Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

22nd & 23rd May 2023

Agenda

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1. Empagliflozin results
2. Update on COVID-19
3. Current active comparisons:
   - Molnupiravir – closing now
   - Paxlovid – closing now
   - Sotrovimab
   - High-dose corticosteroids
4. Trial procedures
5. Future plans for RECOVERY
6. Q&A

Note there are no specific obstetric or paediatric updates

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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EMPAGLIFLOZIN

SGLT-2 inhibitors and COVID-19 Background

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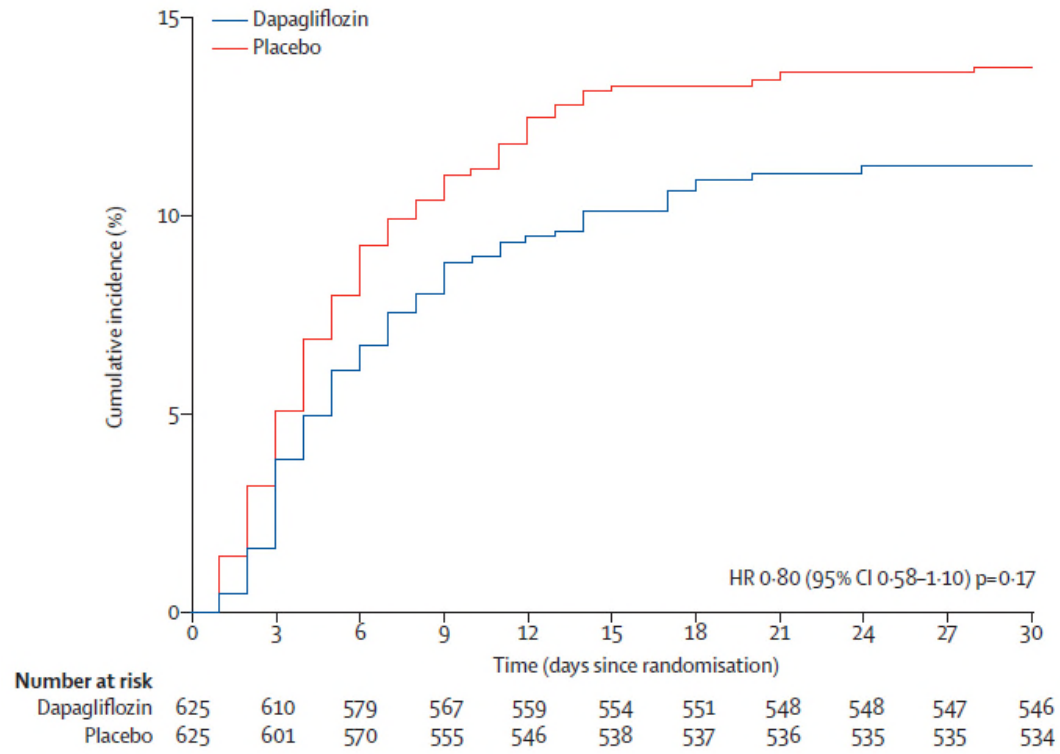
- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- SGLT-2i were proposed to 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 – inconclusive but fewer deaths in dapagliflozin group

Empagliflozin Trial profile

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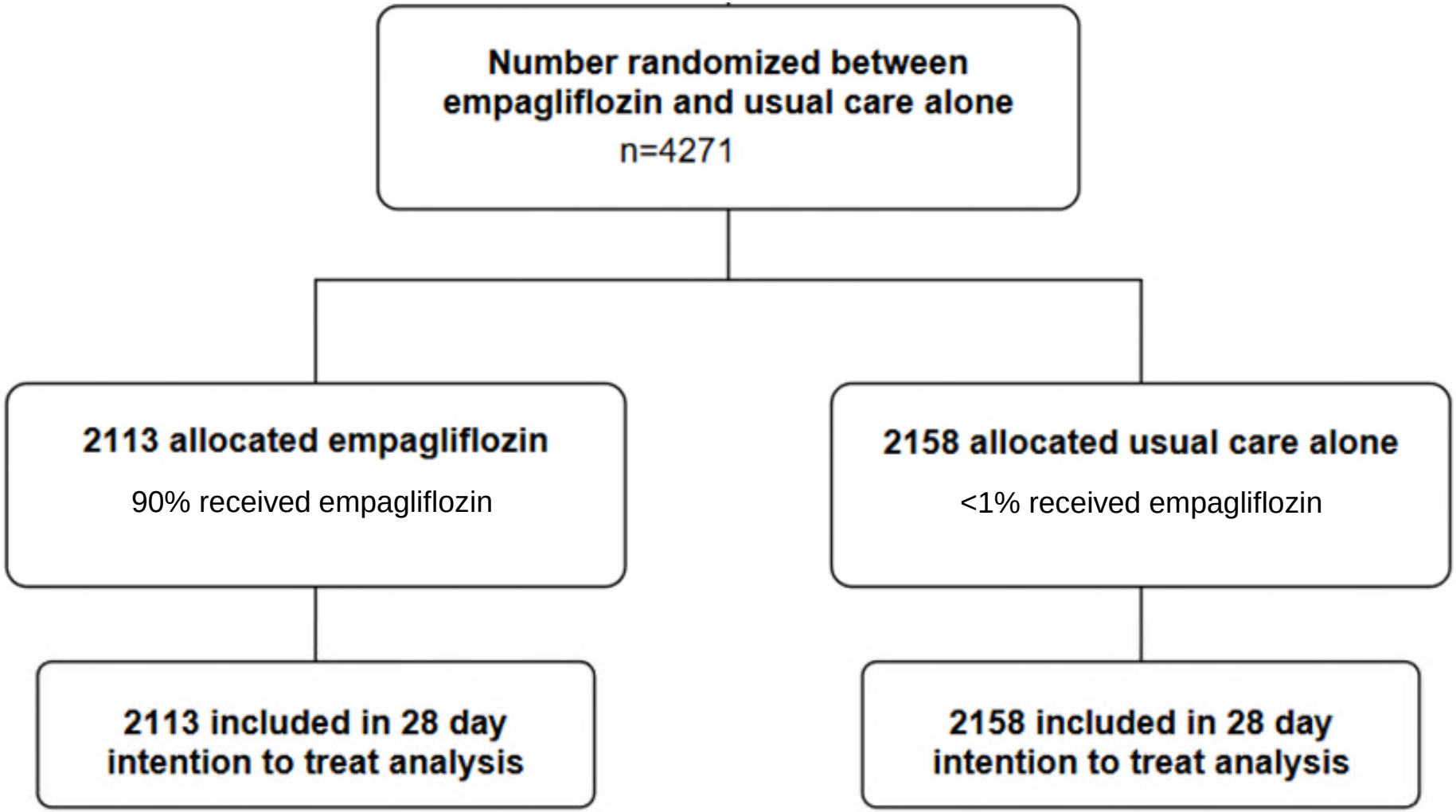

Empagliflozin
Baseline characteristics

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	Treatment allocation	
	Empagliflozin (n=2113)	Usual care (n=2158)
Age, years	61.1 (16.3)	61.8 (16.4)
<70	1412 (67%)	1393 (65%)
≥70 to <80	434 (21%)	479 (22%)
≥80	267 (13%)	286 (13%)
Sex		
Male	1326 (63%)	1339 (62%)
Female*	787 (37%)	819 (38%)
Number of days since symptom onset	8 (5-11)	8 (5-12)
Number of days since hospitalisation	2 (1-3)	2 (1-3)
Respiratory support received		
None	255 (12%)	260 (12%)
Simple oxygen	1317 (62%)	1383 (64%)
Non invasive ventilation	512 (24%)	500 (23%)
Invasive mechanical ventilation	29 (1%)	15 (1%)
Previous diseases		
Diabetes	333 (16%)	356 (16%)
Heart disease	471 (22%)	455 (21%)
Chronic lung disease	533 (25%)	508 (24%)
Tuberculosis	9 (<0.5%)	7 (<0.5%)
HIV	21 (1%)	13 (1%)
Severe liver disease†	20 (1%)	21 (1%)
Severe kidney impairment‡	66 (3%)	80 (4%)
Any of the above	1014 (48%)	1039 (48%)
Received a COVID-19 vaccine	1412 (67%)	1453 (67%)
Use of other treatments		
Corticosteroids	1910 (90%)	1932 (90%)
Remdesivir	541 (26%)	547 (25%)
Tocilizumab	504 (24%)	491 (23%)
Plan to use tocilizumab within the next 24 hours	208 (10%)	240 (11%)

Empagliflozin
28-day mortality

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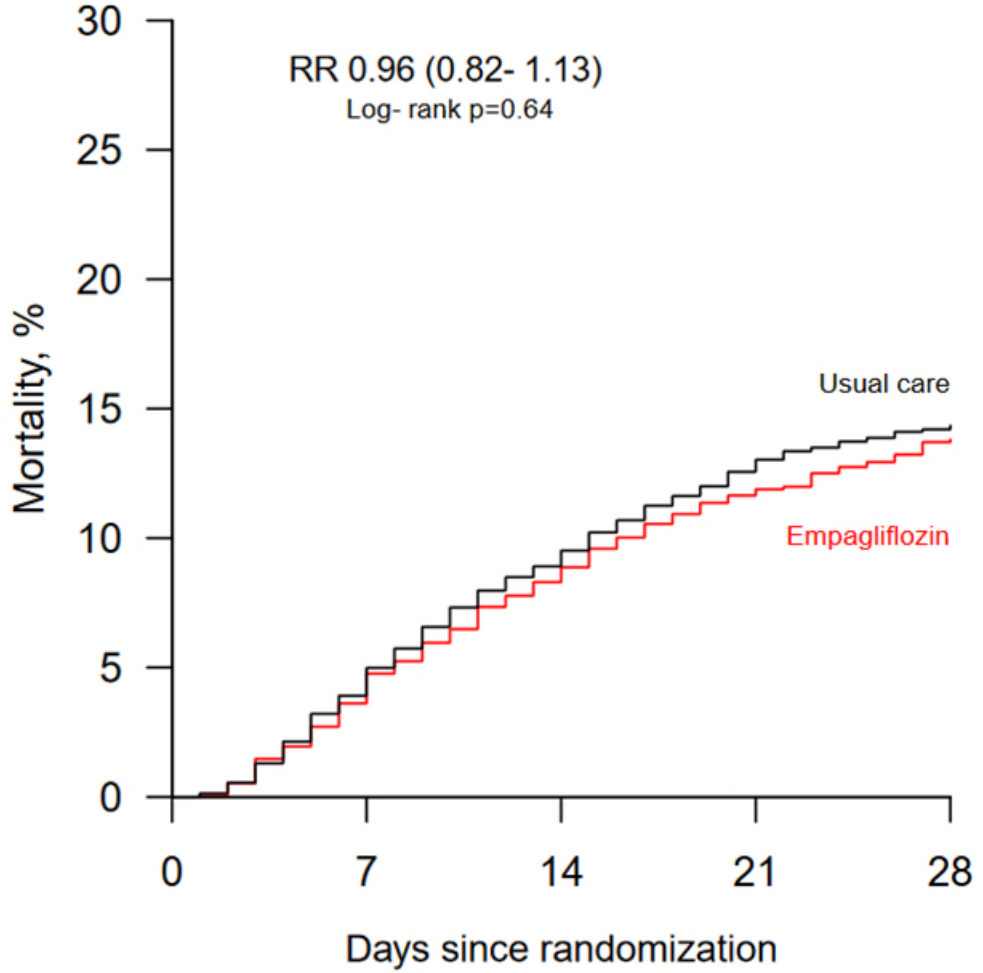

Number at risk					
Empagliflozin	2113	1995	1907	1841	1800
Control	2158	2035	1933	1856	1828

Empagliflozin
Secondary outcomes

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	Treatment allocation			
	Empagliflozin (n=2113)	Usual care (n=2158)	RR (95% CI)	p value
Primary outcome:				
28-day mortality	289 (14%)	307 (14%)	0.96 (0.82-1.13)	0.64
Secondary outcomes:				
Median time to being discharged alive, days	8 (5 to 19)	8 (5 to 20)		
Discharged from hospital within 28 days	1678 (79%)	1677 (78%)	1.03 (0.96-1.10)	0.44
Receipt of invasive mechanical ventilation or death*	338/2084 (16%)	371/2143 (17%)	0.95 (0.84-1.08)	0.44
Invasive mechanical ventilation	130/2084 (6%)	133/2143 (6%)	0.97 (0.77-1.21)	0.77
Death	274/2084 (13%)	302/2143 (14%)	0.96 (0.84-1.11)	0.59

*Excluding those on invasive ventilation at randomisation

Empagliflozin
Safety outcomes

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	Treatment allocation		
	Empagliflozin (n=2113)	Usual care (n=2158)	Absolute percent difference (95% CI)
Number with follow-up form	2089	2138	
Metabolic complications			
Ketoacidosis	5 (0.2%)	2 (0.1%)	0.1 (-0.1,0.4)
Hyperglycaemic hyperosmolar state	9 (0.4%)	14 (0.6%)	-0.2 (-0.7,0.2)
Other hyperglycaemia requiring new use of insulin	123 (5.8%)	132 (6.1%)	-0.3 (-1.7,1.1)
Severe hypoglycaemia	4 (0.2%)	7 (0.3%)	-0.1 (-0.4,0.2)
Acute kidney injury*			
Stage 1	44/2103 (2.1%)	35/2146 (1.6%)	0.5 (-0.4,1.3)
Stage 2	16/2103 (0.8%)	23/2146 (1.1%)	-0.3 (-0.9,0.3)
Stage 3	72/2103 (3.4%)	72/2146 (3.4%)	0.1 (-1.0,1.2)
Subtotal: Any AKI	132/2103 (6.3%)	130/2146 (6.1%)	0.2 (-1.2,1.7)

*Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Preprint on Medrxiv https://www.medrxiv.org/content/10.1101/2023.04.13.23288469v1

Empagliflozin Conclusions

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- Unfortunately, empagliflozin had no material mortality benefit in patients hospitalised with COVID-19
- Without the scale provided by the RECOVERY collaboration it would not have been possible to rule out an important benefit
- SGLT2 inhibitors are beneficial for many patients with diabetes, heart failure and kidney failure, so their use is increasingly common
- Risk of ketoacidosis in acutely ill patients has been a major concern
- Safety data from RECOVERY will assist the appropriate use of SGLT2i beyond COVID-19

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COVID-19 UPDATE

State of the pandemic

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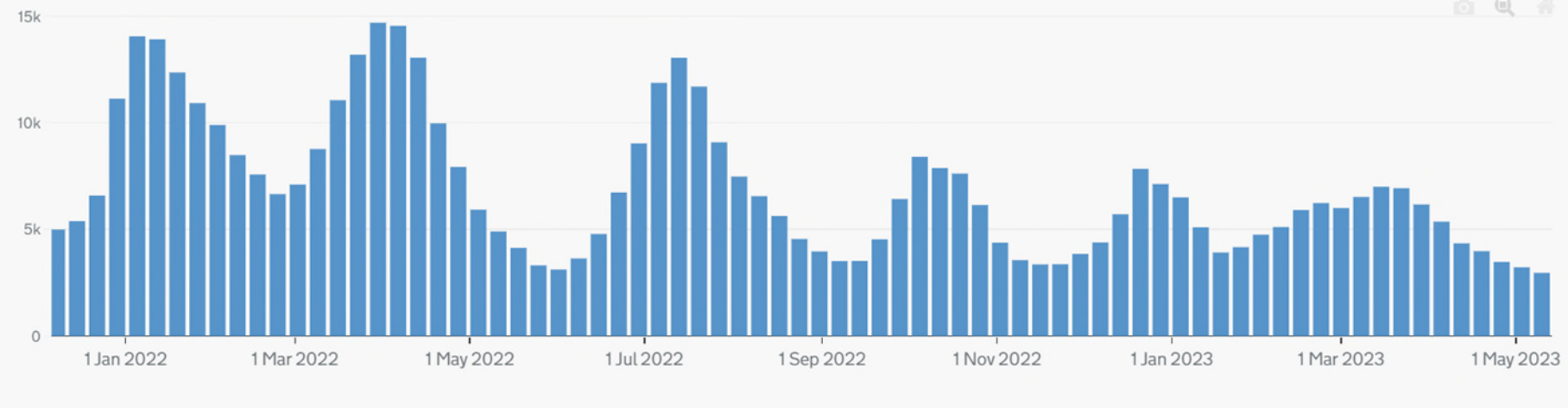
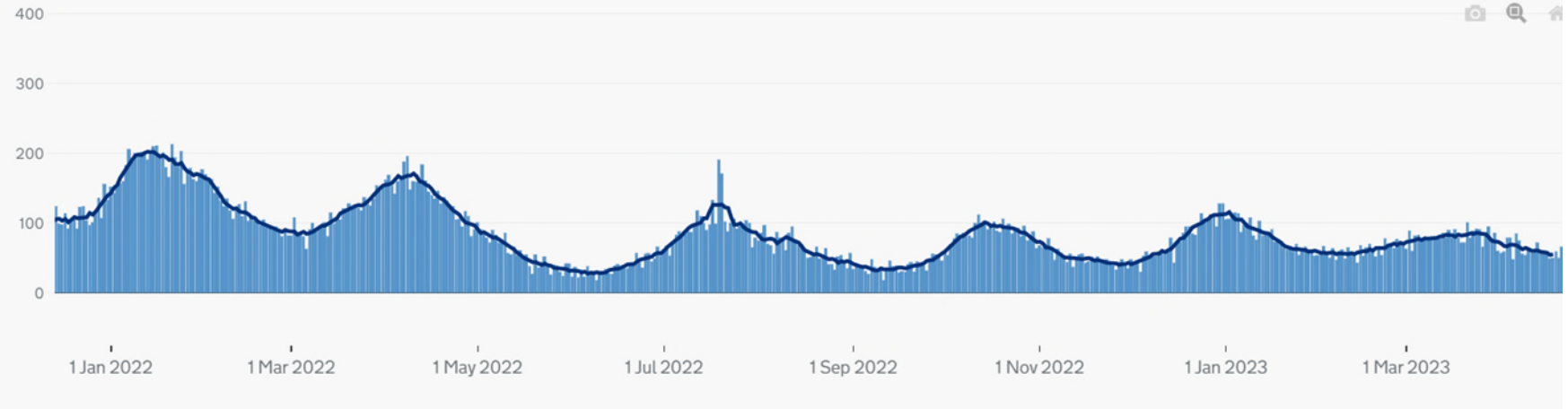
UK weekly hospital admissions with COVID-19



UK daily deaths caused by COVID-19



COVID-19 has become an endemic disease, but remains ***as important as many other major public health problems***

We will continue to see:

- Severe disease in the most vulnerable
- Epidemics with high rates of hospitalisation and death

The risk of a more virulent SARS-CoV-2 variant arising seems low, but is not trivial

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CURRENT DESIGN

Current comparisons for adults with COVID-19

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Current NIHR & UKRI support for COVID-19 comparisons ends 30th November 2023

ELIGIBLE PATIENTS

High-dose corticosteroids (on ventilatory support)

E: High dose steroids *or* Usual care alone

Antiviral 2

K: Molnupiravir *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 3

L: Paxlovid *or* Usual care alone

OUTCOMES

Eligibility

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1. Hospitalised

2. Viral pneumonia syndrome, e.g.
   a. Typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and
   b. Compatible chest imaging (consolidation or ground-glass shadowing); and
   c. Alternative causes considered unlikely or excluded (e.g. heart failure, bacteria pneumonia)

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 they were to participate

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MOLNUPIRAVIR & PAXLOVID

Molnupiravir & Paxlovid

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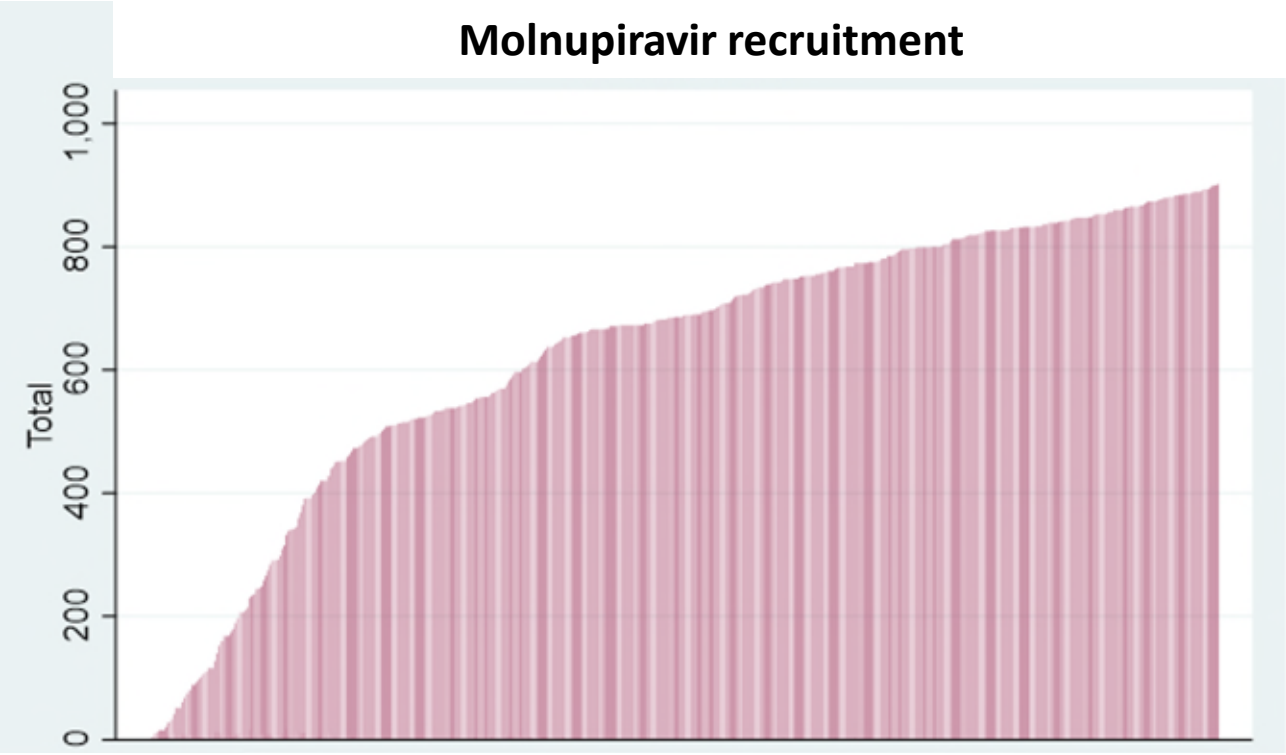

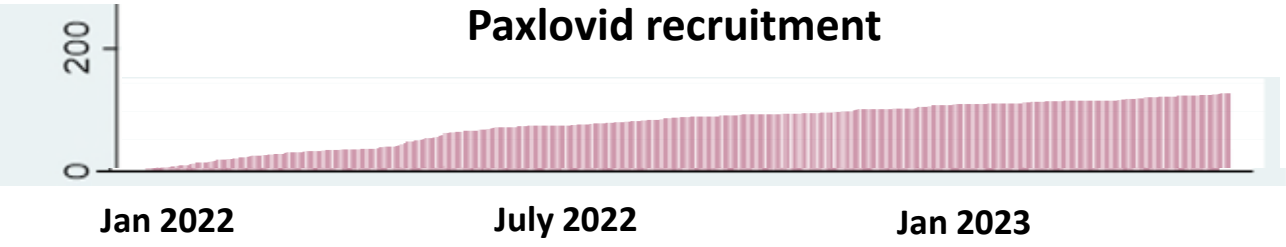

- Molnupiravir - 920 participants
- Paxlovid - 137 participants

- It is unlikely that we'll recruit enough patients to rule out a moderate reduction in risk of death

- It is *possible* that current recruitment will be enough to show a benefit of treatment

- The Trial Steering Committee have decided to close these comparisons and analyse existing data

- Current patients should complete treatment

- Please ensure all follow up forms are completed

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SOTROVIMAB

Sotrovimab

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- Derived from an antibody identified in a patient who had SARS-CoV-1 infection – target may be more “conserved” so less likely to mutate in future variants

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

- Only one small trial in hospitalised patients, so there remains uncertainty around benefits of sotrovimab for **inpatients**

In vitro efficacy of sotrovimab

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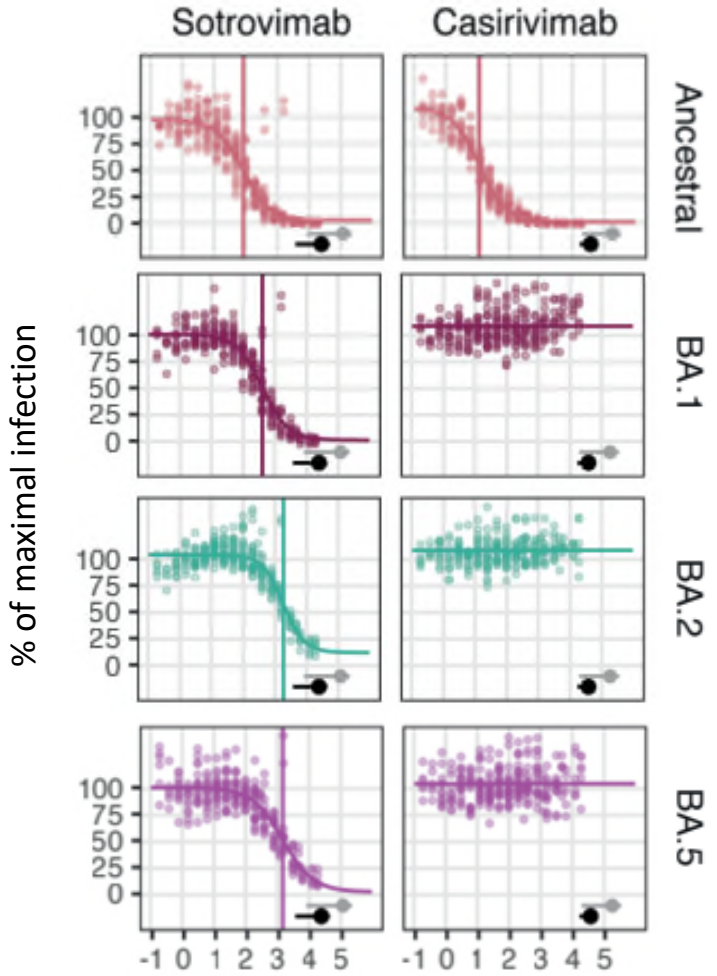
- Most anti-SARS-CoV-2 monoclonal antibodies are completely inactive against current variants
- Neutralisation by sotrovimab is only moderately reduced, and serum concentration remain above the level needed to neutralise virus
- The significance of these *in vitro* results is uncertain & the assays are far removed from clinical outcomes
- Sotrovimab remains promising and we need randomised evidence!



Grey points = max serum conc.
Black points = serum conc. at 1 week

Wu MY, et al. Lancet. 2022 Oct 6. PMID36209762

Sotrovimab in RECOVERY

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- 1571 participants to date
- Blinded mortality rate 22%
- Key importance of subgroups defined by antibody & serum antigen status
- All adult participants potentially eligible, including those who have received sotrovimab previously (RECOVERY dose is 1g)
  - 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

Sotrovimab in RECOVERY

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- Sotrovimab recruitment has slowed since the initial Omicron wave in early 2022
  - Many sites have recruited only a few patients in the past 12 months, but
  - Recruitment is very variable, and some sites continue to recruit 1-2 patients per week

- If most sites aimed to recruit ~1 patient/week until Nov 2023 we would produce **reliable evidence** on the efficacy of sotrovimab

- We hope that RECOVERY remains a relatively simple study for clinical & research staff

- Please let us know of any specific difficulties in recruitment in the Q&A

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HIGH-DOSE CORTICOSTEROIDS

High-dose corticosteroids

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- Now open only to adult patients <u>on ventilatory support</u>
  - This includes high-flow nasal oxygen, CPAP, BiPAP and IMV/ECMO

- Results for patients not on ventilatory support published in *The Lancet* last month

- **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)

High-dose corticosteroids

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- 465 participants currently in active comparison (not counting the subgroup already reported)
- Recruiting in all countries in RECOVERY
- Blinded mortality rate 35%

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TRIAL PROCEDURES

Biological sampling

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- Samples only needed from participants in sotrovimab comparison
- Includes those allocated usual care in sotrovimab comparison (i.e. if the computer *could* have allocated them to sotrovimab, we need samples)
- Baseline serostatus has been crucial in understanding effects of monoclonal antibody therapy (but alternatives may now be needed)
- Measuring effects on viral load may help us understand the effects of treatment
- Swabs also allow us to see whether resistance develops on treatment

Biological sampling

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

Full instructions are on our website ('For Site Teams' page)

Consent monitoring

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- We ask that a copy of every consent form is now e-mailed to RECOVERY trial

- Please ensure that you write you name clearly on the consent form, so we can ensure that those taking consent have done consent training

- **Remember: the current version of the PIS/ICF is V24.0 (adults) and V14.0 (children)**

Delegation of duties log

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- PIs were emailed in March to update their delegation of duties logs
- Some have not replied, or not confirmed that their updates are correct (we need email confirmation in lieu of signature)
- We will send these out again soon, copying research teams
- We need reply from PIs even if there are no changes, as we need to know these are up-to-date

Completeness of follow-up

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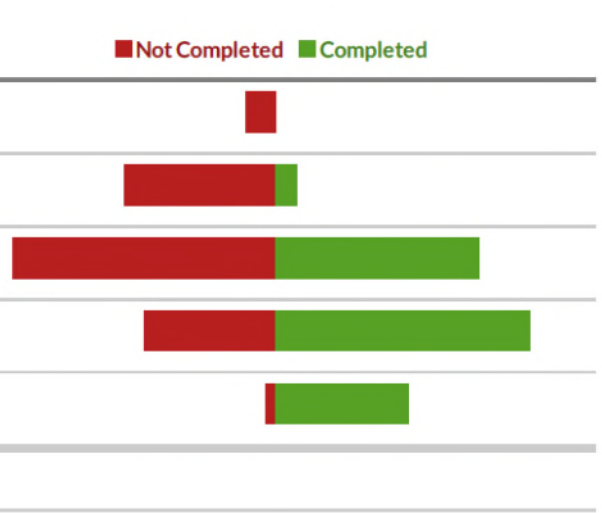
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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**



- Completeness of follow-up is excellent; please keep this up!

Future plans

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Influenza

- Kills 100,000s of people every year, but we know much less about its treatment than COVID-19
- Comparisons are **oseltamivir**, **baloxavir** & **dexamethasone**
  - Currently these are only active at Scottish sites in the UK
  - Expanding to new sites this year
  - Focus is on preparing for winter 2023/24

Many other important unanswered questions in acute respiratory infection

Please carry on recruiting!

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- The visibility of COVID-19 has decreased but it remains important
- We will continue to see new variants and waves of infection
- We are closing the molnupiravir and Paxlovid arms to simplify the trial design and focus on the two remaining COVID-19 treatments
- We could get answers in the next 6 months if most sites allocate modest capacity to RECOVERY
- We are extremely grateful for your efforts to recruit to RECOVERY and identify new treatments for patients with COVID-19