Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

28th & 29th November 2022

Agenda

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1. Introductions
2. Update on COVID-19
3. Current active comparisons:
   - Empagliflozin
   - High-dose corticosteroids
   - Sotrovimab
   - Molnupiravir
   - Paxlovid
4. Trial procedures
5. Q&A

Note: 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

RECOVERY influenza comparisons

- Three influenza comparisons were added to the RECOVERY protocol last year, but we have not had specific funding to support them

- Unfortunately, we were unsuccessful in our application for NIHR funding to open the influenza comparisons

- We are exploring alternatives, but at the moment we are not opening these comparisons

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COVID-19 UPDATE

State of the pandemic

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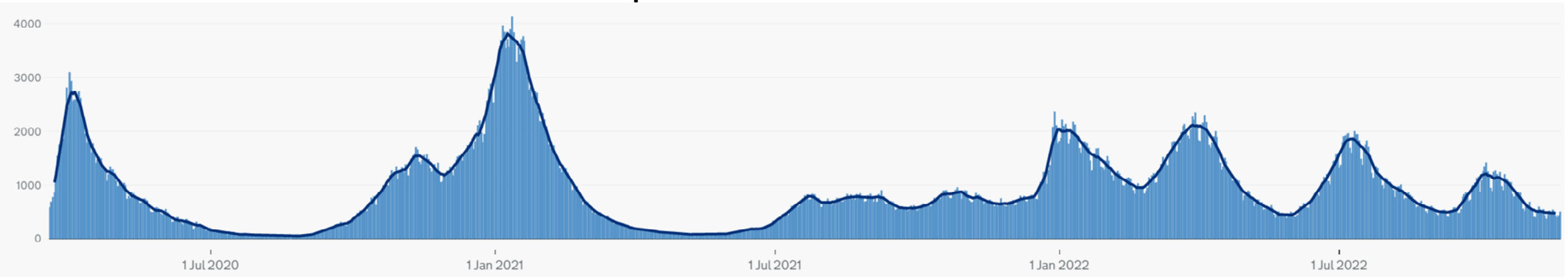
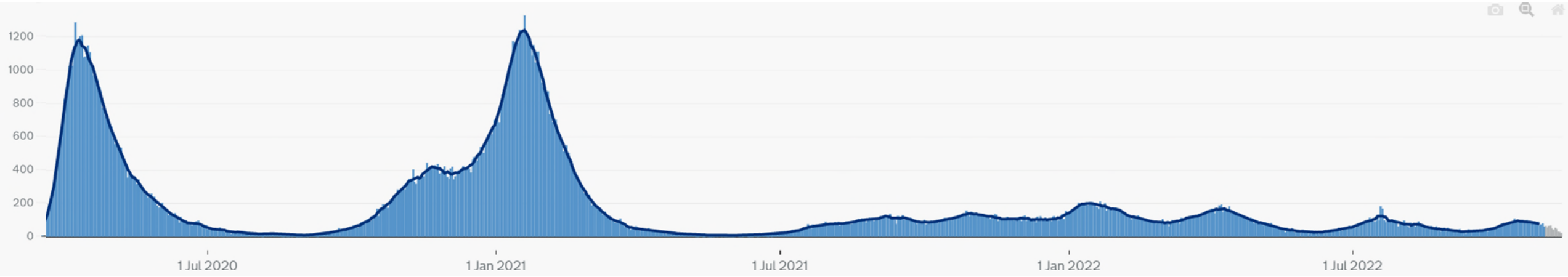
UK hospital admissions with COVID-19



UK deaths caused by COVID-19



Recruitment challenges

- NIHR ‘Research Reset’ processes have meant RECOVERY has been de-prioritised at some hospitals
- Influenza may also be circulating this winter, adding to pressure on research teams
- Thank you for trying to embed RECOVERY into standard clinical care

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CURRENT DESIGN

Current comparisons for adults with COVID-19

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ELIGIBLE PATIENTS

OUTCOMES

High-dose corticosteroids (on ventilatory support)

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

Antiviral 3

L — Paxlovid *or* Usual care alone

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 s/he were to participate

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EMPAGLIFLOZIN

SGLT-2 inhibitors and Empagliflozin (empa)

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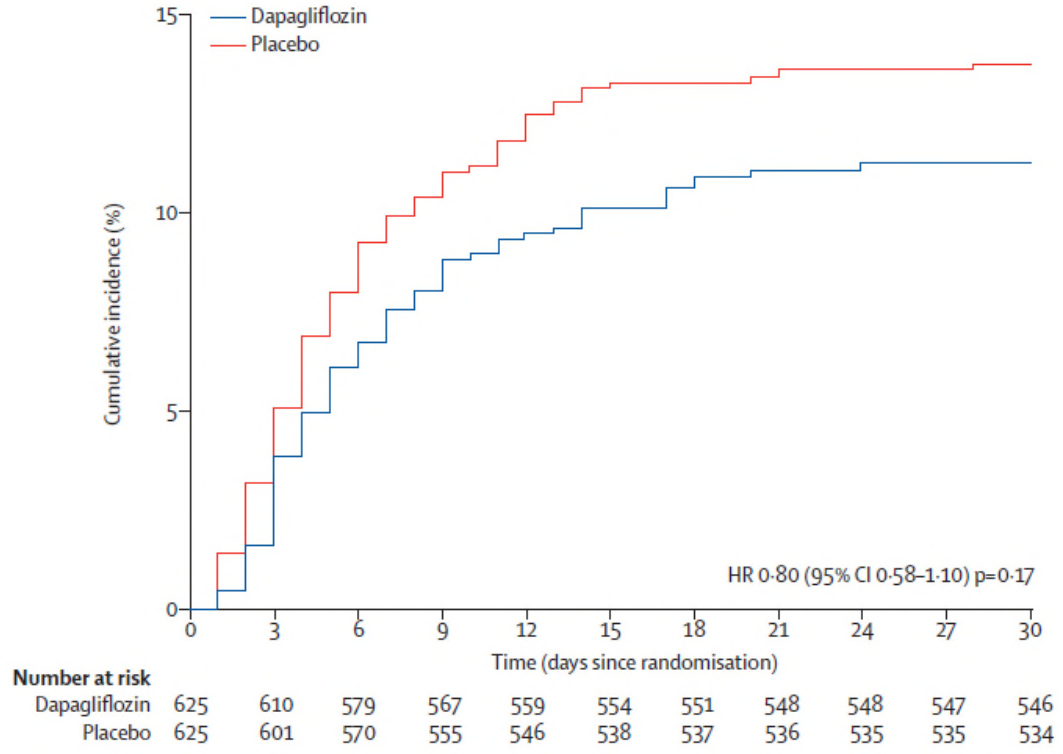
- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- 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

- **Important to monitor of ketones for participants with diabetes**
  - Twice daily blood ketones (or once daily urine ketones if blood ketone testing not available) <u>or</u> if clinical concern



DARE-19 trial – inconclusive but fewer deaths in dapagliflozin group

Empagliflozin in RECOVERY

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- 4150 participants in the comparison to date
- Recruiting in UK, Nepal, India, Vietnam, and Indonesia
- Blinded 28 day mortality rate ~14% in this comparison, meaning about 8000 participants needed

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HIGH-DOSE CORTICOSTEROIDS

High-dose corticosteroids

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- Following USM in May, this is now open only to adult patients on ventilatory support
  - This includes high-flow nasal oxygen, CPAP, BiPAP and IMV/ECMO

- **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 methylprednisolone/prednisolone/hydrocortisone

High-dose corticosteroids

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- 447 participants currently in active comparison (not counting the subgroup excluded by the Urgent Safety Measure)
- Recruiting in all countries in RECOVERY
- Blinded mortality rate 35%, so 3,000-4,000 participants required
- Results for 1272 patients on simple oxygen will be reported soon

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SOTROVIMAB

Sotrovimab

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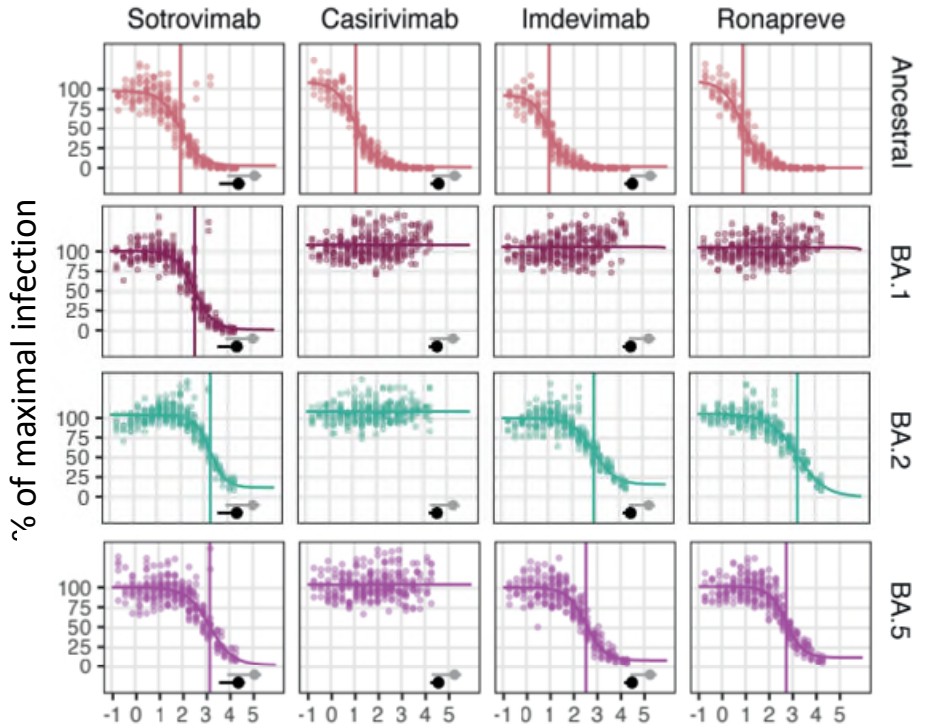
- Derived from an antibody identified in a patient who had SARS-CoV-1 infection – target may be more “conserved” so less likely to mutate in future variants

- 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**

Efficacy of sotrovimab

- Omicron BA.1 had ~5-fold reduction in neutralisation potency by sotrovimab compared to previous variants
- Omicron BA.2 had further ~5-fold reduction in neutralisation potency
- But, serum concentration are still well above the level needed to neutralise virus
- These assays are far removed from clinical efficacy
- Sotrovimab remains promising and we need randomised evidence!



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

Wu MY, et al. WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. Lancet. 2022 Oct 6. PMID36209762

Sotrovimab in RECOVERY

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- 1406 participants to date
- Blinded mortality rate ~21%
- Key importance of subgroups defined by serostatus
- 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

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MOLNUPIRAVIR

Molnupiravir

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- Molnupiravir makes the SARS-CoV-2 RNA polymerase introduce errors into its genetic code
- Eventually these errors are too great and replication is blocked
- In 1433 participants in MOVe-OUT trial it reduced risk of hospitalisation or death by ~30% (from 9.7% to 6.8%)
- Very little data from patients in hospital

Molnupiravir

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- Results from PANORAMIC recently released, including 25,783 outpatients at increased risk of complications
- No reduction in hospitalisation/death but very low risk: 103 molnupiravir vs 96 control (0.8% in both groups)
- Molnupiravir associated with a substantial reduction in time to self-reported recovery, but this is hard to interpret as it was open-label
- This population very different to RECOVERY, and benefit still plausible for patients hospitalised with COVID-19 lung disease

Molnupiravir in RECOVERY

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- 773 participants to date
- Blinded mortality rate is about 17%
- Protocol exclusions:
  - Age <18 years old
  - Pregnant or breast-feeding women.
  - Prior treatment with molnupiravir during same illness
  - Must be able to swallow capsules
- No exclusion criteria around liver or kidney function
- Can be given if people have already received sotrovimab or Paxlovid
- Course to be completed at home if discharged before complete

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PAXLOVID

Paxlovid

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- Paxlovid is a combination of nirmatrelvir, which inhibits viral protease, and ritonavir which inhibits nirmatrelvir metabolism

- In the EPIC-HR trial of 2,085 outpatients, hospitalisation or death occurred in 8/1039 (1%) allocated Paxlovid versus 66/1046 (6%) allocated placebo (reduction of 88%)

- Approved for use in early COVID-19 but not data in hospitalised patients

Paxlovid drug interactions

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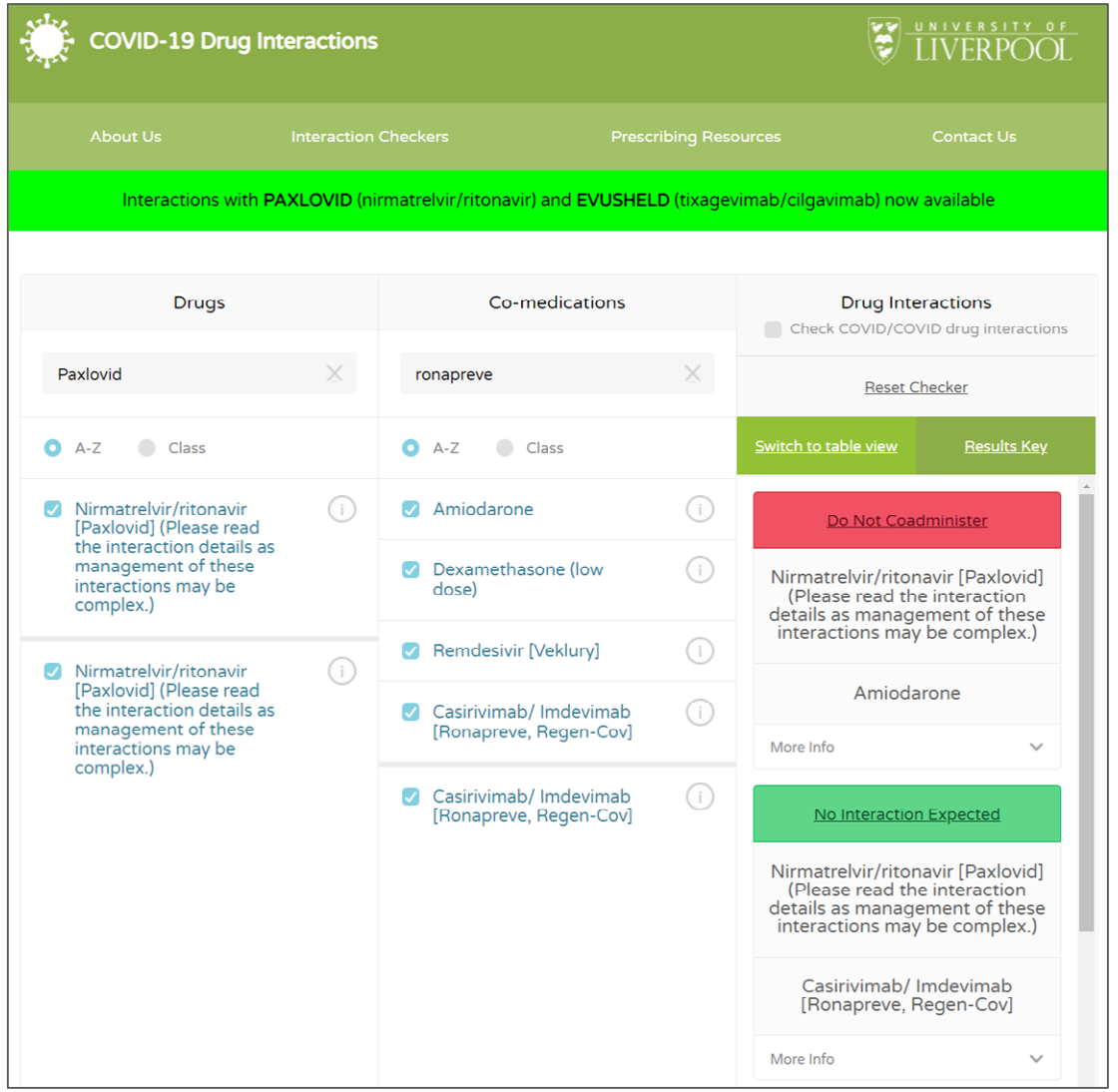
- Ritonavir interacts with many drugs
- The Liverpool COVID-19 therapies interaction checker incudes Paxlovid (www.covid19-druginteractions.org)
- Contraindicated medications listed in the protocol appendix
- No significant interaction with tocilizumab, baricitinib, remdesivir, Ronapreve, sotrovimab, molnupiravir, or empagliflozin



Paxlovid in RECOVERY

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- Paxlovid *does* interact with dexamethasone
  - Effectively means low-dose dexamethasone plus Paxlovid is equivalent to high-dose dexamethasone
  - Participants cannot enter Paxlovid and high-dose dexamethasone comparison
- If patients receiving Paxlovid require corticosteroid therapy for COVID-19, then instead of dexamethasone they should receive
  - Prednisolone 40mg once daily, or
  - Hydrocortisone 80mg twice daily
- May affect combined oral contraceptives, so women of child-bearing potential should use an effective alternative for one complete menstrual cycle after stopping
- The course should be completed at home if participants are discharged before it is finished

Paxlovid in RECOVERY

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- 97 participants to date

- Blinded mortality rate is about 14%

Contraindications

- Patients aged < 18 years
- Severe liver or renal impairment
- Inability to swallow tablets (no NG or IV formulations are available)
- Patients who have received Paxlovid during the current illness
- First trimester of pregnancy (<12 weeks)
- Concomitant drugs that may have dangerous interactions with ritonavir (if they cannot be withheld)

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TRIAL PROCEDURES

Biological sampling in RECOVERY

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- RECOVERY demonstrated that knowledge of baseline serostatus was crucial to understand effects of monoclonal antibody therapies (although other tests may be preferable in future)

- Only for participants in antiviral comparisons:
  - Sotrovimab
  - Molnupiravir
  - Paxlovid

- Includes those allocated usual care in these comparisons (i.e. if the computer *could* have allocated them to an antiviral, we need samples)

- 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 have been distributed to sites
- 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)
- **Patients discharged before day 5 should be asked to self-swab and post kits themselves if possible**
  - Printable instructions are on the website Site Staff>Site Teams> Self swabbing instructions

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)**

Consenting pregnant women

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- Please ensure a medical consultant with expertise in pregnancy medicine (e.g. obstetrician or obstetric physician) is involved in decision making

- Please document discussion of benefits and risks with woman in medical notes

- Please send a copy of that discussion to RECOVERY trial team

Safety reporting

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- Trial protocol requires all Suspected Serious Adverse Reactions (SSARs) to be reported within 24 hours of local investigator becoming aware

- SSAR is an adverse event that is **both**:
  - **Serious** (i.e. prolongs admission, is fatal or life-threatening or is otherwise considered to be serious by local investigator); **and**
  - **Related** (i.e. reasonable probability of causal association in opinion of local investigator)

- (Unrelated SAEs do not require reporting in the UK)

Completeness of follow-up

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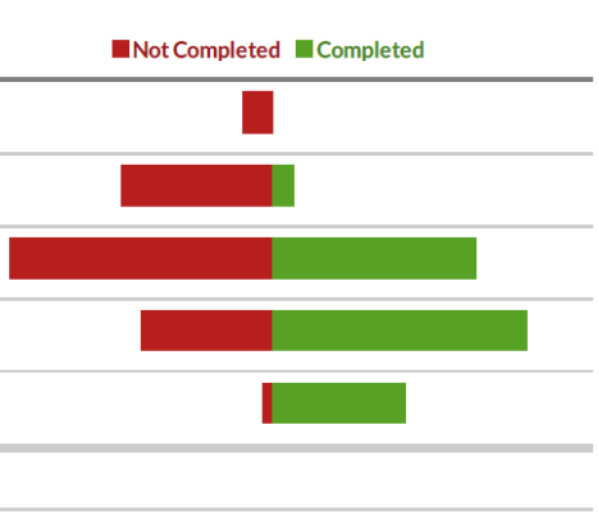
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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!

Carry on recruiting!

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- We will continue to see new variants and waves of infection for some time
- Visibility of COVID-19 has decreased dramatically but it has not gone away
- We recognise other challenges to clinical service and research delivery, but hope that RECOVERY will remain a local priority as it is still a significant cause of morbidity and mortality
- We are extremely grateful for your efforts to recruit to RECOVERY and help us identify new treatments for patients with COVID-19