Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

2nd November 2021

Agenda

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1. Introductions
2. Update on progress
3. REGEN-COV
4. Dimethyl fumarate
5. Baricitinib
6. Empagliflozin
7. Trial procedures including changes to consent process
8. Future plans
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

Planned design (adults)

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ELIGIBLE PATIENTS

early immunomodulation - 1

A — Dimethyl fumarate *or* Usual care alone

SGLT-2i comparison

F — Empagliflozin *or* Usual care alone

Participants enter ≥1 randomisation A, D, E or F

R

Outcomes collected at earliest of death, discharge or 28 days

OUTCOMES

For hypoxic patients only:

corticosteroids

E — High-dose corticosteroids *or* Usual care alone

early immunomodulation - 2

D — Baricitinib *or* Usual care alone

Recruitment by site and by time

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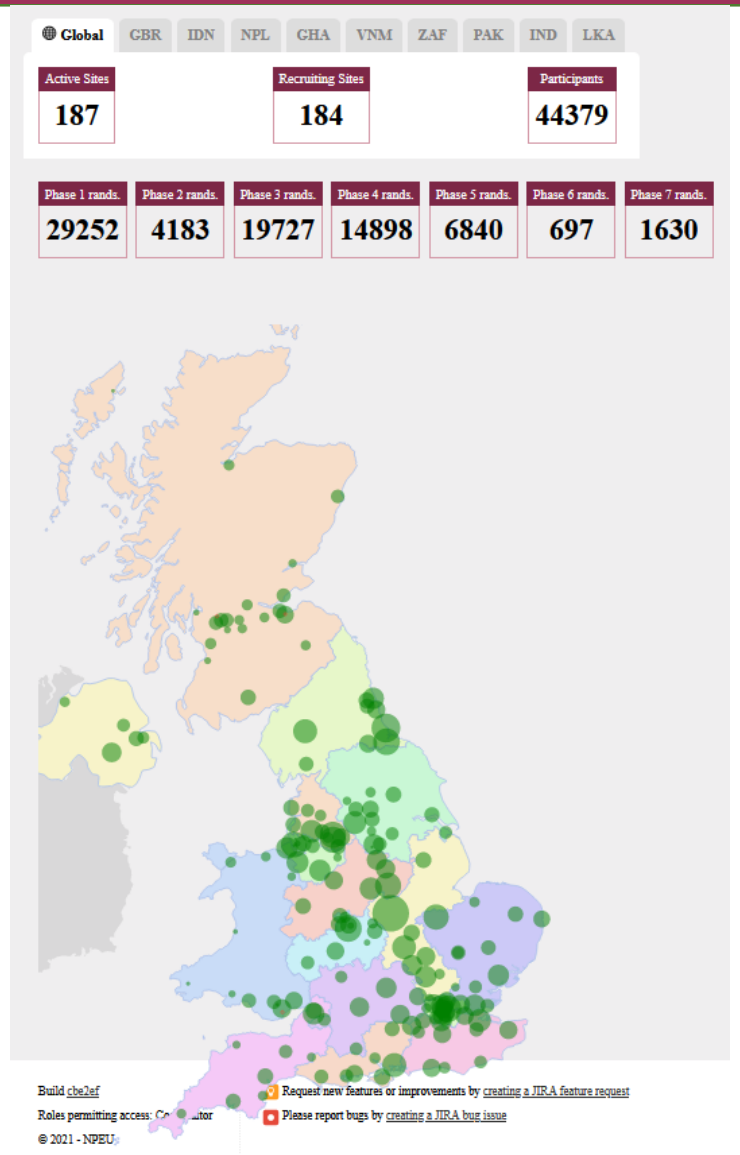

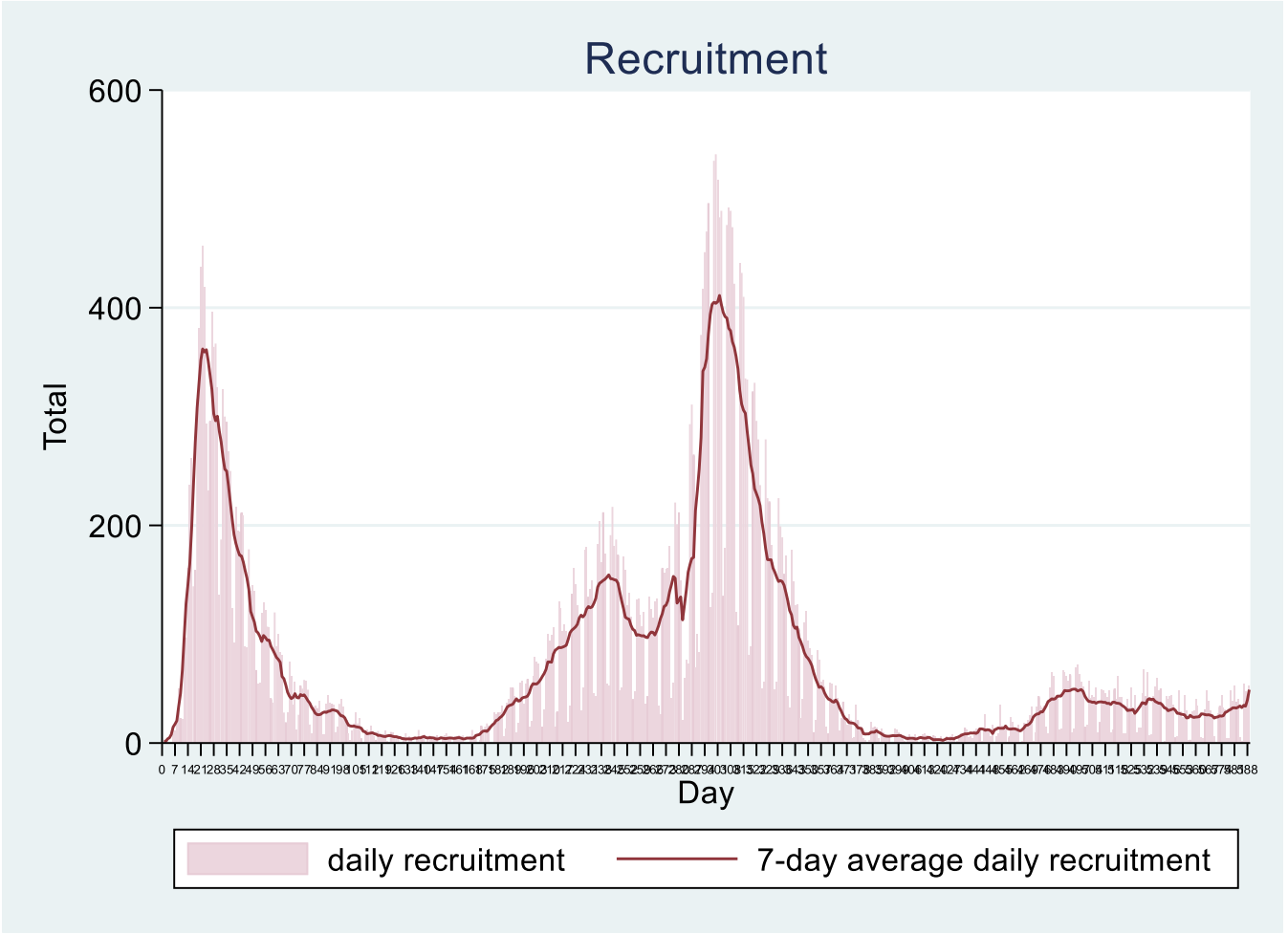

Current numbers in comparisons

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- Baricitinib *vs* usual care: ~6800
- Dimethyl fumarate *vs* usual care: 640
- Empagliflozin: ~1600
- High-dose corticosteroids: ~700

Recruitment

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- Many staff will be returning to previous research studies, but please do ensure that your site continues to have a strategy to identify, invite and recruit patients presenting with COVID-19

- Numbers being admitted is fairly static, but remains important to offer trial to as many as possible

- Proportion of admitted patients has fallen from average of 10% to about 3%

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REGEN-COV (CASIRIVIMAB AND IMDEVIMAB)

REGEN-COV

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- Results published online earlier this year; currently under peer-review
- REGEN-COV = REGN-COV2 = Ronapreve = Casirivimab and imdevimab
- Analysis plan slightly different to previous analyses: focus on seronegative participants because of earlier trials with REGEN-COV showing effects different among seronegative and seropositive individuals

Primary outcome, by serostatus

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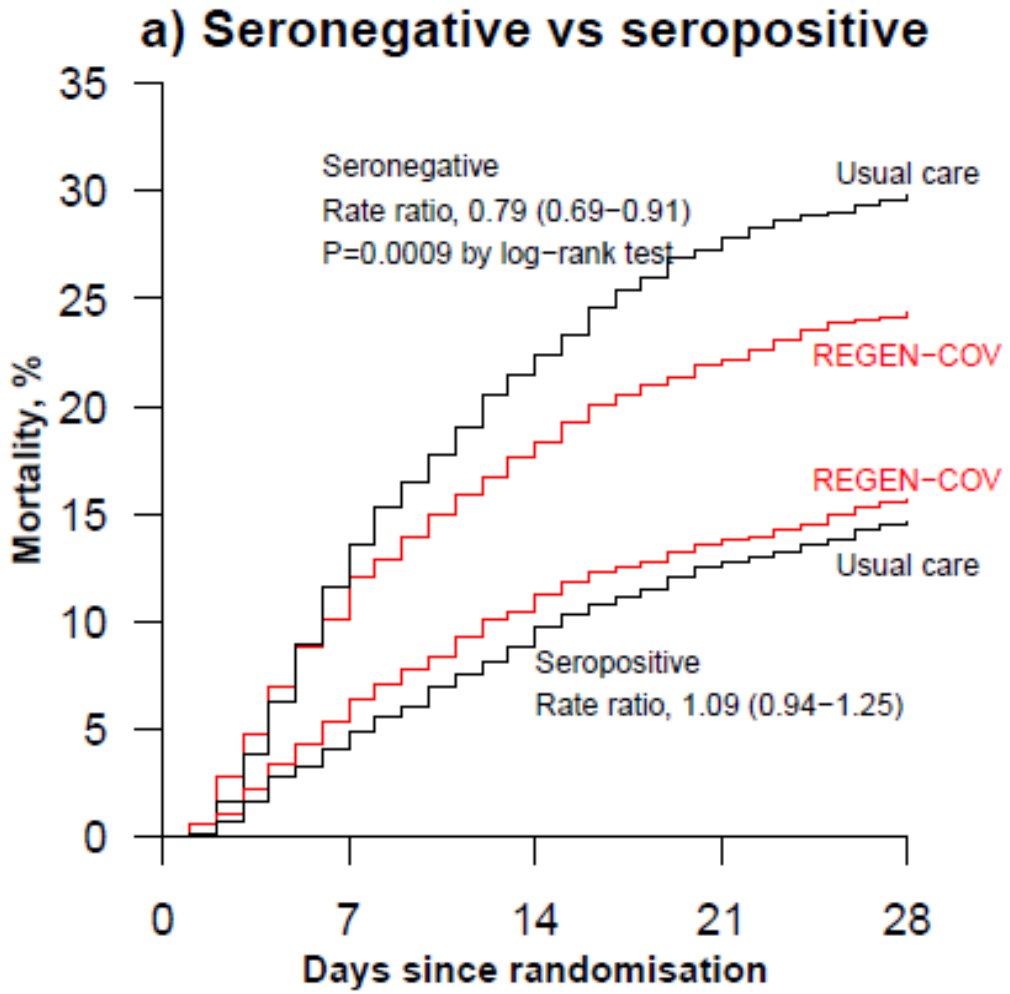

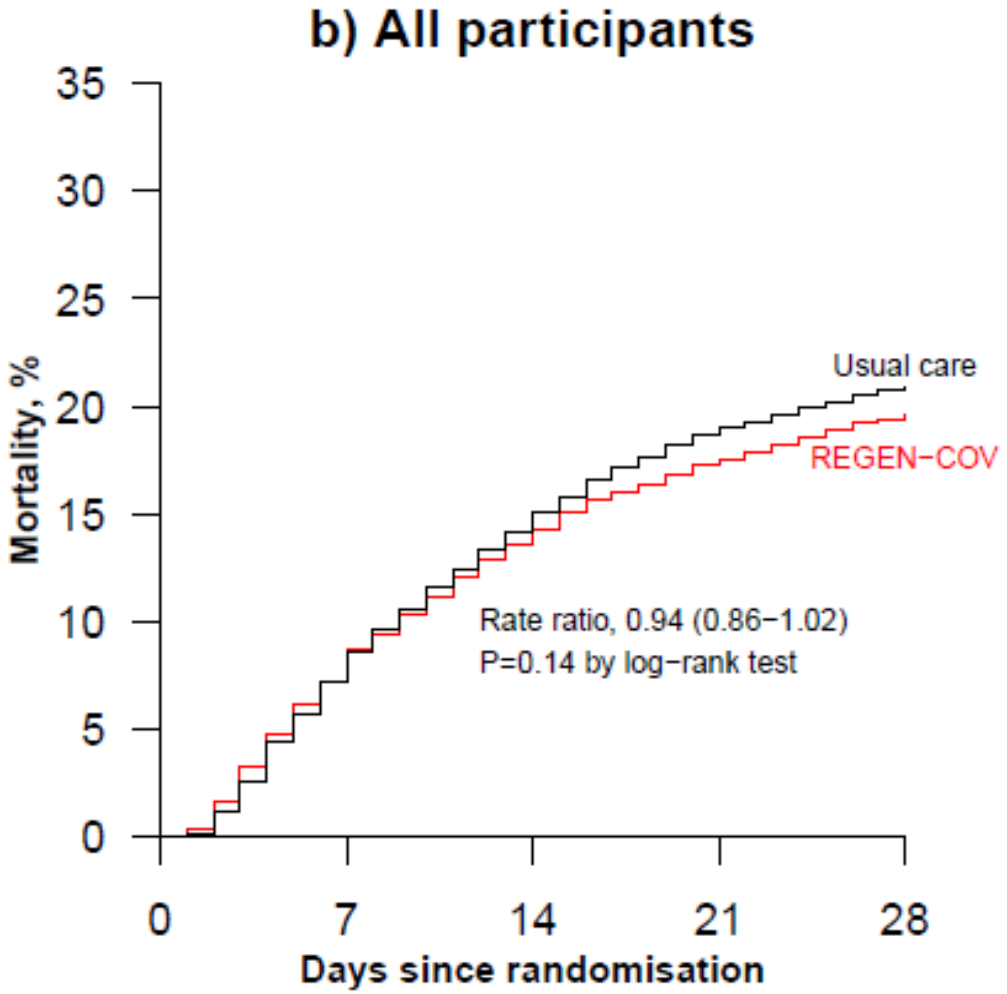

Impact

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- REGEN-COV has been licensed by MHRA for treatment of outpatients
- NHS England are preparing guidance on use (off license initially) in hospitalised patients, based on RECOVERY results
- RECOVERY results will be submitted to international regulators to update the license to include hospitalised patients

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DIMETHYL FUMARATE

Dimethyl fumarate

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- Recently added to protocol and has been piloted at some sites

- Includes extra data collection on:
  - S/F_{94} (measurement of oxygenation function of lungs)
  - WHO scale
  - Lab results
  - Tolerability of DMF

- Sites can still express an interest in participating in this arm

Dimethyl fumarate

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- Analysis of blinded data so far shows that duration of admission has shortened, so many participants do not have day 5 S/F_{94} measurement recorded as they have left hospital
- Some sites have not recorded measurements for participants in control arm. **All participants in DMF comparison (both on DMF and in usual care group) must have S/F_{94} measurements.**
- Protocol amendment has been made to change primary outcome to WHO score (which can account for discharge before day 5) and consequent increase in sample size to 700 participants

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BARICITINIB

Baricitinib in COVID-19

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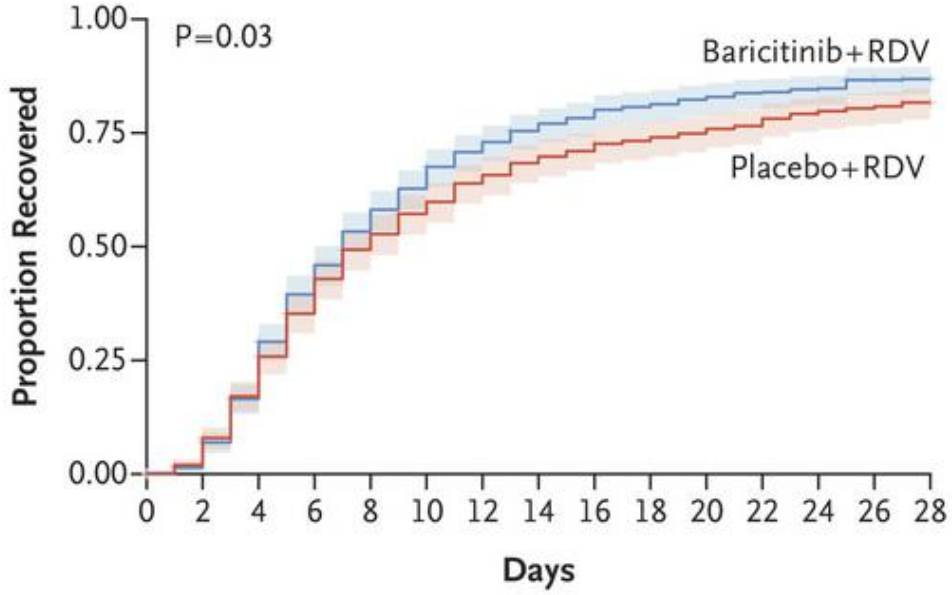
- JAK/STAT system is key to immune activation so modulating it may be beneficial

- Data from ACTT-2 show quicker time to recovery



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

Baricitinib in COVID-19

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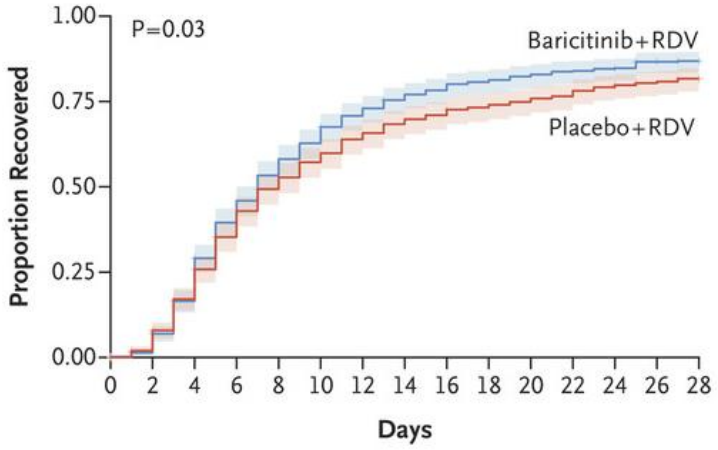
- JAK/STAT system is key to immune activation so modulating it may be beneficial
- Data from ACTT-2 show quicker time to recovery
- Data from COV-BARRIER show possible mortality benefit (and reassuring safety data)



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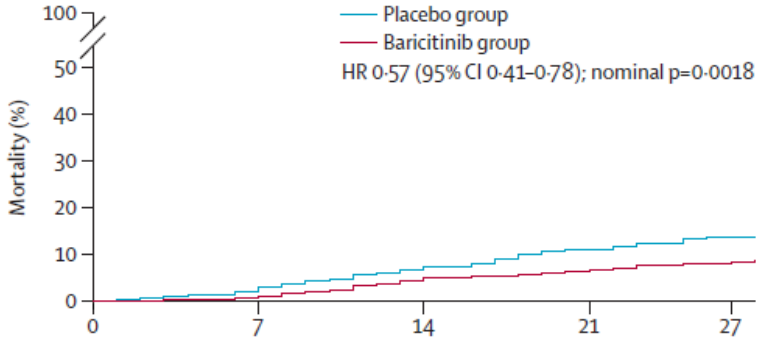

Number at risk (number censored)					
Placebo group	761 (0)	717 (20)	679 (28)	639 (40)	617 (44)
Baricitinib group	764 (0)	725 (30)	684 (44)	664 (50)	648 (55)

Baricitinib in RECOVERY

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- >6800 participants recruited to date
- Overall 28 day mortality rate is ~13% (compared to 20-25% earlier in pandemic)
- This means about 7500 participants are needed to identify a 20% reduction (e.g. 13% to 10.5%) reliably

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EMPAGLIFLOZIN

SGLT-2 inhibitors and Empagliflozin (empa)

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- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)
- SGLT-2 = sodium-glucose co-transporter 2 and is the main process by which glucose filtered into the urine is reabsorbed by the kidney
- SGLT-2i were developed as treatments for diabetes because they can lower blood sugar
- In addition to lowering blood sugar they have also been found to reduce the risk of:
  - Atherosclerotic cardiovascular events (eg, myocardial infarction) in people with type 2 diabetes
  - Cardiovascular death in people with heart failure
  - Progression of chronic kidney disease in people with diabetes and CKD

SGLT-2i in COVID-19

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- SGLT-2i may have beneficial effects in COVID-19
  - Shift in energy metabolism from glucose (which SARS-CoV-2 may rely on) to lipids
  - Improve endothelial function
  - Anti-inflammatory effects

- DARE-19 trial compared dapagliflozin with placebo among 1250 patients hospitalised for COVID-19 with another ‘risk factor’ (eg, diabetes, cardiovascular disease)

SGLT-2i in COVID-19: DARE-19 results

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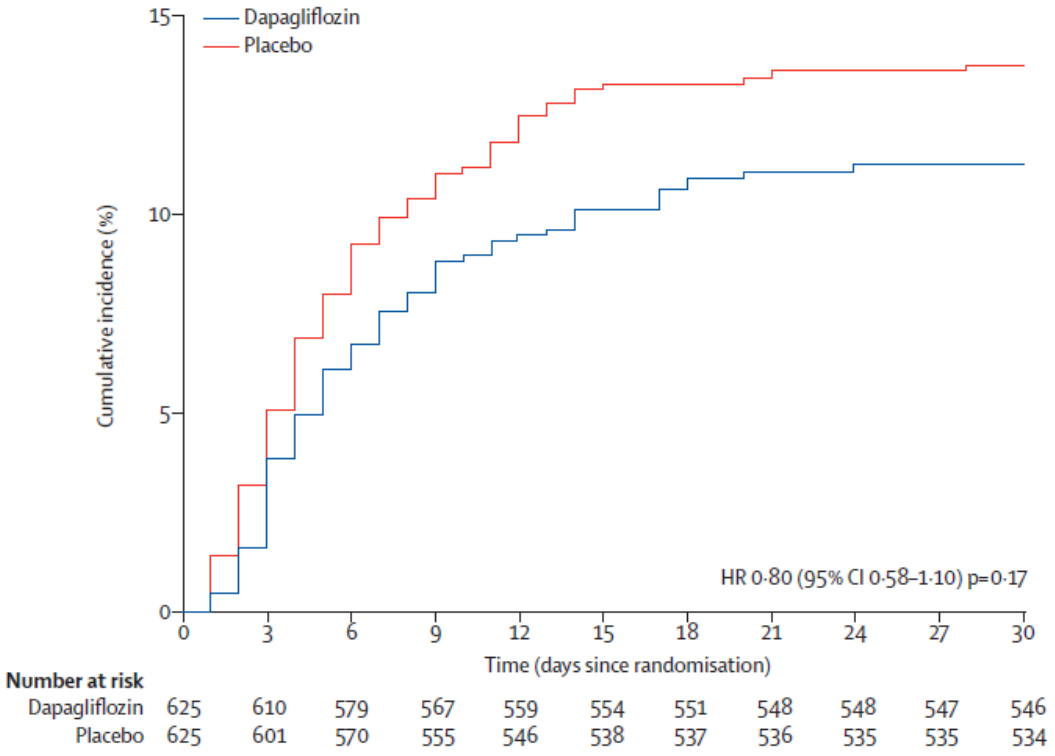
Primary outcome: organ failure or death

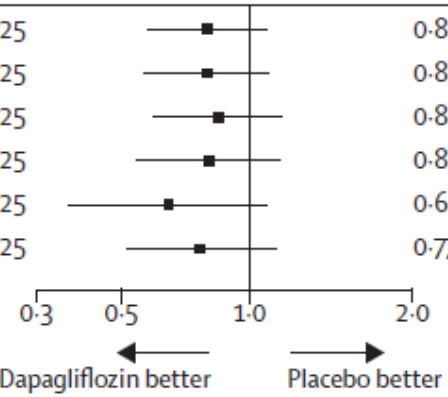


Number at risk

Dapagliflozin	625	610	579	567	559	554	551	548	548	547	546
Placebo	625	601	570	555	546	538	537	536	535	535	534

Primary outcome: components

	Dapagliflozin n/N	Placebo n/N	HR (95% CI)
Primary composite outcome	70/625	86/625	0·80 (0·58–1·10)
New or worsening organ dysfunction	64/625	80/625	0·80 (0·57–1·11)
Respiratory decompensation	58/625	70/625	0·85 (0·60–1·20)
Cardiac decompensation	47/625	58/625	0·81 (0·55–1·19)
Kidney decompensation	24/625	35/625	0·65 (0·38–1·10)
Death from any cause	41/625	54/625	0·77 (0·52–1·16)



Empagliflozin in RECOVERY

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- Available in all countries
- Separate factorial randomisation to others (so can be given in addition to other study treatment allocations)
- **Dose: 10 mg once daily for up to 28 days** (stopped at discharge if sooner)
- **Exclusions:**
  - Type 1 diabetes mellitus* or post-pancreatectomy diabetes mellitus
  - History of ketoacidosis
  - Current blood ketones ≥1.5 mmol/L (or urine ketones ≥2+)
  - Pregnancy or breast-feeding
  - (No exclusions around kidney or liver function)

  * If patient is only on insulin, consider carefully whether diabetes is type 1 and seek advice if necessary

Adverse effects of SGLT-2i

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- Mycotic genital infection (eg, vulvovaginal candidiasis or candidal balanitis)
  - Commonest adverse effect
  - Easily treated with topical antifungal eg, clotrimazole cream
- Hypoglycaemia
  - SGLT-2i do not cause hypoglycaemia unless given with insulin or insulin secretagogue (eg, sulphonylurea such as gliclazide)
- Volume depletion
  - SGLT-2i cause natriuresis and osmotic diuresis so care required with fluid balance

Adverse effects of SGLT-2i

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- Ketoacidosis
  - Defined as combination of both **ketosis** (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) and **metabolic acidosis** (bicarbonate <15 mmol/L)
  - Only occurs in people with diabetes
  - NB can occur with relatively normal blood sugar if on SGLT-2i

- Participants with diabetes should have regular checks of ketones
  - Twice daily blood ketones (or once daily urine ketones if blood ketone testing not available) or if clinical concern*
  - If ketosis (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) develops:
    - Ensure adequate fluid and calorific intake
    - Refer to local diabetes team (if available) and follow local protocols for ketosis
    - Consider increasing insulin (if participant on it) and withholding empagliflozin while ketotic

* Blood ketones are quantitative whereas urine ketones only semi-quantitative

Additional outcomes to be collected

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- Ketoacidosis: defined as combination of both **ketosis** (blood ketones ≥1.5 mmol/L or urine ketones ≥2+) and **metabolic acidosis** (bicarbonate <15 mmol/L
- Severe hypoglycaemia i.e. hypoglycaemia causing a reduced conscious level requiring another person to recover
- Hyperglycaemia requiring new insulin or with hyperosmolar state
- Peak creatinine during admission

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TRIAL PROCEDURES

Consent

- RECOVERY allows consent to be given:
  - By patient (either in person or witnessed)
  - By legal representative (either relative or – if not available in person – independent doctor) if patient does not have capacity

- Some issues have been identified with consent by legal representative:
  - Original protocol required consent to be sought from such patients if they regain capacity
  - Doctors acting as legal representative not always independent (as defined by regulations)

Consent

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- We strongly recommend that sites identify a small group of doctors to act as legal representatives
  - Such individuals can complete trial training (so they understand trial) but should not be involved in trial in any other way
  - Number of such individuals can be determined depending on the site size and organisation

Consent

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- Participants whose consent was given by legal representative should be informed of their participation prior to discharge
  - From 8 November (when protocol V18.1 goes 'live') such participants do **not** need to give written consent
  - They **do** need to be given written information (e.g. PIS) about the trial which informs them of their rights and how to exercise them
  - **Please** document in medical notes that such information has been provided

- Please also include participation in RECOVERY in discharge summaries

Consent monitoring

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- It has always been intention to monitor consent process, but delayed until now

- All sites will be asked to review a random sample of 20-40 consent forms
  - Precise number depends on number recruited at site
  - Sites who recruited ≤20 patients will review all

- CCO in Oxford will do random selection and provide tool for completion

Consent training

- Consent training materials will be updated

- **All staff** who will continue to obtain consent for RECOVERY will be required to complete new training (and online confirmation form)

Newsletters

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- Earlier this year we wrote to ~8000 participants to inform them of trial results etc

- We will soon mail all participants to:
  - Inform them of trial results and their impact
  - Remind them of their participation and how to withdraw if they wish

- CCO may receive contact from participants. REC were keen that they could speak to site team if they wish, so some contacts may be passed to site PIs if requested by participants

Completeness of follow-up

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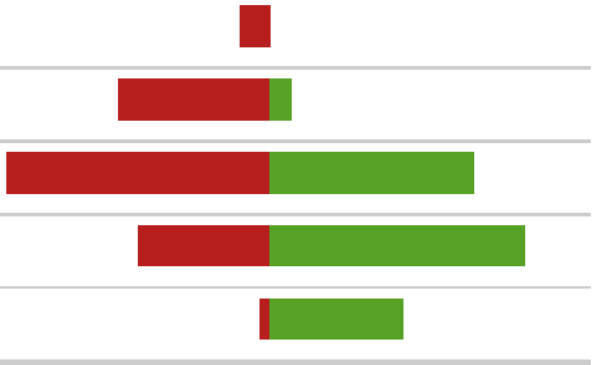
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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**



- Please keep filling them in!

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FUTURE PLANS

RECOVERY international

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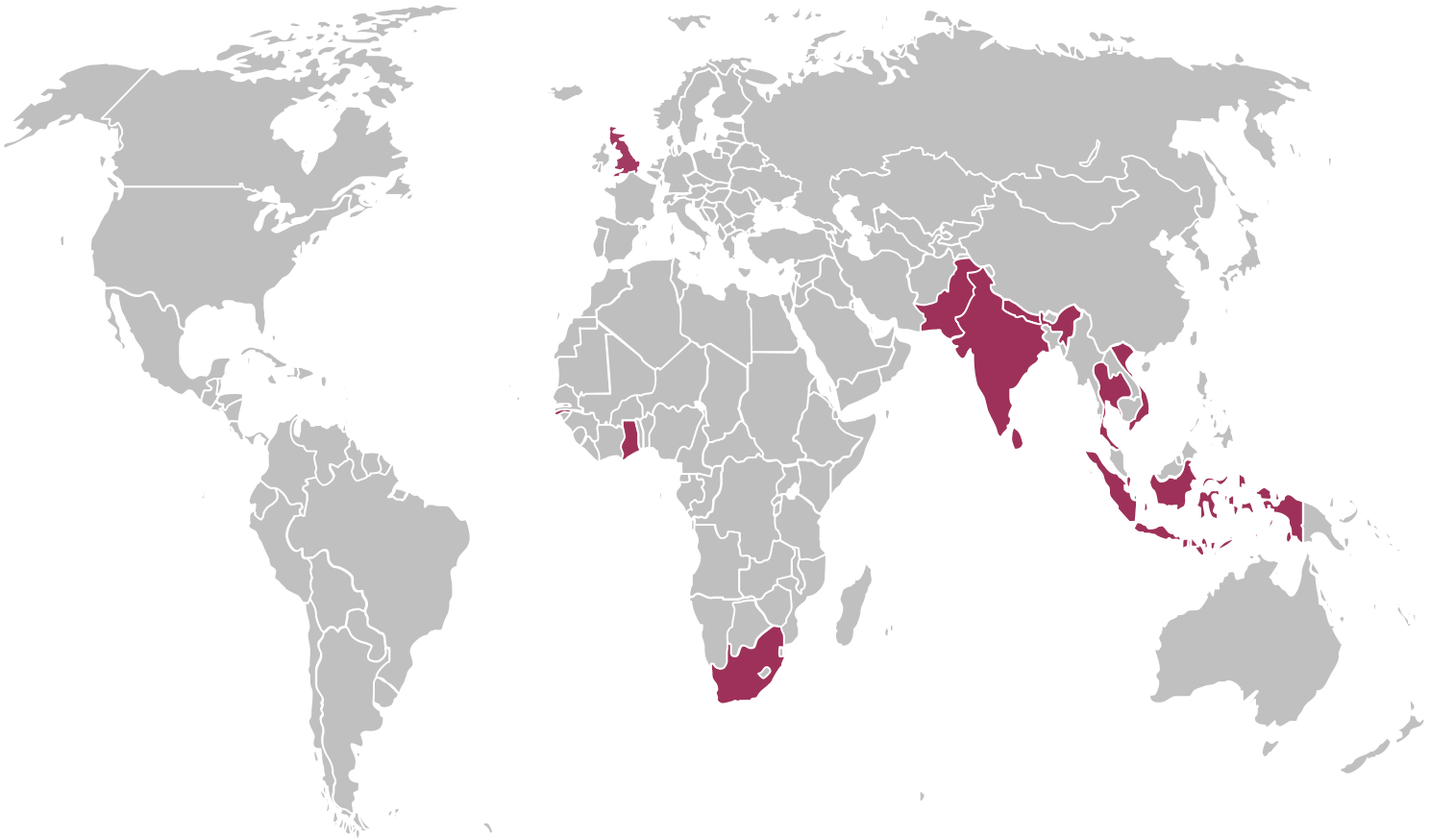

Influenza

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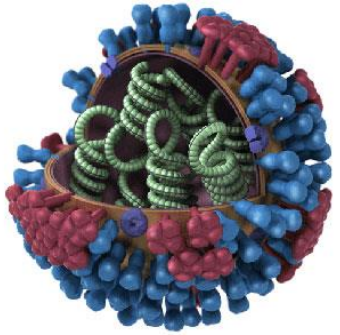
- Seasonal influenza often kills several thousand patients a year in the UK
- Social distancing meant that 2020/21 season was much attenuated, so community resistance levels are low
- 2021/22 season could therefore be more significant
- RECOVERY is ideally positioned to assess treatments for hospitalised patients
  - Antiviral therapies
  - Corticosteroids



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 all your support to date and please don't forget RECOVERY!

Q&A

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