Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

23rd February 2021

Agenda

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1. Introductions
2. Update on progress
3. Tocilizumab
4. REGN-COV2
5. Next version of the protocol
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

Current design (adults)

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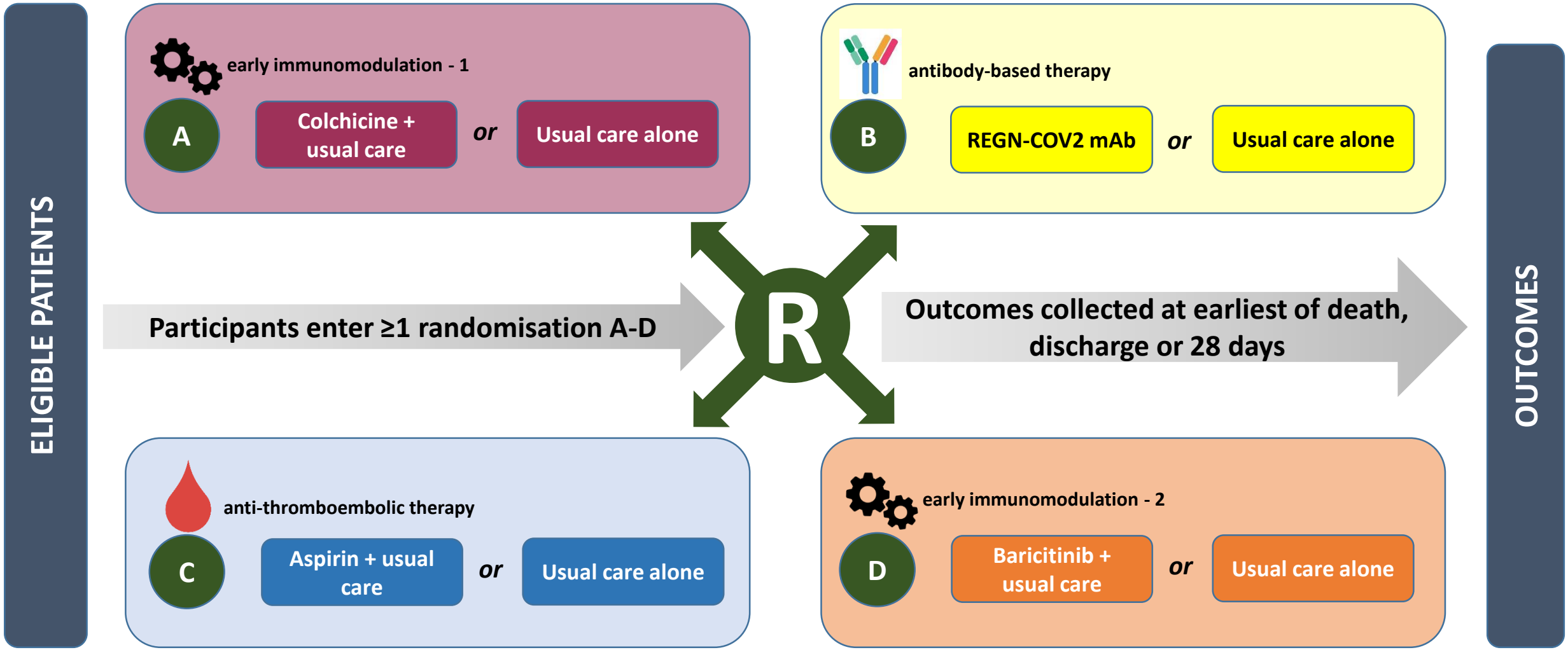

Recruitment by site and by time

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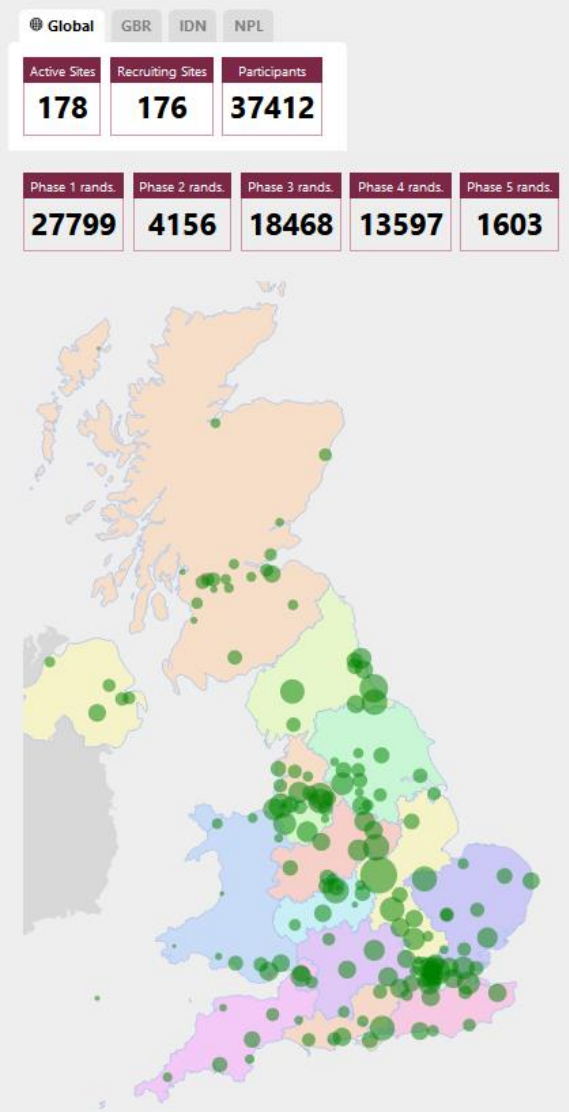

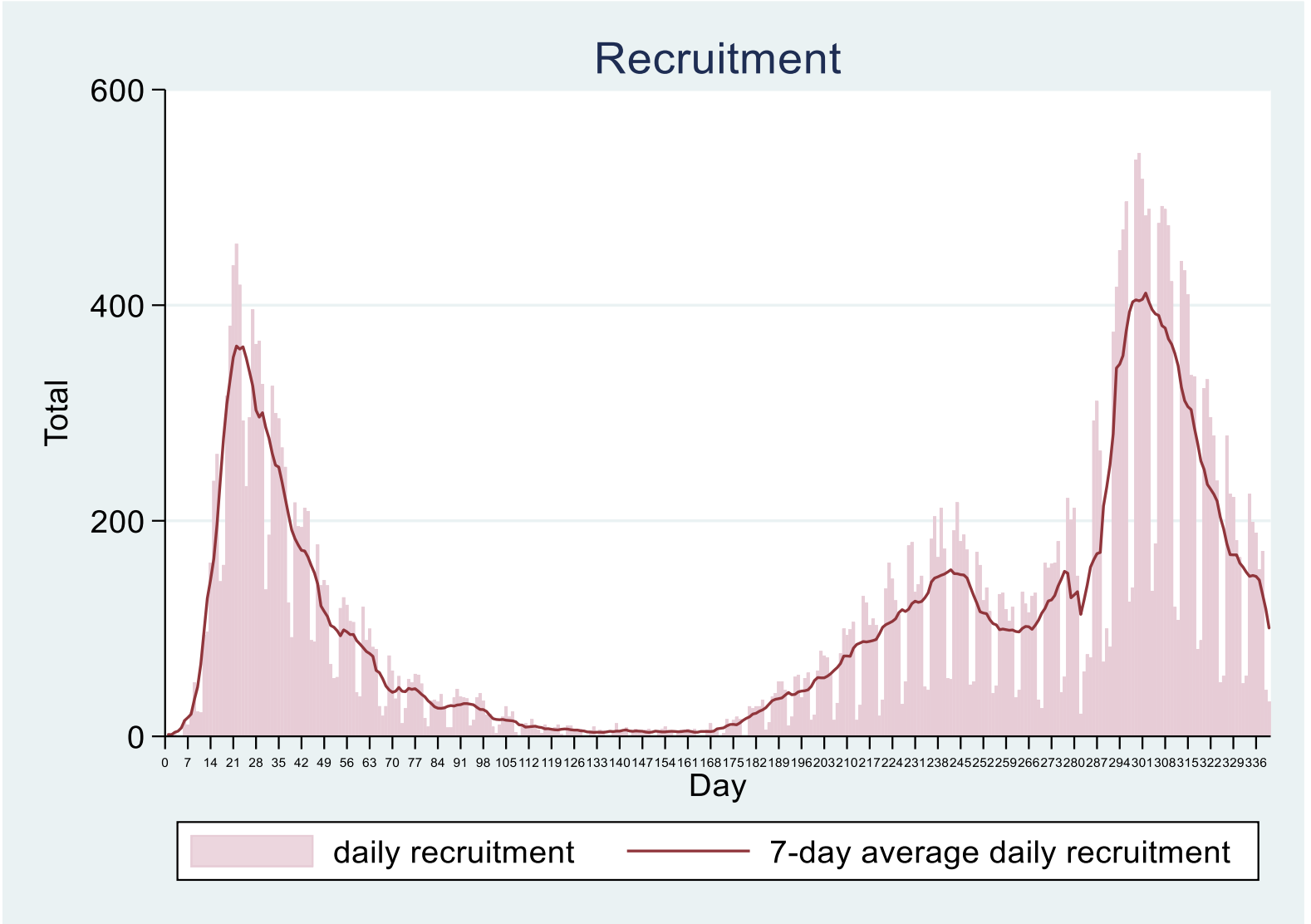

Current numbers in comparisons

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- Colchicine *vs* usual care: ~10,500
- REGN-COV2 *vs* usual care: ~8500
- Aspirin *vs* usual care: ~13,500
- Baricitinib *vs* usual care: ~1600

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

- Recruitment is really important as the epidemic shrinks: it is vital we get answers to our current comparisons before cases become uncommon. **This means the next few weeks are crucial.**

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TOCILIZUMAB

What we knew before RECOVERY

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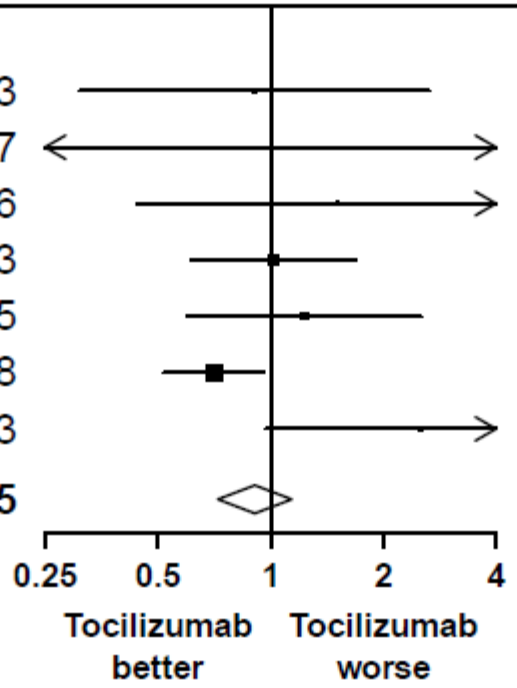
	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**



Tocilizumab in RECOVERY

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Baseline characteristic (mean [SD] or n [% or IQR])		Tocilizumab (n=2022)	Usual care (n=2094)
Age		63.3 (13.7)	63.9 (13.6)
Male sex		1335 (66)	1437 (69)
Ethnicity	White	1356 (67)	1426 (68)
	BAME	341 (17)	357 (17)
Days since hospitalisation		2 (1-5)	2 (1-5)
Respiratory support	No ventilatory support	935 (46)	933 (45)
	Non-invasive ventilation	819 (41)	867 (41)
	IMV or ECMO	268 (13)	294 (14)
CRP		143 (103-203)	144 (106-205)
Previous comorbidity		1100 (54)	1163 (56)

Primary outcome

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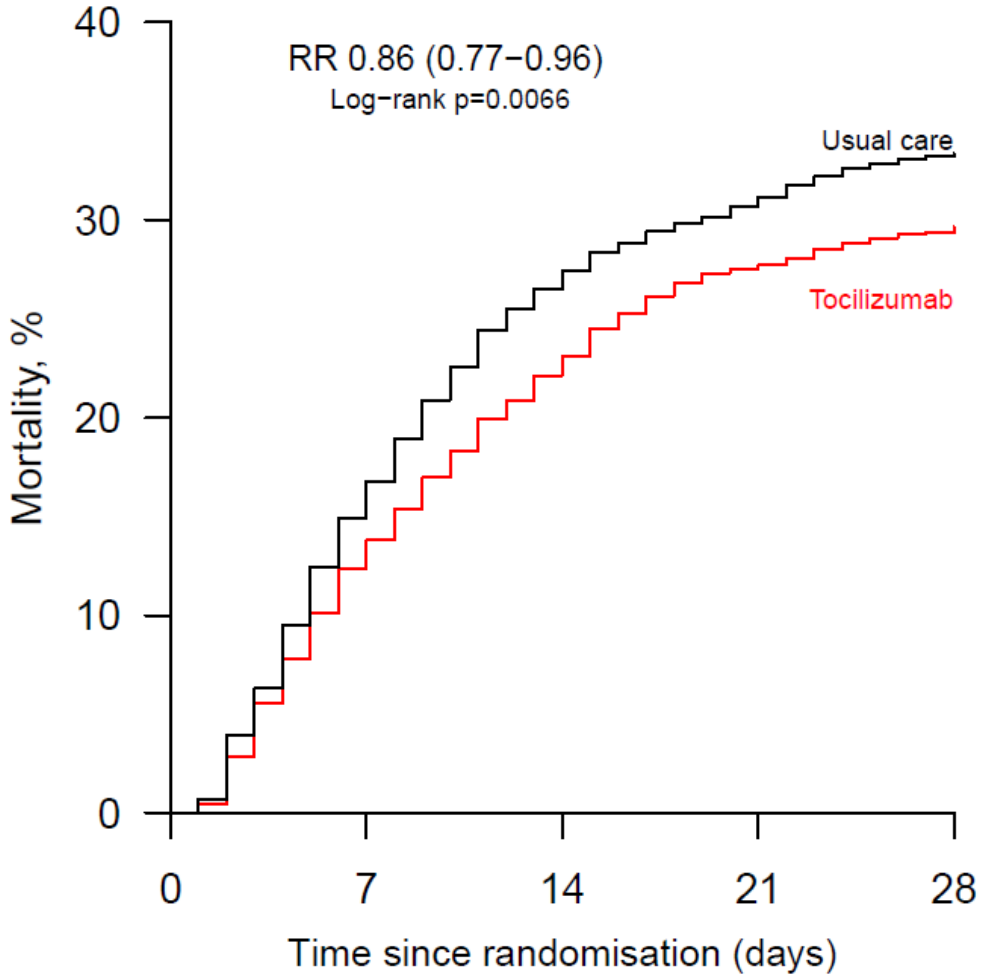

Number at risk					
Active	2022	1741	1553	1386	1284
Control	2094	1740	1518	1372	1250

Primary outcome, by subgroups

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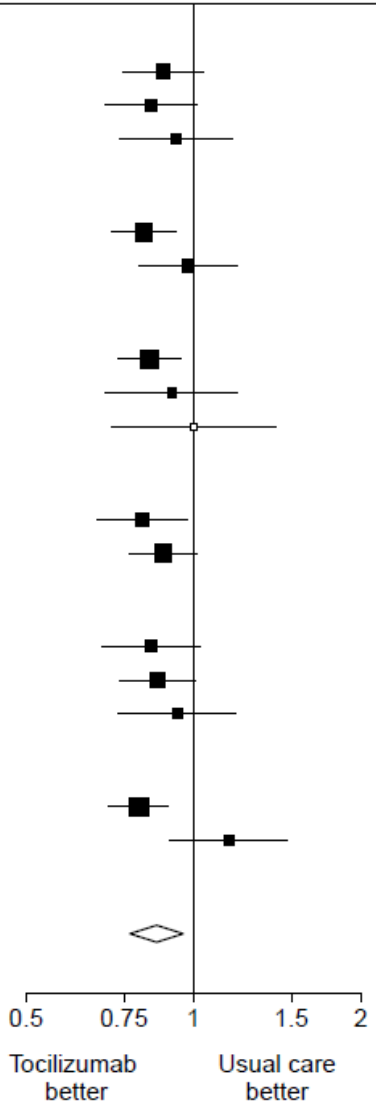
	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=0.1; p=0.80)			
<70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74–1.04)
≥70 <80	206/477 (43%)	234/480 (49%)	0.84 (0.69–1.01)
≥80	134/213 (63%)	171/260 (66%)	0.93 (0.74–1.17)
Sex (χ^2_1=2.2; p=0.14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71–0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80–1.20)
Ethnicity (χ^2_1=0.3; p=0.56)			
White	429/1356 (32%)	519/1426 (36%)	0.83 (0.73–0.95)
Black, Asian, or Minority Ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69–1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71–1.41)
Days since symptom onset (χ^2_1=0.6; p=0.46)			
≤7	210/668 (31%)	245/660 (37%)	0.81 (0.67–0.97)
>7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77–1.01)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69–1.03)
Non−invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74–1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73–1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77–0.96) p=0.0066**



Secondary outcomes

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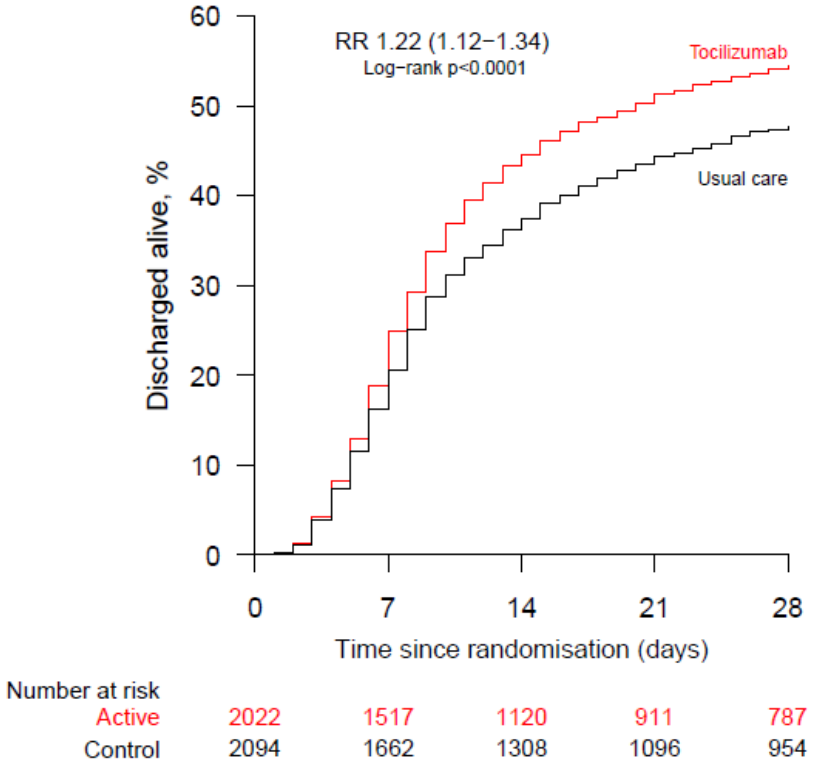
Time to discharge alive within 28 days



Receipt of IMV or death

Outcome		TCZ	Usual care	RR (95% CI)	p
	IMV	215	273	0.81 (0.68-0.95)	0.01
	Death	471	552	0.88 (0.79-0.97)	0.01
IMV or death		**571**	**687**	**0.85 (0.79-0.93)**	**0.0005**

Totality of evidence to date

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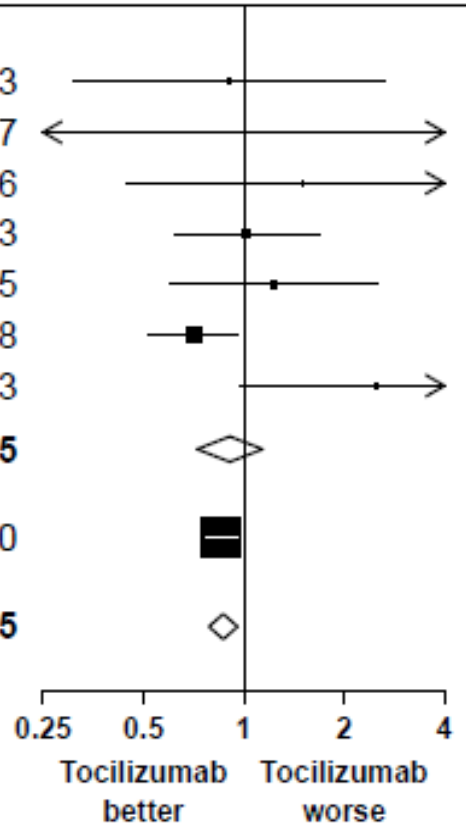
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



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REGN-COV2

REGN-COV2

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- 8500 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)
- Aim is to recruit 12,000 participants

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**

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NEXT VERSION OF PROTOCOL

Dimethyl fumarate

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- Licensed for long-term oral immunomodulatory therapy in relapsing-remitting multiple sclerosis and plaque psoriasis
- Proposed modes of action: inhibition of NLRP3 inflammasome activation + anti-viral effect against SARS-CoV-2 *in vitro*
- Immunomodulatory agents have produced best therapeutic results for patients with COVID-19 so far
- Limited current clinical evidence with DMF in COVID-19: no other clinical trials worldwide

Early Phase assessment

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- UK CTAP request for RECOVERY to perform early phase assessment of DMF
- Additional information is required before considering large-scale assessment of impact on mortality
- Estimated to need 400 participants
- Review results for decision as to whether to include in main trial

Early Phase assessment

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- Many study procedures as for main trial:
  - Eligibility criteria
  - Consent process and Patient Information Sheet (updated to include DMF information)
  - Randomisation website – DMF included in Part A randomisation for selected sites
  - SSAR reporting

- Specific outcome measures and follow-up form
  - Primary outcome:
    - Non-invasive, bedside measure of patient oxygenation: the S/F_{94} ratio
    - Similarities to PaO_2:FiO_2 ratio but not requiring arterial blood gases
  - Other outcome measures:
    - Simple ordinal scale clinical progression score
    - Laboratory results: CRP, Creatinine, ALT/AST
    - Incidence of adverse side effects and treatment adherence

Design including DMF

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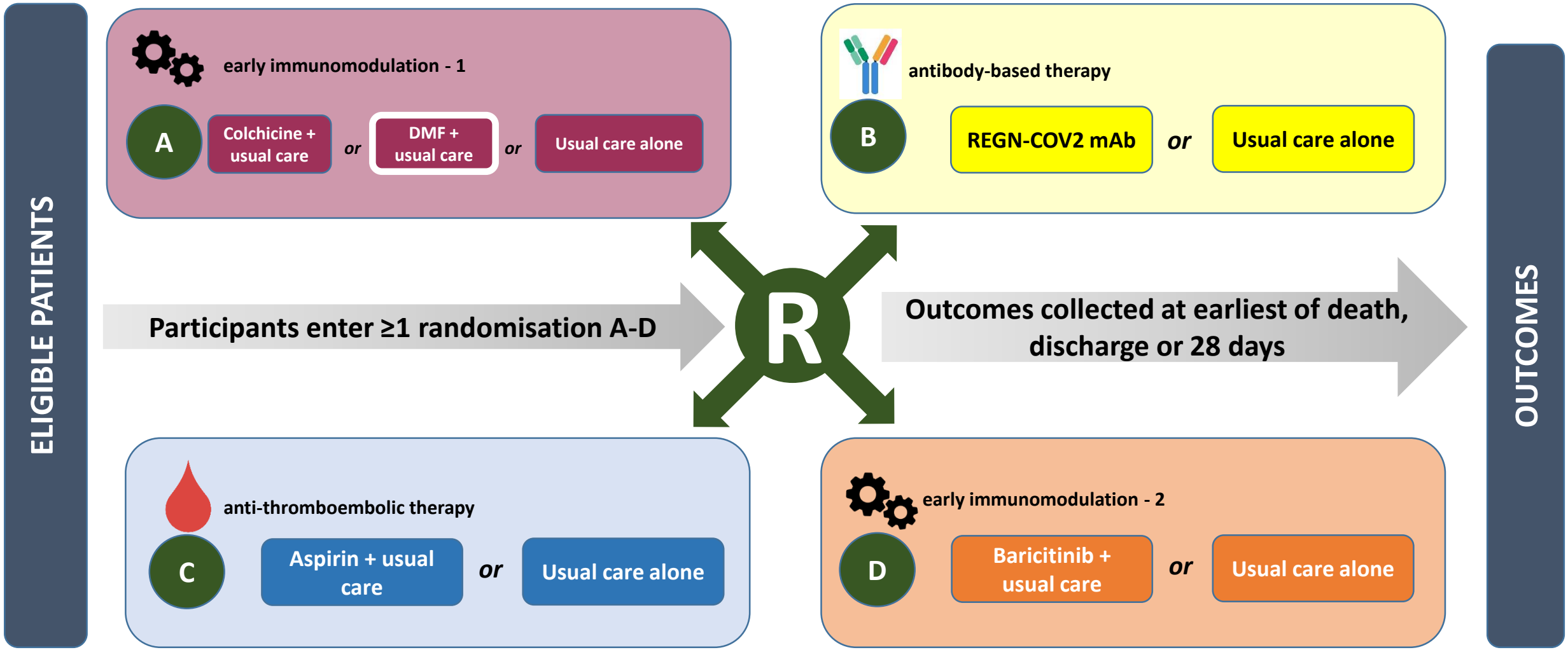

Plans

- **Site selection:**
  - Initial plan is to roll out this in 3-4 local CRNs
  - Depending on progress and experience, we may contact other sites

- **Drug supply:**
  - Under discussion with DHSC and NHSE

- Aim to start no later than next week

Baricitinib in RECOVERY

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- Excellent progress to date

- Change to eligibility criteria around previous or planned tocilizumab use:
  - **No longer contraindicated**
  - May be used together according to clinician discretion
  - Additional information about non-COVID infections will be captured on Follow-up form from now on

- The changes go ‘live’ from **Wednesday**

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TRIAL PROCEDURES

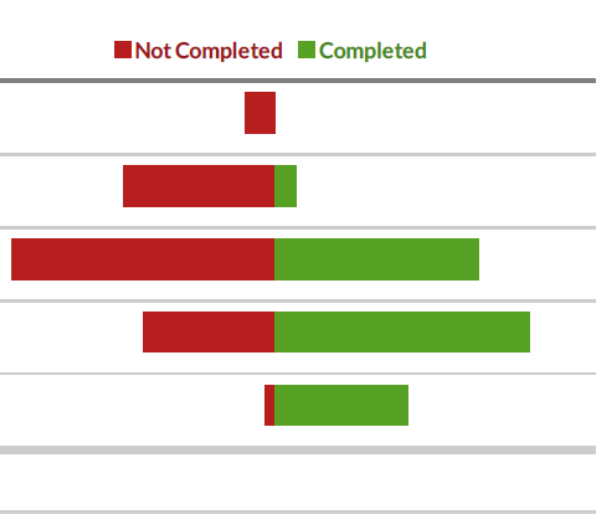
Completeness of follow-up

- 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 need a focus on maximising recruitment now to have answers of national and international relevance
- THANK YOU!