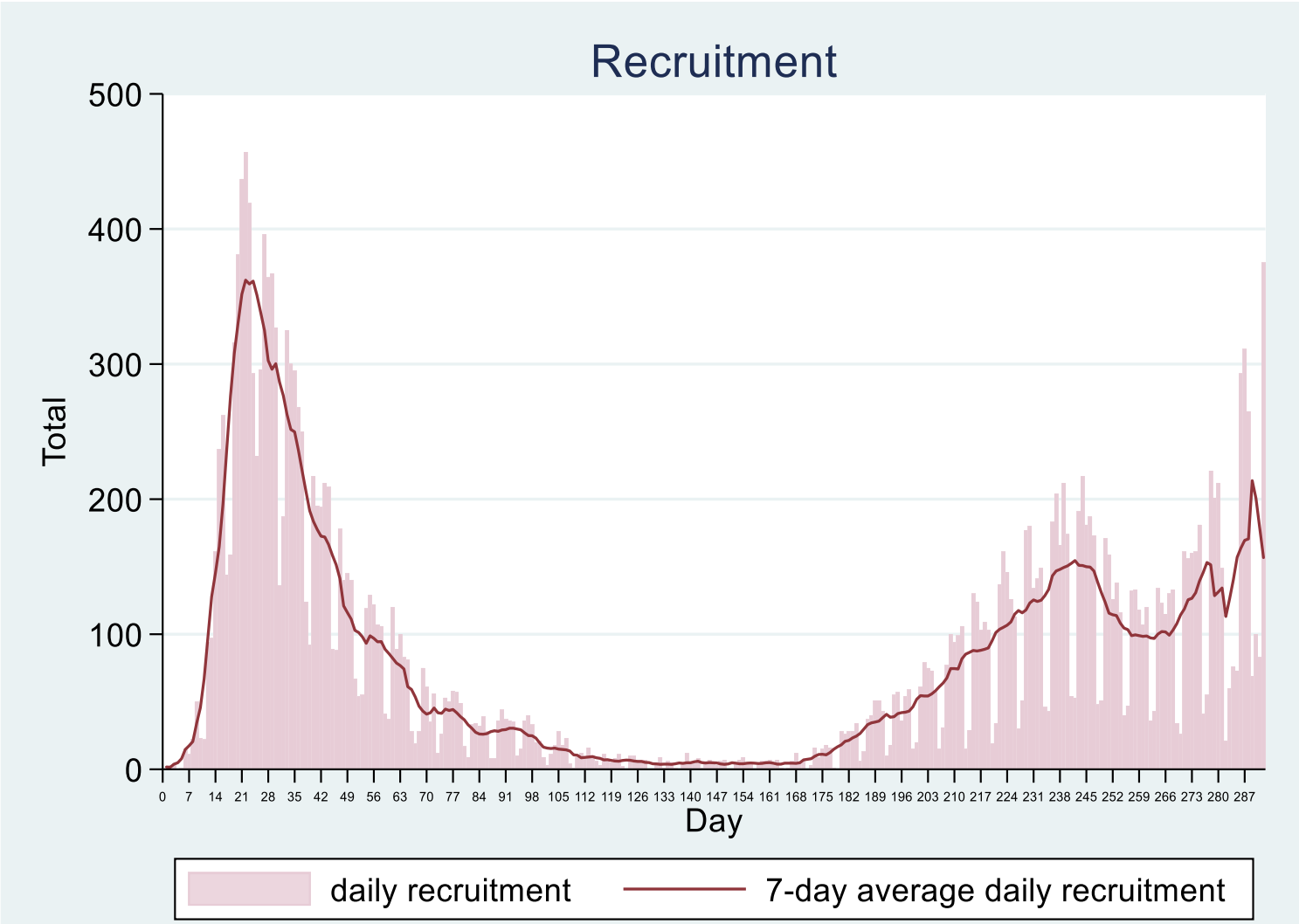
Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.
176	174	24023	2727	10224	4617





Current numbers in comparisons

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- Colchicine *vs* usual care: ~2200
- Convalescent plasma *vs* usual care: ~8400
- REGN-COV2 *vs* usual care: ~2500
- Aspirin *vs* usual care: ~4300
- Tocilizumab *vs* usual care: ~2700

Recruitment

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- 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
- NIHR CRN has set a target of minimum 10% recruitment by each CRN
- Please let us know how we could support recruitment at your site

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TOCILIZUMAB

Tocilizumab in RECOVERY

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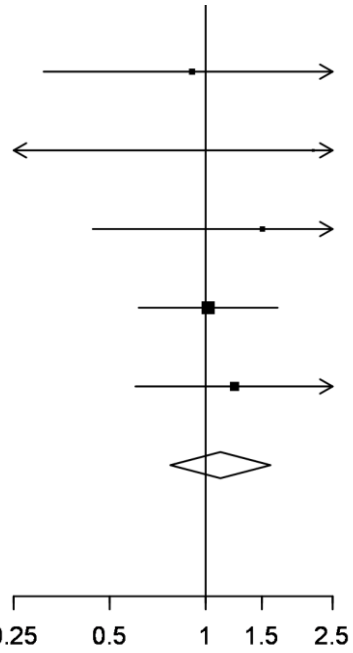
Trial	Events/Participants (%) Tocilizumab	Usual care	Odds Ratio (95% CI)
CORIMUNO-TOCI	7/64 (11%)	8/67 (12%)	0.91 (0.31-2.65)
RCT-TCZ-COVID-19*	2/60 (3%)	1/66 (2%)	2.17 (0.22-21.33)
BACC Bay	9/161 (6%)	3/82 (4%)	1.51 (0.44-5.13)
COVACTA	58/294 (20%)	28/144 (19%)	1.02 (0.62-1.68)
EMPACTA	26/249 (10%)	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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- REMAP-CAP preliminary results are encouraging, but unknown whether tocilizumab reduces mortality

- RECOVERY can provide a clear answer to this question, but recruitment must continue

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CONVALESCENT PLASMA

Convalescent plasma

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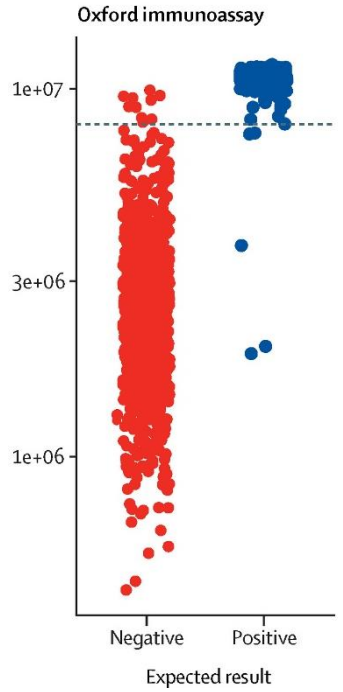
- Over 8400 participants in this comparison now
- Recent ‘negative’ trial from Argentina only included 300 participants
- Baseline serum samples now being analysed using Oxford immunoassay
  - Cut-off at 8 million for diagnosis



Antibody levels from first 3668 participants

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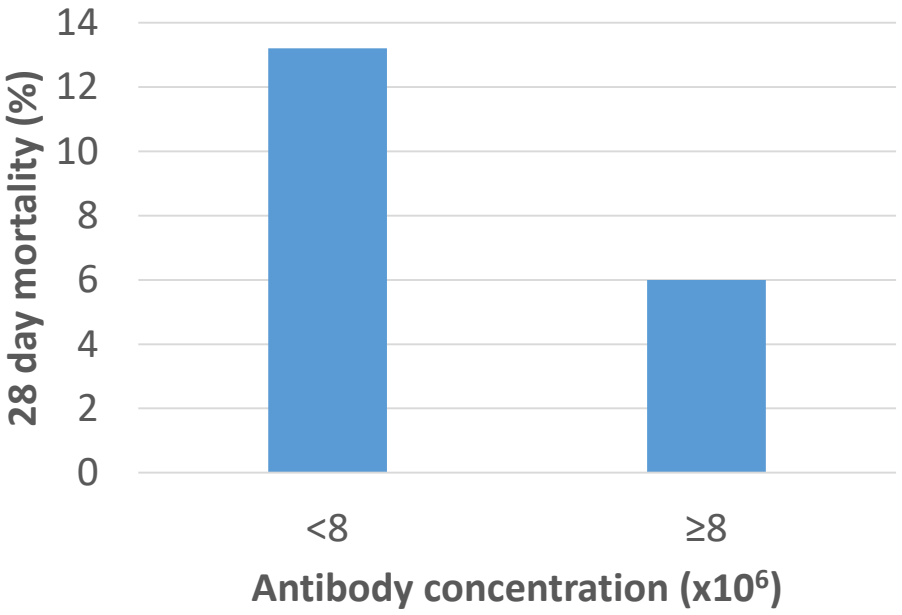
Baseline antibody level and risk of death



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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RECENT TRIAL RESULTS

Baricitinib in COVID-19

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- Exaggerated immune response is a well-recognised part of the COVID-19 syndrome among people requiring hospitalisation

- Significant interest in treatments that modulate this response

- Recent genetic data from GenoMICC study suggest some inflammatory pathways are strongly linked to severe disease
  - e.g. people with more active *TYK2* are at higher risk of severe disease

Baricitinib in COVID-19

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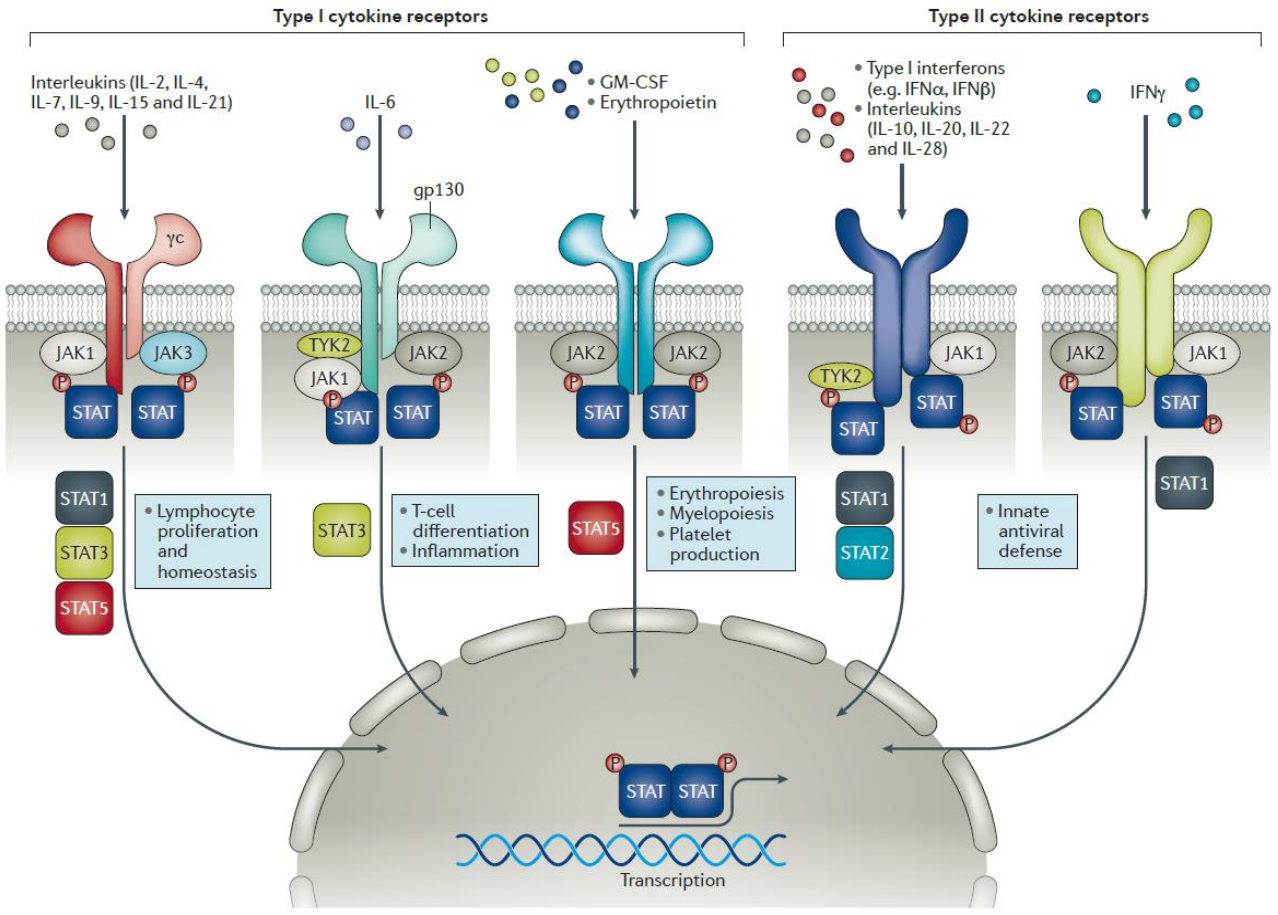
- *TYK2* encodes a protein called tyrosine kinase 2 which is one part of an intracellular signalling pathway common to many cytokines

- JAK proteins are in same family and work with STAT proteins to transmit signals from outside the cell to the nucleus and hence gene transcription

- Therefore inhibiting JAK/TYK2 might helpfully modify the immune response



ACTT-2 trial

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- 1033 participants hospitalised with COVID-19
- Randomly allocated to either:
  - Baricitinib plus remdesivir; or
  - Placebo plus remdesivir
- Primary outcome = time to recovery

ACTT-2 participants

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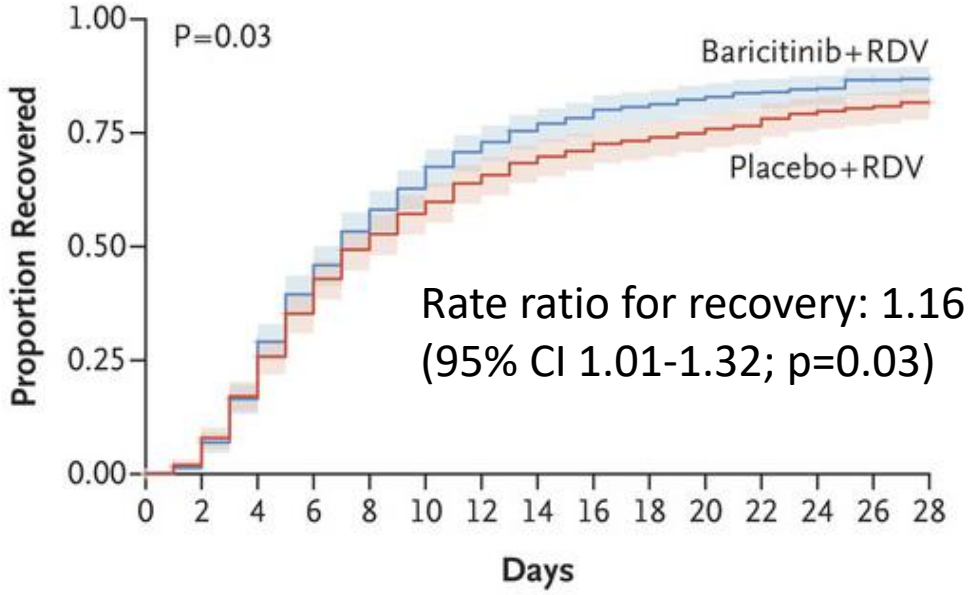
- Mean age 55 years old
- 63% men
- Recruited 8 days after symptoms started
- 32% on non-invasive or invasive ventilation

ACTT-2 results



Rate ratio for recovery: 1.16
(95% CI 1.01-1.32; p=0.03)

No. at Risk

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44

Outcome	Rate ratio (95% CI)
Mortality	0.65 (0.39-1.09)
Death or IMV	0.69 (0.50-0.95)
IMV	0.64 (0.44-0.93)

Safety:
SAEs in 16.0% *vs* 21.0% (p=0.03)

Implications for RECOVERY

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- Genetic data and data from ACTT-2 both support baricitinib as a potential treatment for COVID-19
- Larger outcomes trial now required
- Baricitinib is undergoing detailed review by CTAP

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FUTURE AMENDMENTS TO THE PROTOCOL

Anakinra in RECOVERY

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- Anakinra is an interleukin-1 receptor antagonist
- Commonly used in paediatric disorders with hyperinflammation
- Anakinra will be a third option in the second randomisation **for children** >1 year old with PIMS-TS
- Second randomisation for children will become 2:2:1 randomisation
  - Tocilizumab *vs* Anakinra *vs* usual care alone

Anakinra in RECOVERY

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- Dose = 2 mg/kg per day for 7 days

- **Contraindications:**
  - Neutrophils <1.5 x10^9/L
  - Pregnancy*
  - No drug-drug interactions

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TRIAL PROCEDURES

Review of amendments

- HRA has decided that RECOVERY amendments may be implemented **3 days** after full HRA approval given

- We recognise this is much shorter than standard 35 days but RECOVERY must take priority in R&D review process

- Some sites have tried to not implement amendments but this creates significant risk as IT system is centralised.

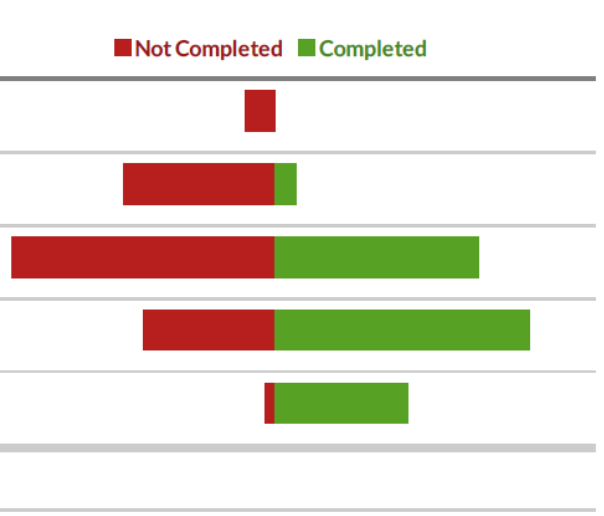
Completeness of follow-up

- 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**



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
- We recognise challenge that current situation in the NHS presents and remain extremely grateful for your support, so THANK YOU!

Paediatric RECOVERY 5th Jan 2021

1. new guidance document v8 (https://www.recoverytrial.net/files/recovery_paeds_guidance_v8_20201216.pdf)

2. new consent forms (azithromycin not mentioned) now live on website

3. for children with PIMS-TS who are so sick they have received IVIG and MP, these children can now be randomised to R2 SOC vs tocilizumab without needing to randomise to R1

- select PIMS-TS and already given IVIG and MP
- select all other R1 drugs as unsuitable
- the system will let you move straight to R2.

4. please remember for the mild cases a key comparison is SOC vs IVIG vs high dose methyl pred

PIMS-TS

- Will be adding anakinra to R2
  - Will need pregnancy test for post pubertal females
- change randomisation schedule for R2 to 2:2:1 tocalizumab:anakinra:SOC (ie 80% chance of active treatment),
- specific Bayesian analysis with primary outcome no. of days hospitalisation (secondaries including PICU days).
- New CRF in preparation with specific outcome measurements including 6 week telephone f/up for children treated with biologicals
- New PIS also addresses 16/17 year olds being able to sign own consent where feasible.

- Follow up form – please keep on top of the paediatric CRF completion.