Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

26th January 2021

Agenda

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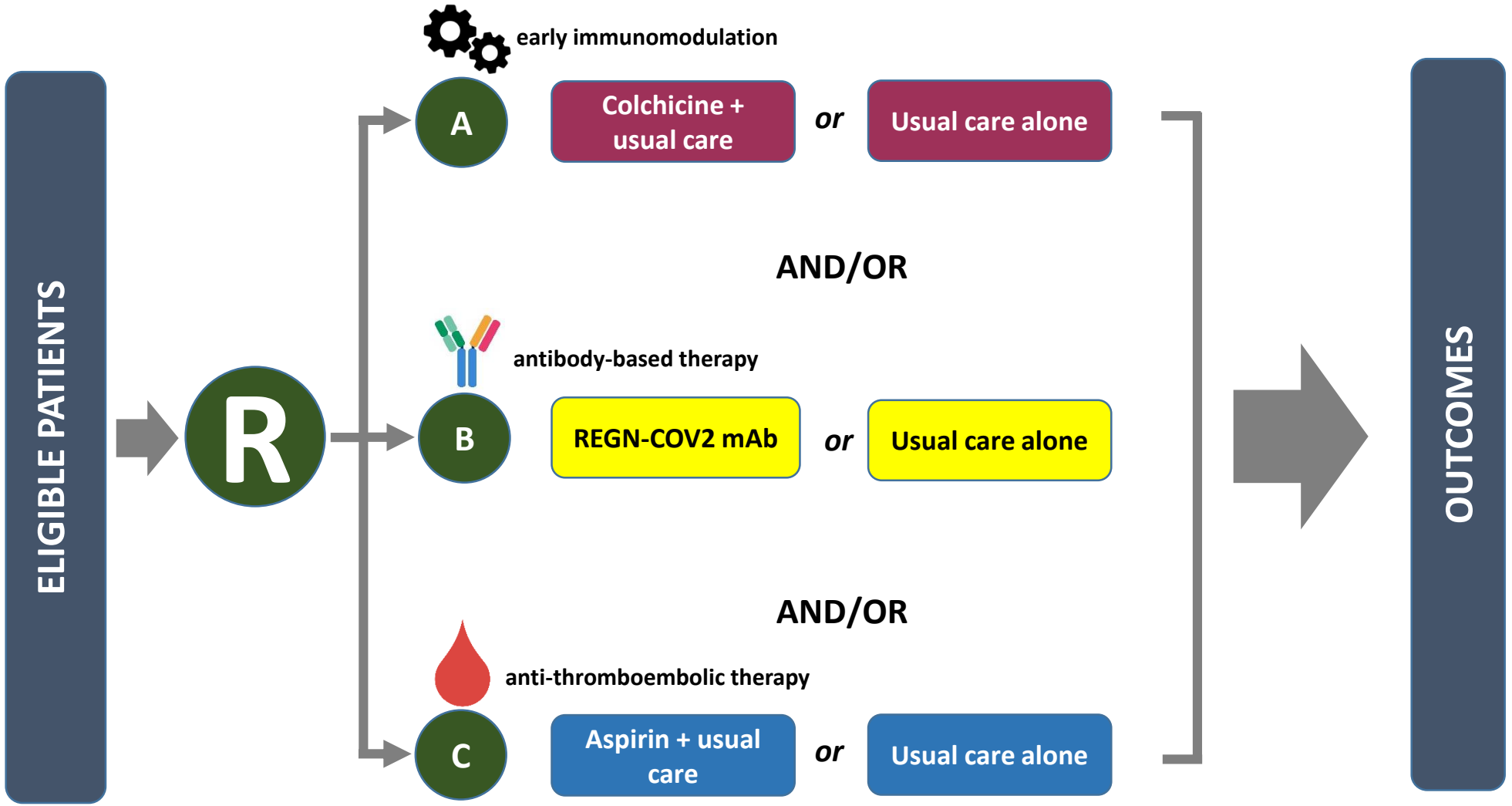

Recruitment by site and by time

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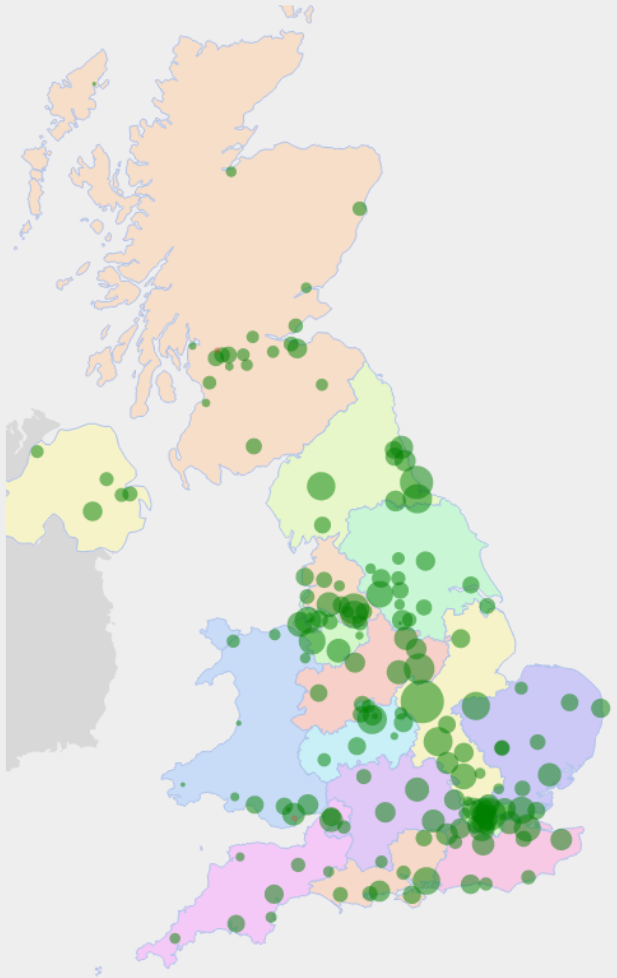
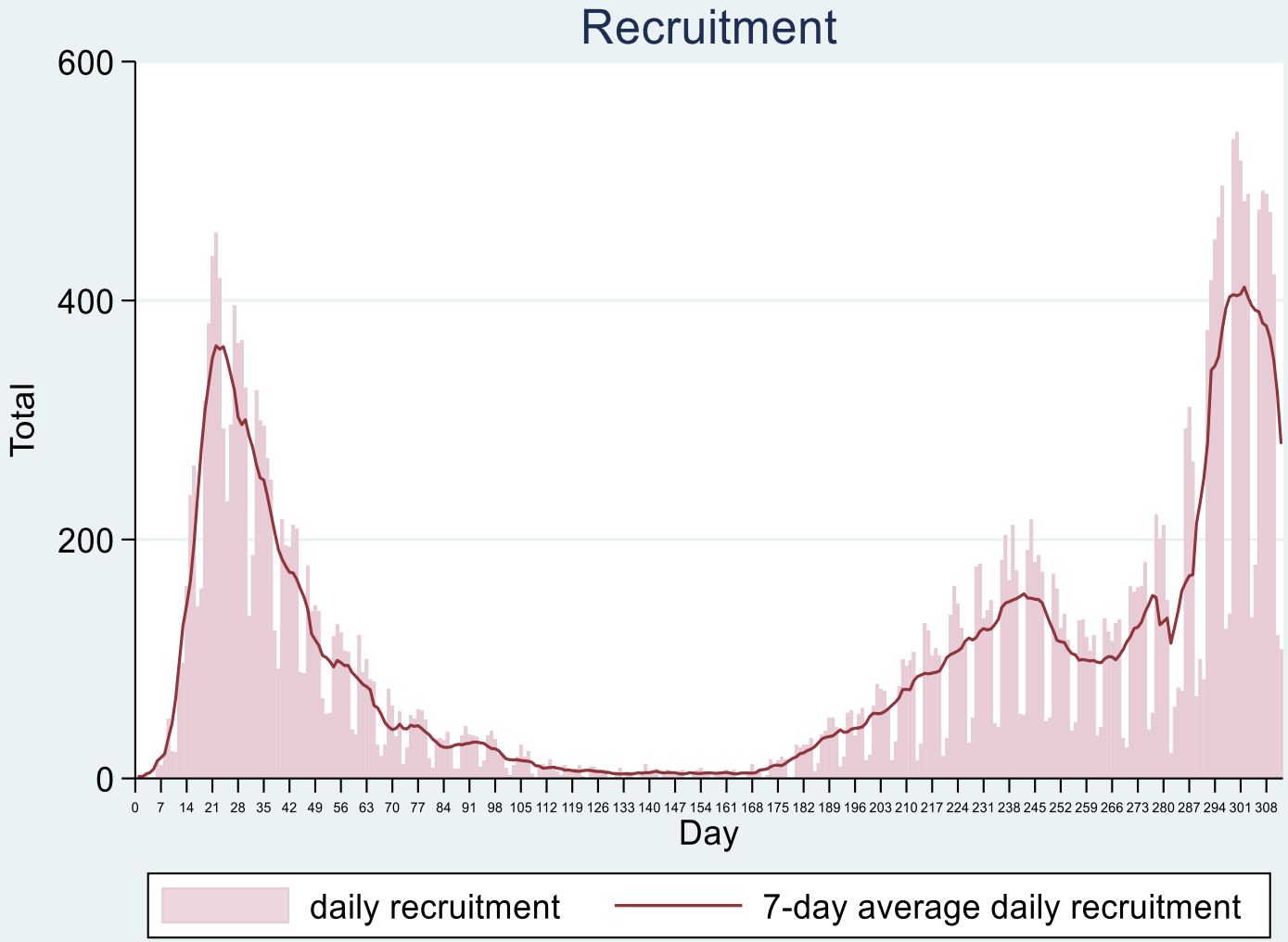
Active Sites	Recruiting Sites	Participants	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.
177	175	31569	4137	15407	9797





Current numbers in comparisons

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- Colchicine *vs* usual care: ~6800
- REGN-COV2 *vs* usual care: ~5500
- Aspirin *vs* usual care: ~9800

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

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TOCILIZUMAB

Tocilizumab in RECOVERY

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- Recruitment stopped on 25th January after completion of recruitment of 2000 people to tocilizumab and 2000 people to usual care alone

- Follow-up continues

- Use of tocilizumab within NHS should now either be randomisation in REMAP-CAP (where available) or as defined in the CAS alert on 8 January (https://www.cas.mhra.gov.uk/Help/CoronavirusAlerts.aspx)

Tocilizumab in RECOVERY

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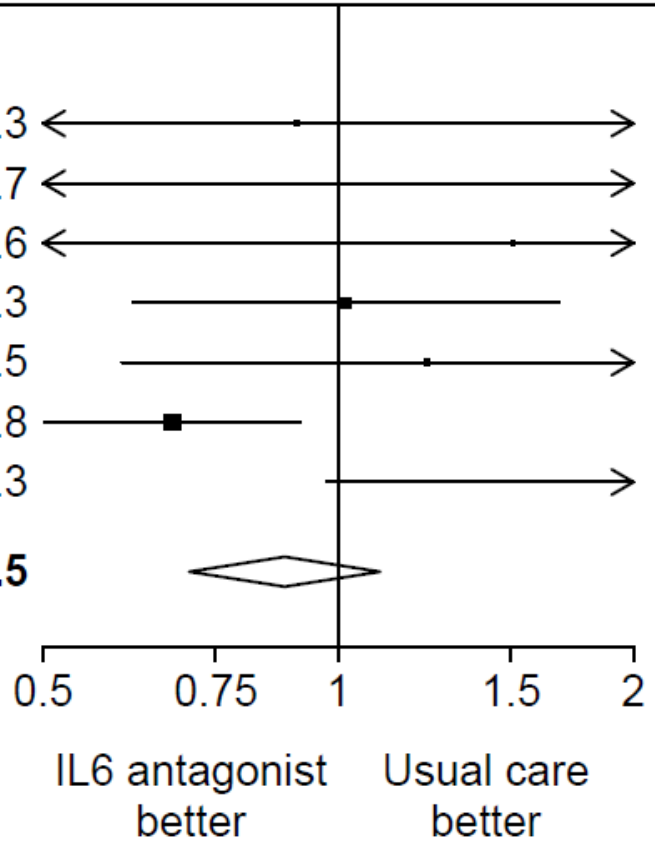
	IL6 antagonist	Usual care	O−E	V	RR (95% CI)
CORIMUNDO−TOCI	7/64 (10.9%)	8/67 (11.9%)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3%)	1/66 (1.5%)	0.6	0.7	2.17 (0.22−21.33)
BACC Bay	9/161 (5.6%)	3/82 (3.7%)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7%)	28/144 (19.4%)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4%)	11/128 (8.6%)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	108/395 (27.3%)	142/397 (35.8%)	−16.7	42.8	0.68 (0.50−0.91)
TOCIBRAS	14/65 (21.5%)	6/64 (9.4%)	3.9	4.3	2.51 (0.97−6.50)
All trials	**224/1288 (17.4%)**	**199/948 (21.0%)**	**−9.6**	**76.5**	**0.88 (0.70−1.10) p=0.27**



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CONVALESCENT PLASMA

Convalescent plasma

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- Recruitment stopped on 15th January on recommendation of the Data Monitoring Committee

  "For convalescent plasma, we saw no convincing evidence that further recruitment would provide conclusive proof of worthwhile mortality benefit either overall or in any pre-specified subgroup."

- This decision was based on about 1800 deaths, but due to speed of recruitment there are several thousand participants without complete follow-up

- Analysis of recipient and donor samples also continues

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REGN-COV2

REGN-COV2

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- Nearly 5000 people in comparison to date
- Other data on REGN-COV2 suggests the biggest effect might be expected in antibody negative patients (but these cannot be identified reliably on admission)
- Regeneron have agreed to provide an additional 4000 doses so comparison can expand to 6000 vs 6000 (in order to recruit sufficient antibody negative patients)

Antibody levels from first 8295 participants

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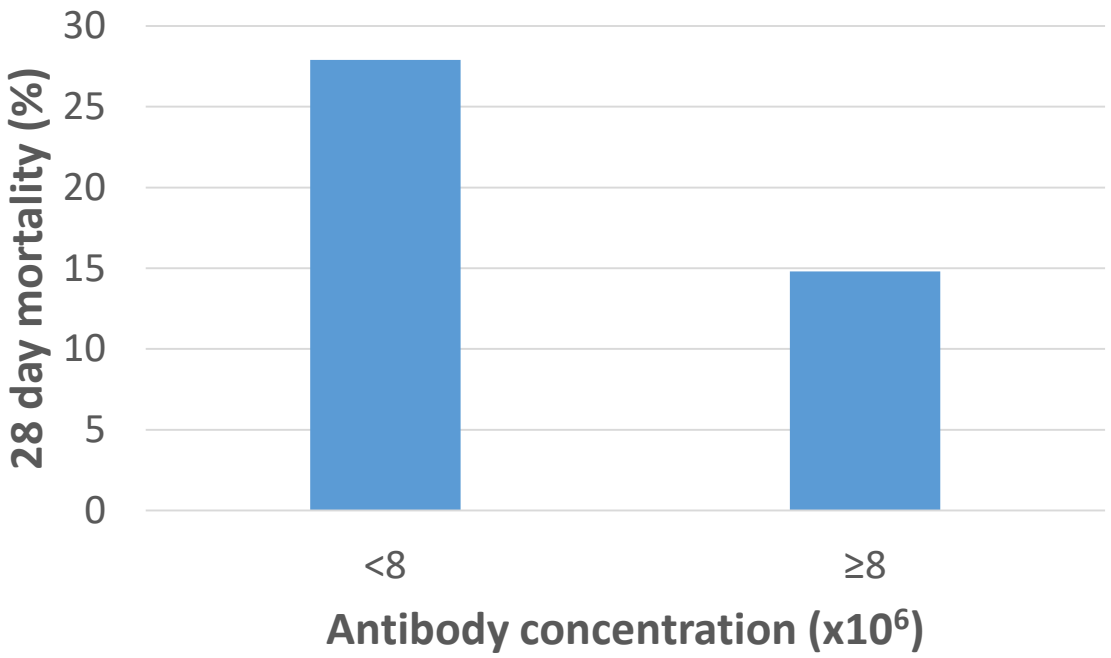
Baseline antibody level and risk of death



Baseline antibody level by arm

Recipient concentration	REGN-COV2	Usual care
Available	58%	55%
Missing	42%	45%

Serum samples

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- **All** participants entering REGN-COV2 comparison 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**

Antibody-based therapies and vaccination

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- Receipt of ‘passive’ antibodies (ie, convalescent plasma or REGN-COV2) might reduce efficacy of vaccination

- JCVI have not made a determination yet, but US CDC does recommend a 90-day period in-between receiving passive antibodies and being vaccinated

- We have asked you to:
  - Inform current participants of this (and include information in discharge summaries)
  - Send text of letter to patients who have received antibody-based therapy in last 90 days

- We will add information to next version of PIS/ICF

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COLCHICINE

Colchicine

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- COLCORONA trial randomised 4488 outpatients with COVID-19 between colchicine (similar dosing to RECOVERY) and placebo
- Primary outcome: hospitalisation or death
- Preliminary results suggest non-significant 21% reduction in risk
  - In subgroup of 4159 patients with positive nasopharyngeal PCR test the results are significant
  - In this subgroup, hospitalisation reduced by 25% and death by 44%

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OTHER RECENT TRIAL RESULTS

Anticoagulation

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- Recent report from REMAP-CAP says that therapeutic anticoagulation is of benefit among patients not requiring organ support

- Results contrast with those among sicker patients (requiring organ support) where trials stopped for futility or harm

- No impact on RECOVERY aspirin comparison (pending full results)

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NEXT VERSION OF PROTOCOL

Baricitinib in COVID-19

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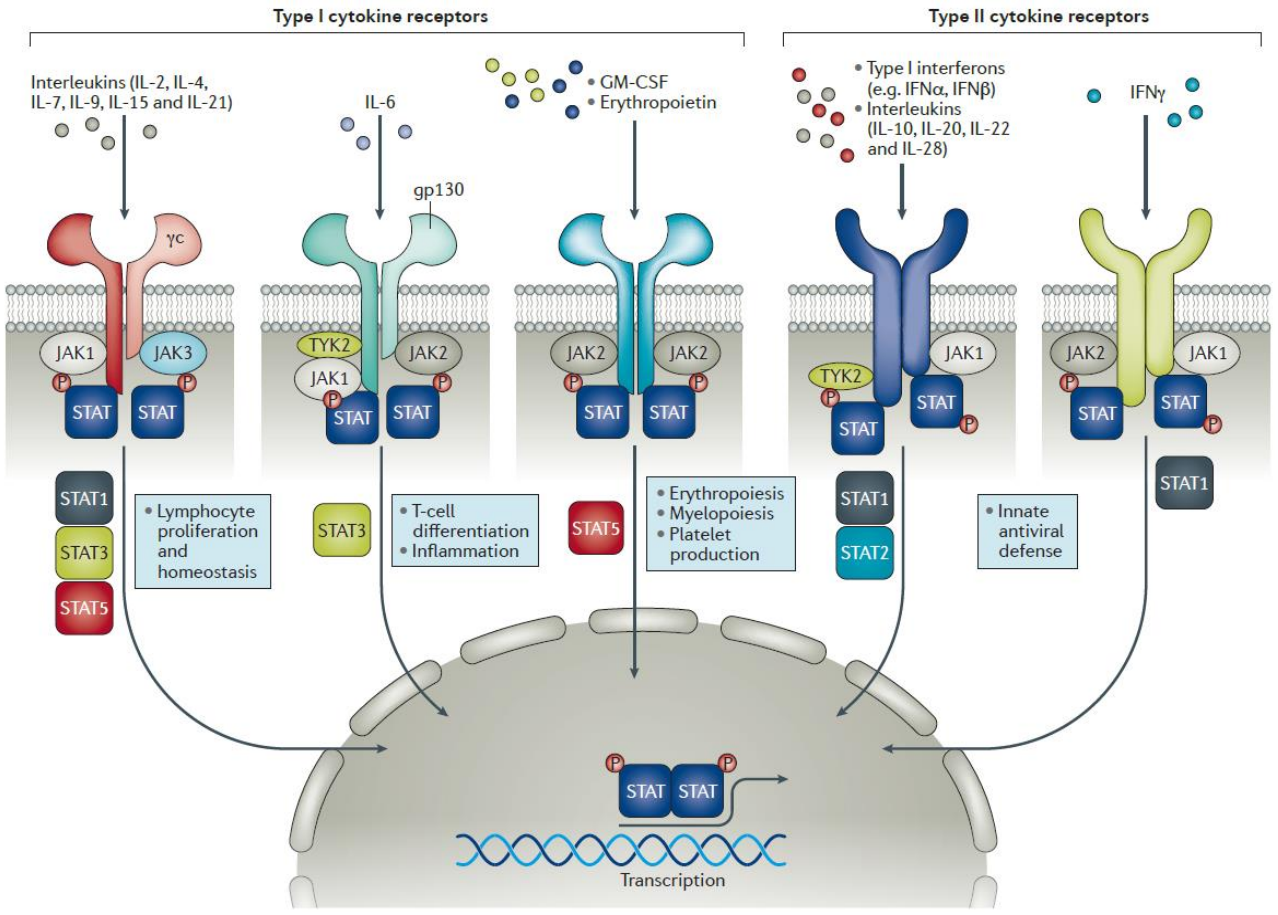
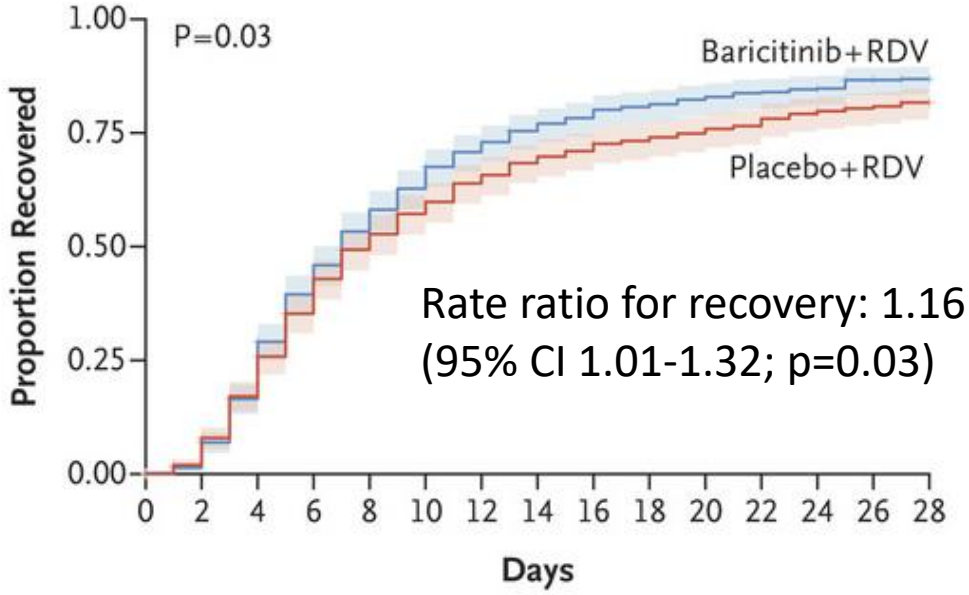
- JAK proteins work with STAT proteins to transmit cytokine signals from outside the cell to the nucleus and hence gene transcription

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



ACTT-2 results



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)

Next design (adults)

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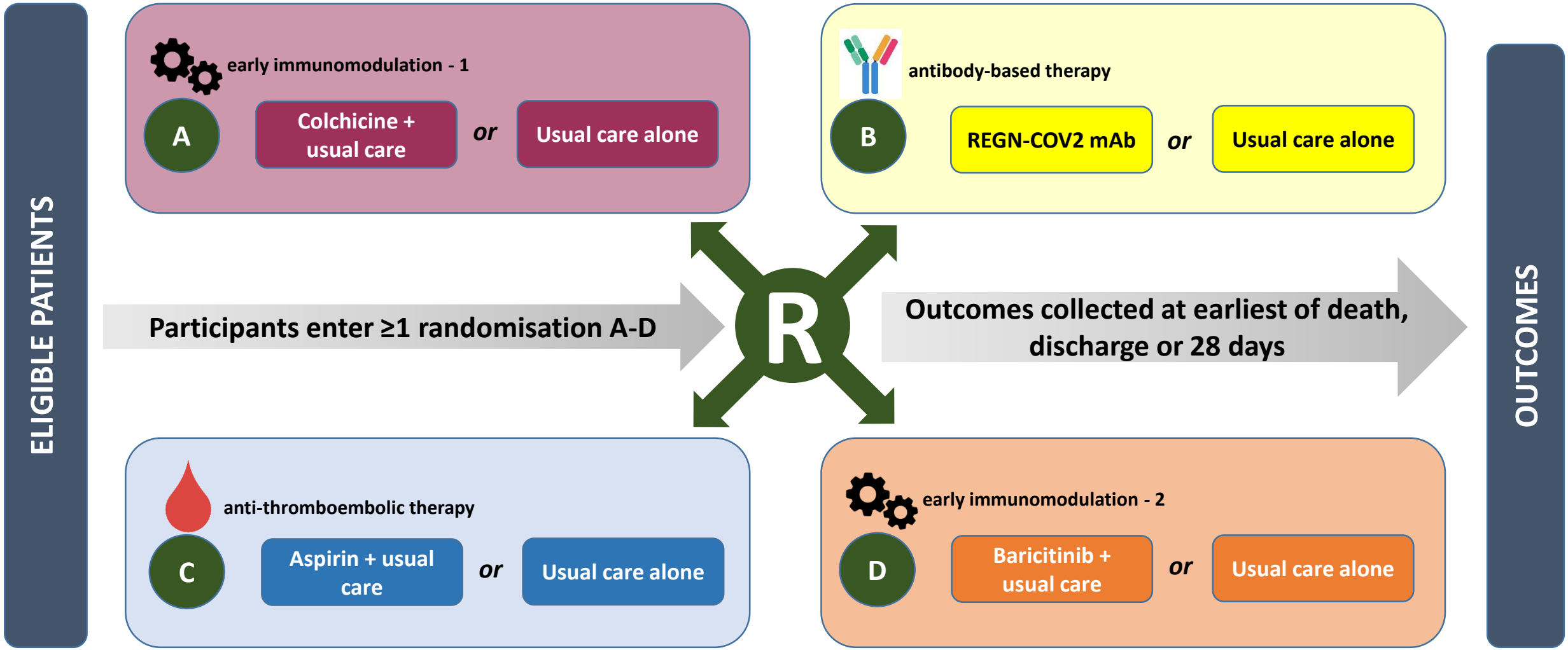

Baricitinib in RECOVERY

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- Dose: 4 mg (one tablet) once daily by mouth/NG tube for 10 days (or until discharge if sooner)

- Contraindicated in pregnancy → all women of child-bearing potential will now require pregnancy test (or if unavailable/declined will be excluded from baricitinib and colchicine arms)

- Should not be given if tocilizumab already given *or* definitely planned in next 24 hours

Baricitinib in RECOVERY

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- **Contraindications:**
  - Pregnancy
  - eGFR <15 mL/min/1.73m^2 (including those on dialysis/haemofiltration)
  - Neutrophil count <0.5 x10^9/L
  - Active TB infection
  - Has received tocilizumab or planned in next 24 hours

- **Cautions:**
  - Dose reduction for kidney impairment
    - eGFR ≥30 <60 mL/min/1.73m^2: 2 mg once daily
    - eGFR ≥15 <30 mL/min/1.73m^2: 2 mg alternate days
  - Dose should be halved if taking probenecid

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

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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.

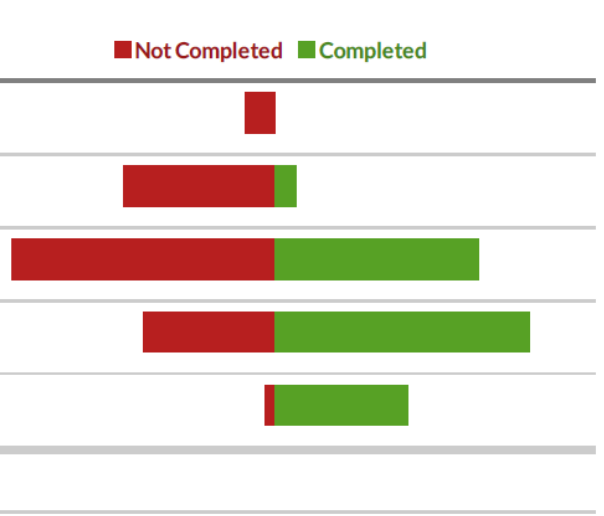
Completeness of follow-up

- Weekly reminders highlighting participants randomised >28 days ago without complete form

- NB 72h antibody safety forms are <u>no longer required</u>

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 – reminder

- 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

- please remember for the mild cases a key comparison is randomisation 1: SOC vs IVIG vs high dose methyl pred

- At the moment there is no option for respiratory phenotype for children 44 weeks – <=11 years or <40 Kg.

Paediatric RECOVERY 26th Jan 2021

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)

RESPIRATORY PHENOTYPE – RANDOMISATION 1

- Neonates <44 weeks gestational age
  - HYDROCORTISONE
- 44 weeks – 2 years
  - NO CURRENT TREATMENTS – DO NOT RANDOMISE TO RECOVERY AT PRESENT
- >=2 years
  - BARICITINIB
  - New guidance document will address practical issues such as mixing with juice/squash, NG administration (OK), NJ administration (TBC), how to dose/administer given formulation etc

GENERAL

- Specific Bayesian analysis SAP 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.
- new guidance document v10 and training slide update in preparation

GENERAL

- Methyl prednisolone shortage due to use in adult ARDS
- Please contact your local pharmacy to secure stock for paediatric RECOVERY use
- New protocol will include dose for different corticosteroid but general feeling is that the MP supply should be adequate for use for children in RECOVERY at this stage.