Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

29th & 30th November 2021

Agenda

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1. Introductions
2. Update on progress
3. Trial procedures
4. Future plans
5. 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

Influenza postponement

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- Plans to implement assessments of influenza therapies have been postponed at the request of DHSC for 2-3 weeks pending further information on impact of Omicron SARS-CoV-2 variant on the UK and NHS

- Work to implement these amendments is greatly appreciated and not wasted

- The active protocol is V18.1 and associated PIS/ICFs
  - PIS/ICF V16.1 for adults and V10.1 for children

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PROGRESS UPDATE

Recruitment by site and by time

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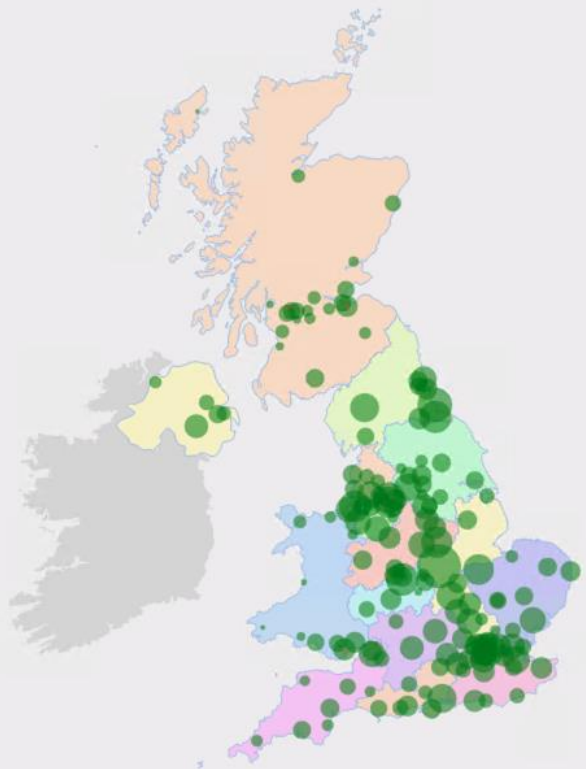
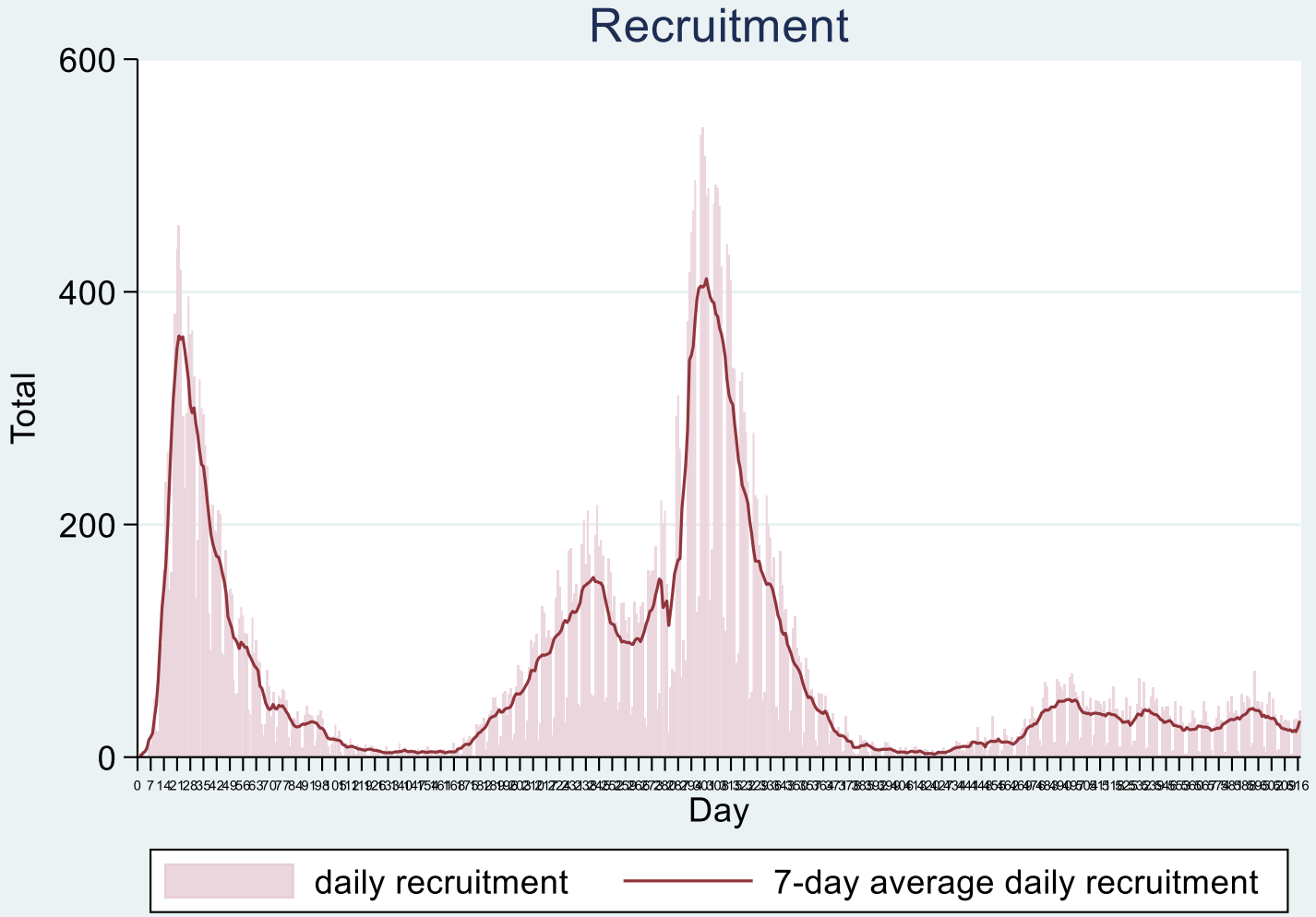
Global | GBR | IDN | NPL | GHA | VNM | ZAF | PAK | IND | LKA

Active Sites	Recruiting Sites	Participants
188	185	45205

Phase 1 rands.	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.	Phase 5 rands.	Phase 6 rands.	Phase 7 rands.
29325	4184	19727	14898	7543	726	2173





Current numbers in comparisons

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- Baricitinib *vs* usual care: ~7500
- Dimethyl fumarate *vs* usual care: 713 (now closed)
- Empagliflozin: ~2200
- High-dose corticosteroids: ~725

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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EMPAGLIFLOZIN

SGLT-2 inhibitors and Empagliflozin (empa)

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- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- 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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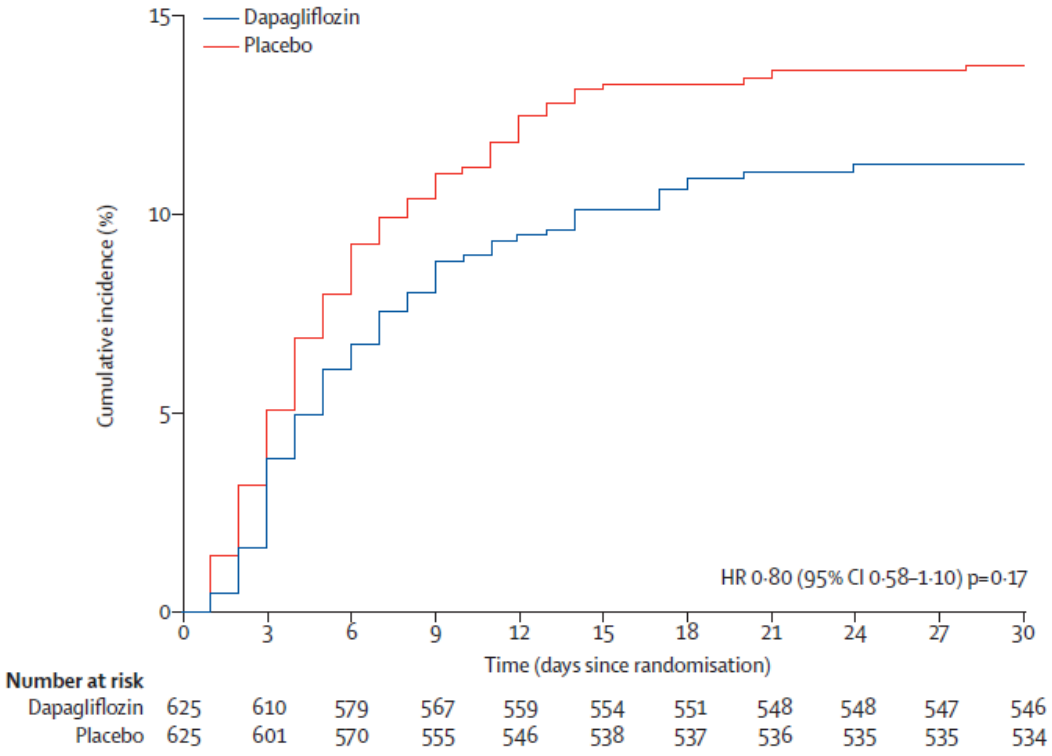
Primary outcome: organ failure or death

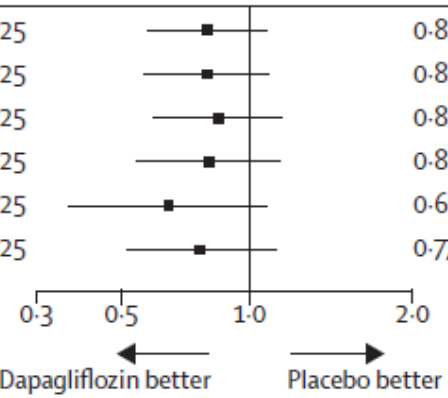


Number at risk

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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- 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

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TRIAL PROCEDURES

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 have been updated

- **All staff** who will continue to obtain consent for RECOVERY are 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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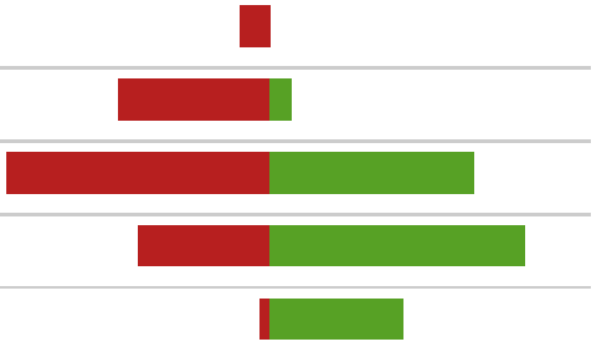
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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

Future COVID arms

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- With DMF comparison now closed, and baricitinib arm approaching completion, protocol only includes empagliflozin in UK (and high-dose steroids outside UK)

- Potential options are under active discussion with DHSC, and include:
  - Antiviral therapies (small molecule, novel monoclonal antibodies)
  - High-dose dexamethasone in UK
  - Further immunomodulatory therapies

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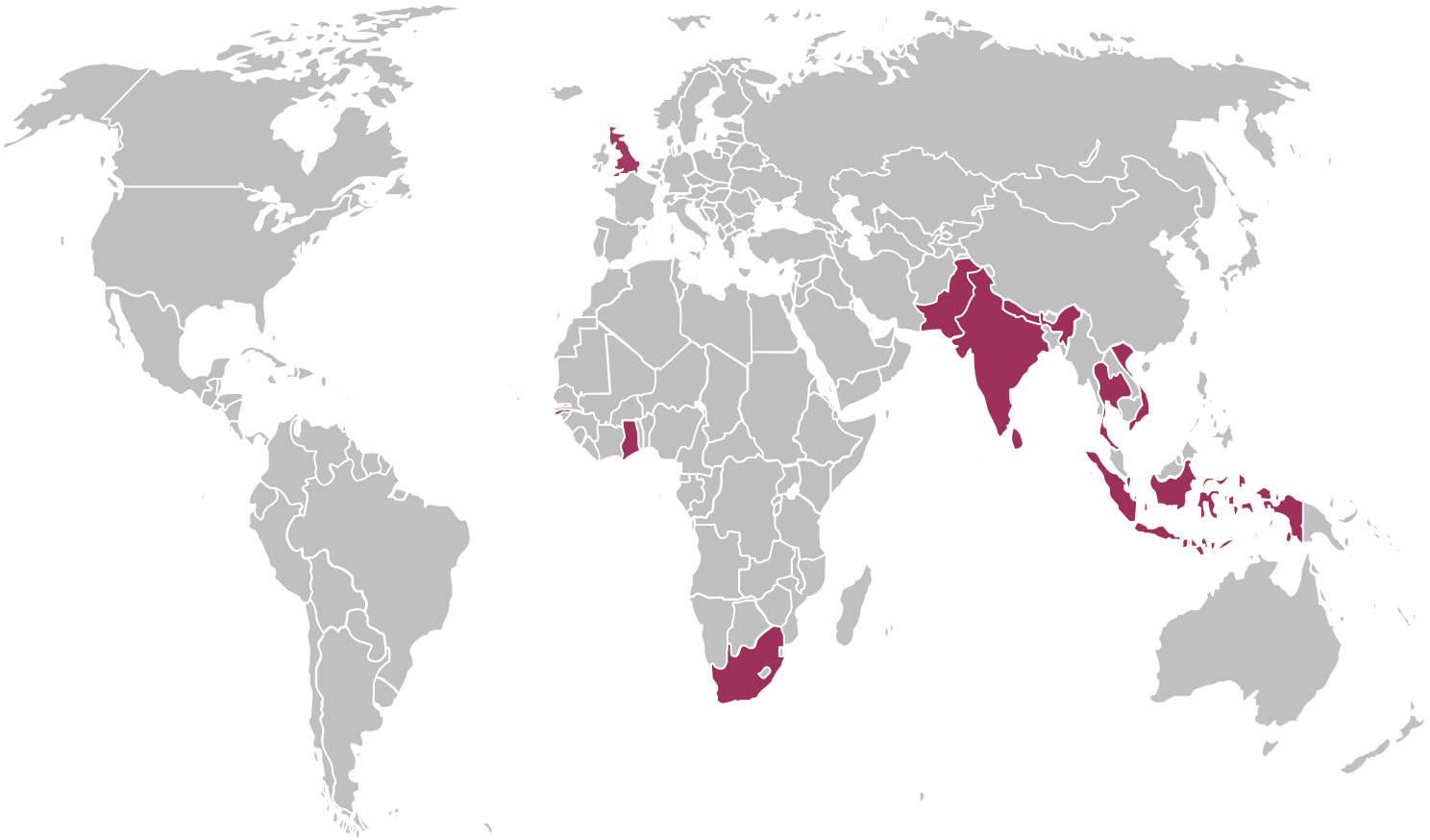

Carry on recruiting!

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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!