# Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

**Collaborators' Meeting**

**5th January 2022**

# Agenda

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1. Introductions
2. Update on progress
3. Current active comparisons:
   - Empagliflozin
   - High-dose corticosteroids
   - Sotrovimab
4. Trial procedures
5. Future plans
6. 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

# Recruitment by time

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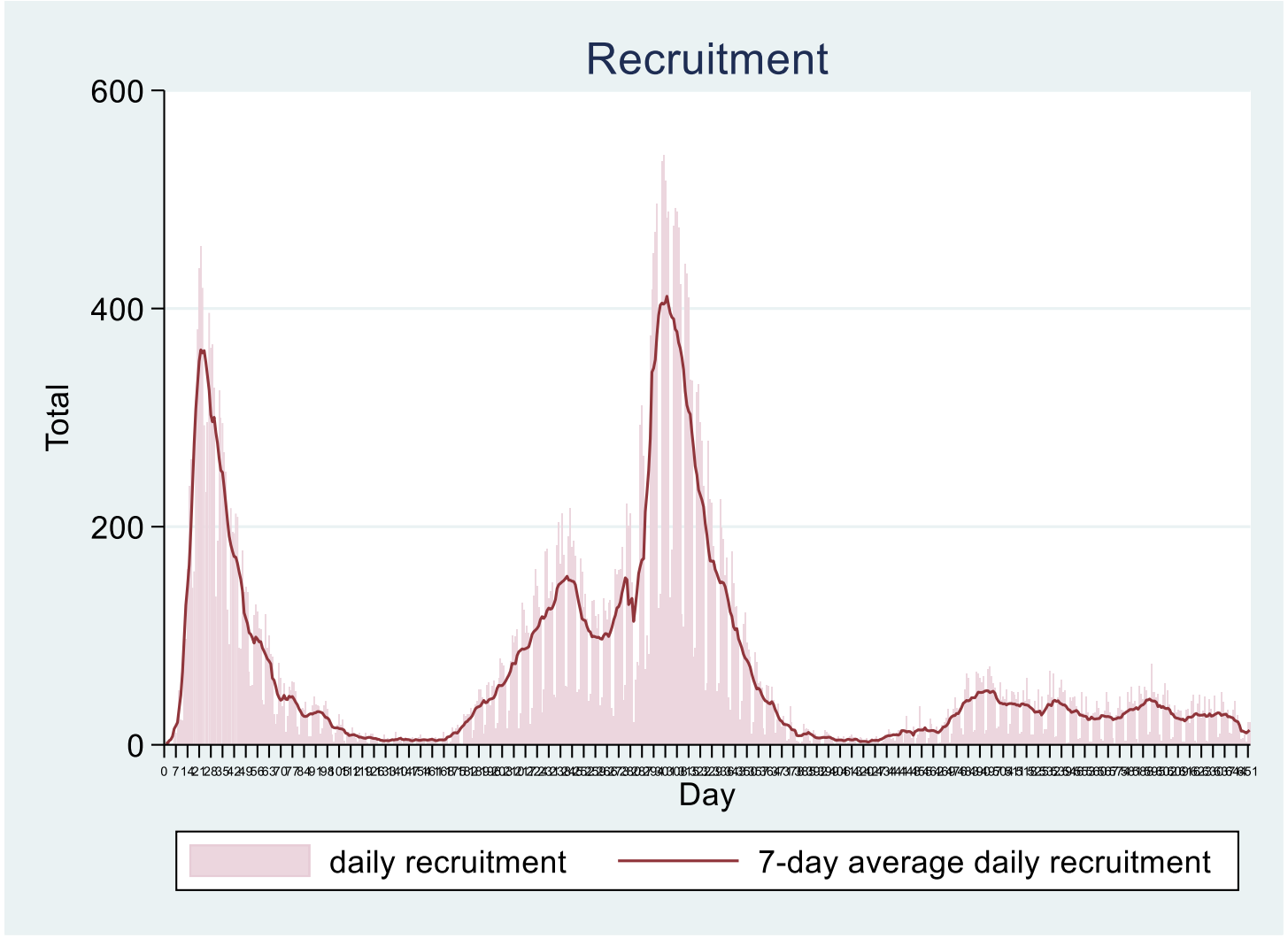

# Current numbers in comparisons

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- Baricitinib *vs* usual care: 8156 (recruitment now closed)
- Empagliflozin: ~2750
- High-dose corticosteroids: ~860

# Recruitment

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- We recognise up to ⅓ of admissions *with* COVID-19 are 'incidental' diagnoses (ie, patient was admitted for something else)
- Such patients are eligible if they develop symptoms of COVID-19 during admission
- Staff absences mean that situation is just as challenging as in January 2020 even though numbers being admitted is not as high
- Thank you for trying to embed RECOVERY into standard clinical care so recruitment can cause minimal disruption

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# CURRENT DESIGN

# Current comparisons for adults with COVID-19

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ELIGIBLE PATIENTS

**High-dose corticosteroids (hypoxic)**

E — High dose steroids *or* Usual care alone

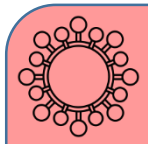
**SGLT-2i comparison**

F — Empagliflozin *or* Usual care alone

Baseline data collected
Participants enter ≥1 comparisons

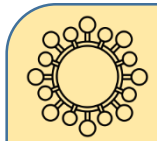
R

Outcomes collected at earliest of death, discharge or 28 days



**Antiviral 1**

J — Sotrovimab *or* Usual care alone



**Antiviral 2**

K — Molnupiravir *or* Usual care alone

OUTCOMES

# Eligibility

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1. Hospitalised

2. Viral pneumonia syndrome
   - or PIMS-TS in children

3. Confirmed SARS-CoV-2 infection
   - PCR (hospital or community) or in-hospital lateral flow test

4. No medical history that might put the patient at risk if s/he were to participate

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# EMPAGLIFLOZIN

# SGLT-2 inhibitors and Empagliflozin (empa)

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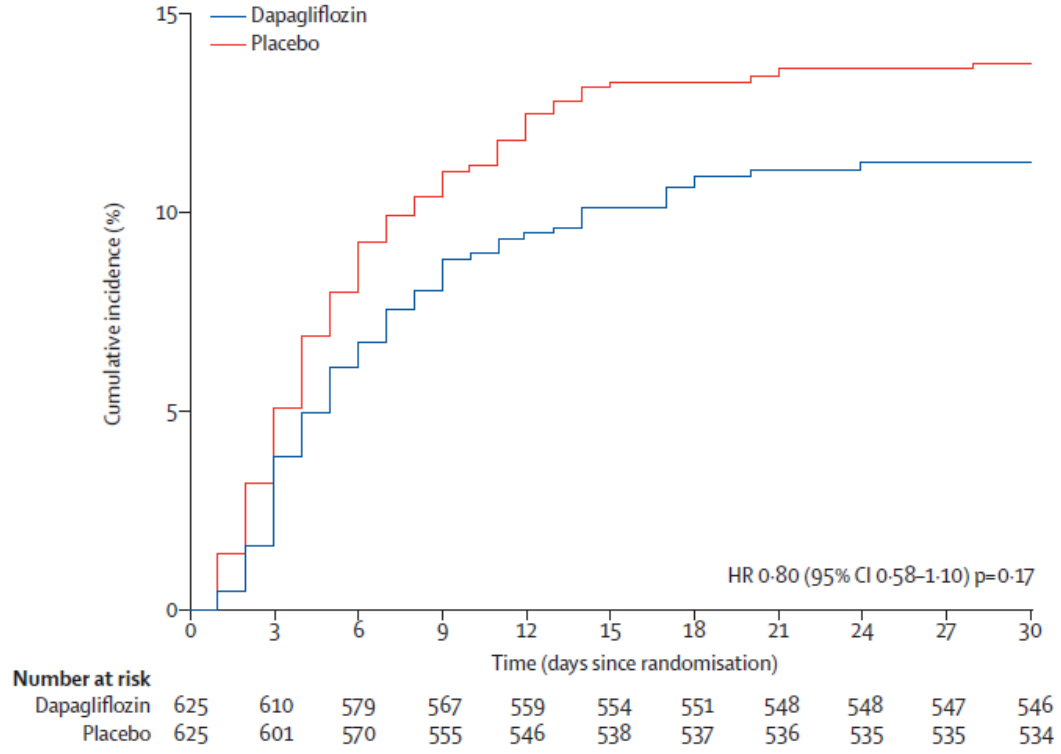
- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- 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)



# Empagliflozin in RECOVERY

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- **Dose: 10 mg once daily for up to 28 days** (stopped at discharge if sooner)

- **Exclusions:**
  - Patients at risk of ketoacidosis (eg, type 1 or post-pancreatectomy diabetes mellitus; history of ketoacidosis; current blood ketones ≥1.5 mmol/L or urine ketones ≥2+)
  - Pregnancy or breast-feeding

- **Important monitoring of ketones for participants with diabetes**
  - Twice daily blood ketones (or once daily urine ketones if blood ketone testing not available) or if clinical concern

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# HIGH-DOSE CORTICOSTEROIDS

# High-dose corticosteroids

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- RECOVERY demonstrated benefits of 6 mg dexamethasone for hypoxic patients with COVID-19
- Additional immunomodulation (tocilizumab) has been shown to be beneficial
- Higher doses of corticosteroids may be beneficial, but risks also may be increased

# High-dose corticosteroids

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- **Eligibility:** adult patients <u>with hypoxia</u>
  - on supplemental oxygen or $SpO_2$ <92% on air

- **Usual care:** should include dexamethasone 6 mg
- **High-dose arm:** 20 mg dexamethasone once daily for 5 days, then 10 mg once daily for 5 days (stopped at discharge if sooner)

- **Pregnant/breastfeeding women:** should receive equivalent doses of prednisolone/hydrocortisone

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# SOTROVIMAB

# Monoclonal antibodies can improve clinical outcome

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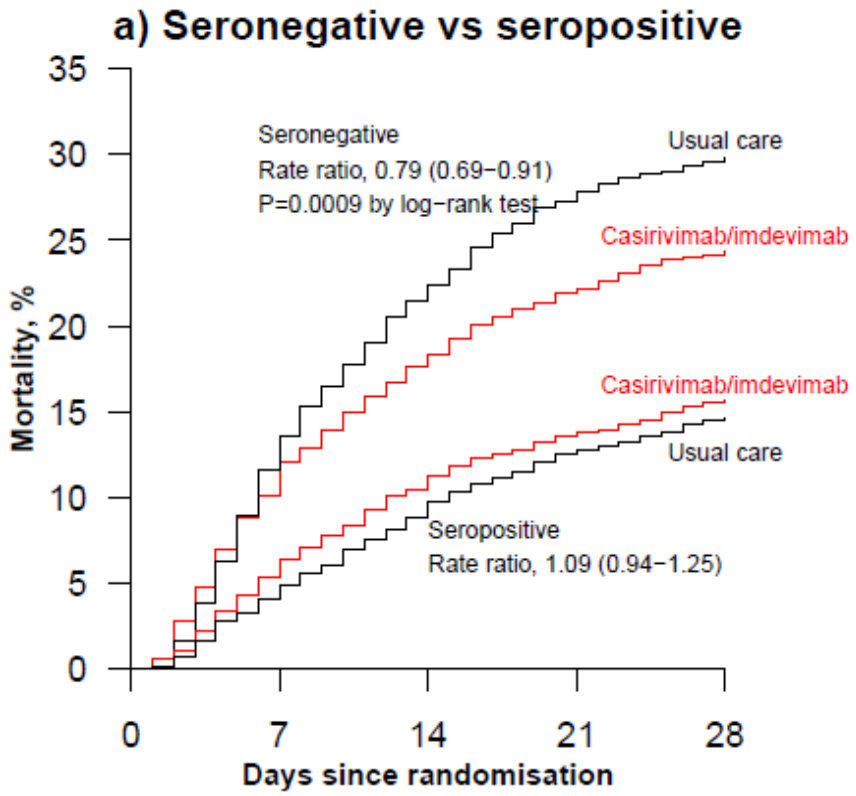


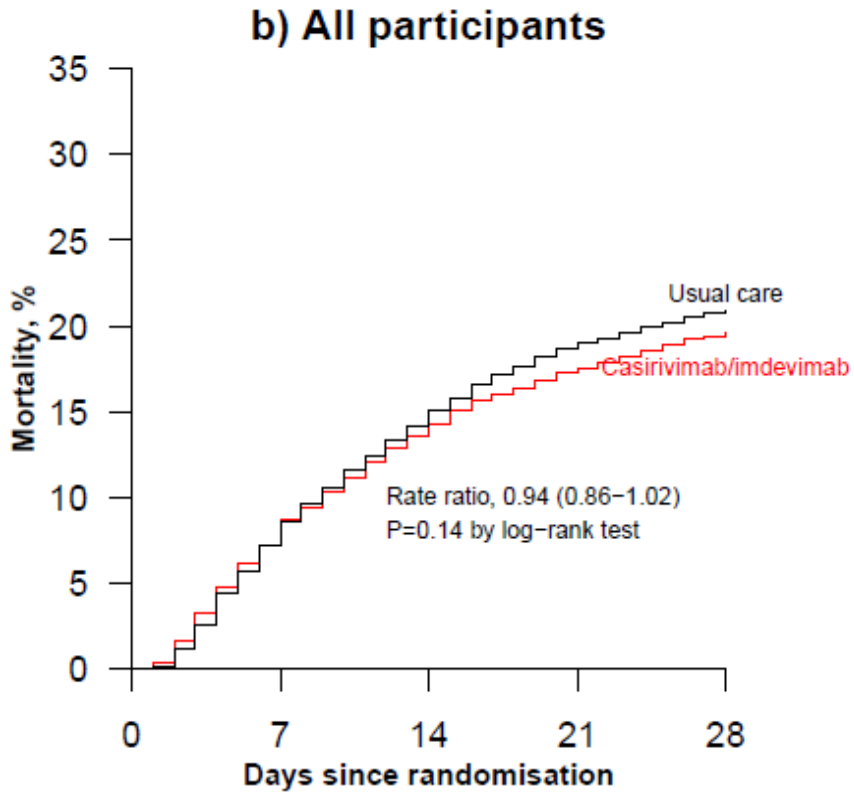


**No. at risk, Seronegative**

| | | | | | |
|---|---|---|---|---|---|
| Casirivimab/imdevimab | 1633 | 1431 | 1328 | 1266 | 1230 |
| Usual care | 1520 | 1310 | 1176 | 1094 | 1064 |

**No. at risk, Seropositive**

| | | | | | |
|---|---|---|---|---|---|
| Casirivimab/imdevimab | 2636 | 2456 | 2329 | 2261 | 2214 |
| Usual care | 2636 | 2504 | 2376 | 2298 | 2249 |

**No. at risk**

| | | | | | |
|---|---|---|---|---|---|
| Casirivimab/imdevimab | 4839 | 4394 | 4122 | 3968 | 3868 |
| Usual care | 4946 | 4508 | 4186 | 3992 | 3899 |

# Variants and monoclonal antibodies

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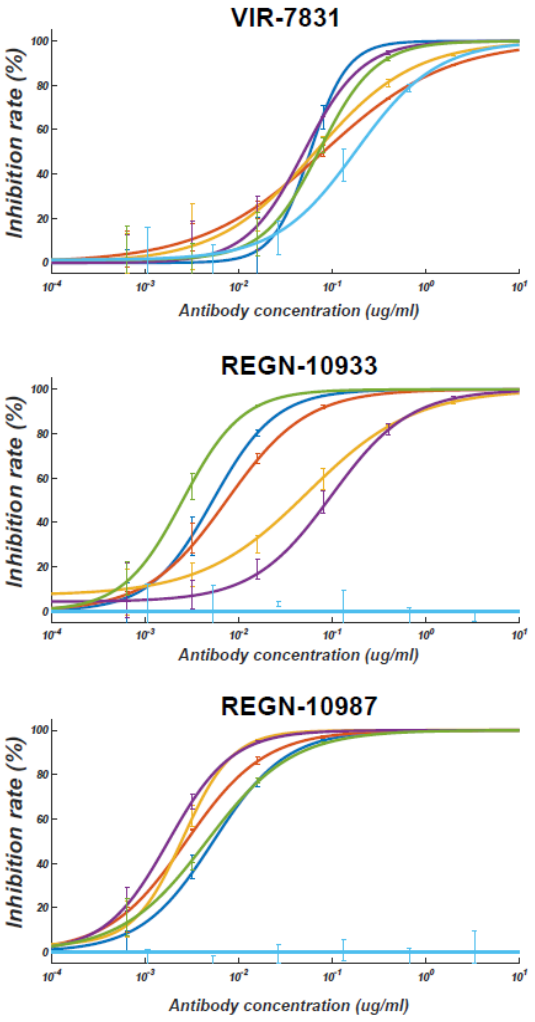
- Because each monoclonal antibody binds to its own specific part of the spike protein, mutations in the binding site can alter the potency of these treatments
- Ronapreve is highly effective against previous variants, but has very little activity against Omicron
- Sotrovimab has preserved efficacy against Omicron




Cao et al. BioRxiv 2021

# Sotrovimab

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- Derived from an antibody identified in a patient who had SARS-CoV-1 infection
- Thought to bind to part of the spike protein which is more “conserved” so may be less likely to mutate in future variants
- Is fully human, but has had Fc portion modified to increase its half-life after infusion

# Efficacy of sotrovimab

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- Among **outpatients** in the COMET ICE trial, sotrovimab reduced need for hospitalisation or death by 85%

- Assessed in NIH ACTIV-3-TICO trial among **inpatients**, but abandoned for futility
  - However, pre-specified analysis did not take into account serostatus, so effects like that seen with Ronapreve in RECOVERY would have been missed

- There remains uncertainty around benefits of sotrovimab for **inpatients**

# Sotrovimab in RECOVERY

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- All adult participants are potentially eligible, including those who have received sotrovimab previously
  - Adolescents ≥12 years old and ≥40 kg are also eligible
  - Pregnant or breast-feeding women are eligible after discussion with them
  - No exclusions around liver or kidney function

- Dose is **1000 mg** in 100 mL 0.9% saline or 5% dextrose given over 1 hour given as soon as possible after randomisation

# Requirements for participation

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- Site PI must complete online training
  - Cascade to other relevant staff
- Provide CCO with addresses for:
  - Delivery of IMP (and days on which it can be received)
  - Delivery of sample kits
- CCO will request shipment of IMP once these details received
  - Comparison will be activated in IT system once receipt of shipment confirmed

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# TRIAL PROCEDURES

# Biological sampling in RECOVERY

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- Only for participants in antiviral comparisons
- RECOVERY has demonstrated that knowledge of baseline serostatus is crucial to understand effects of monoclonal antibody therapies
- Measuring effects on viral load may help reduce time it takes to accept sotrovimab as a treatment for hospitalised patients
- Swab samples also provide opportunity to assess whether resistance develops to antivirals

# Biological sampling in RECOVERY

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| | Serum sample | Nose swabs |
|---|---|---|
| **Baseline** (**Day 1** - <u>after</u> consent, <u>before</u> randomisation) | ✓ | ✓ |
| **Day 3** | ✗ | ✓ |
| **Day 5** | ✗ | ✓ |

Serum samples used to measure antibody levels and possibly viral antigen
Swabs used to measure viral load and presence of resistance markers

# Biological sampling in RECOVERY

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- Kits currently being manufactured and will be sent to participating sites soon
- All materials provided (except for vacutainer)
- Samples should be labelled with participant ID and time/date of collection
  - No requirement for processing in hospital so do NOT send to hospital lab
- Can be returned using standard post (full instructions on website)

# 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)

# Consent monitoring

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- It has always been intention to monitor consent process, but delayed until now
- All sites have been asked to review a random sample of 20-40 consent forms and provided tool for completion
- We recognise current pressures so please say is more time is required

# Completeness of follow-up

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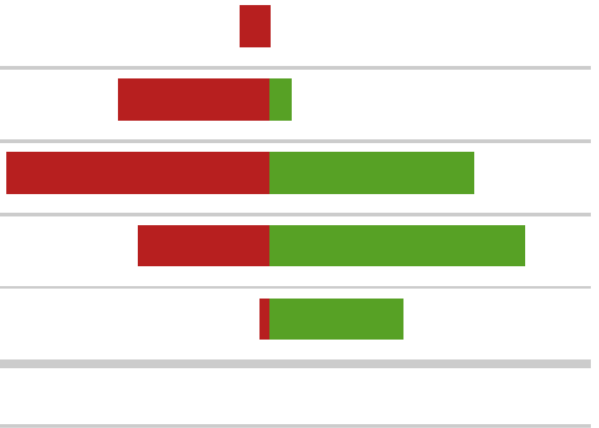
- Weekly reminders highlighting participants randomised >28 days ago without complete form

**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** |




- Baricitinib arm now closed to recruitment, so complete follow-up is essential

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# FUTURE PLANS

# Future COVID arms

- Molnupiravir arm will be activated once supply is agreed with DHSC
- Paxlovid was given a license by MHRA on 31st December and will be considered for RECOVERY
- Further immunomodulatory therapies await results of baricitinib comparison

# RECOVERY international

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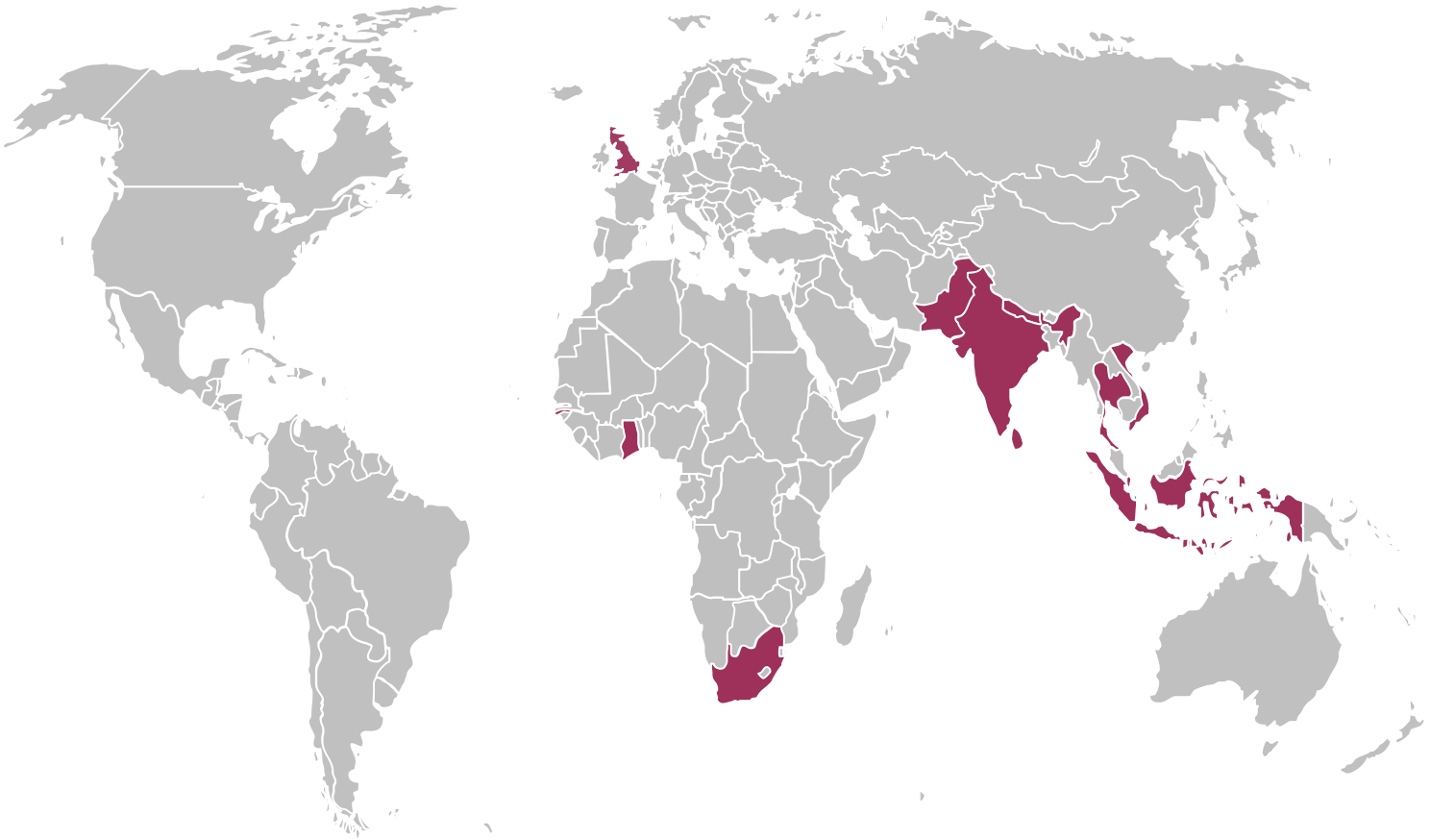

# Carry on recruiting!

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- January 2022 will be a challenging time in the NHS
- In January 2021 over 10,000 participants were recruited in equally challenging (but different) circumstances
- We are extremely grateful for your efforts to recruit to RECOVERY as part of the clinical care pathway and help us identify new treatments as we care for patients with COVID-19