Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

29th & 30th June 2022

Agenda

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1. Introductions
2. Update on progress
3. Current active comparisons:
   - Empagliflozin
   - High-dose corticosteroids
   - Sotrovimab
   - Molnupiravir
   - Paxlovid
4. Trial procedures
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

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PROGRESS UPDATE

State of the pandemic

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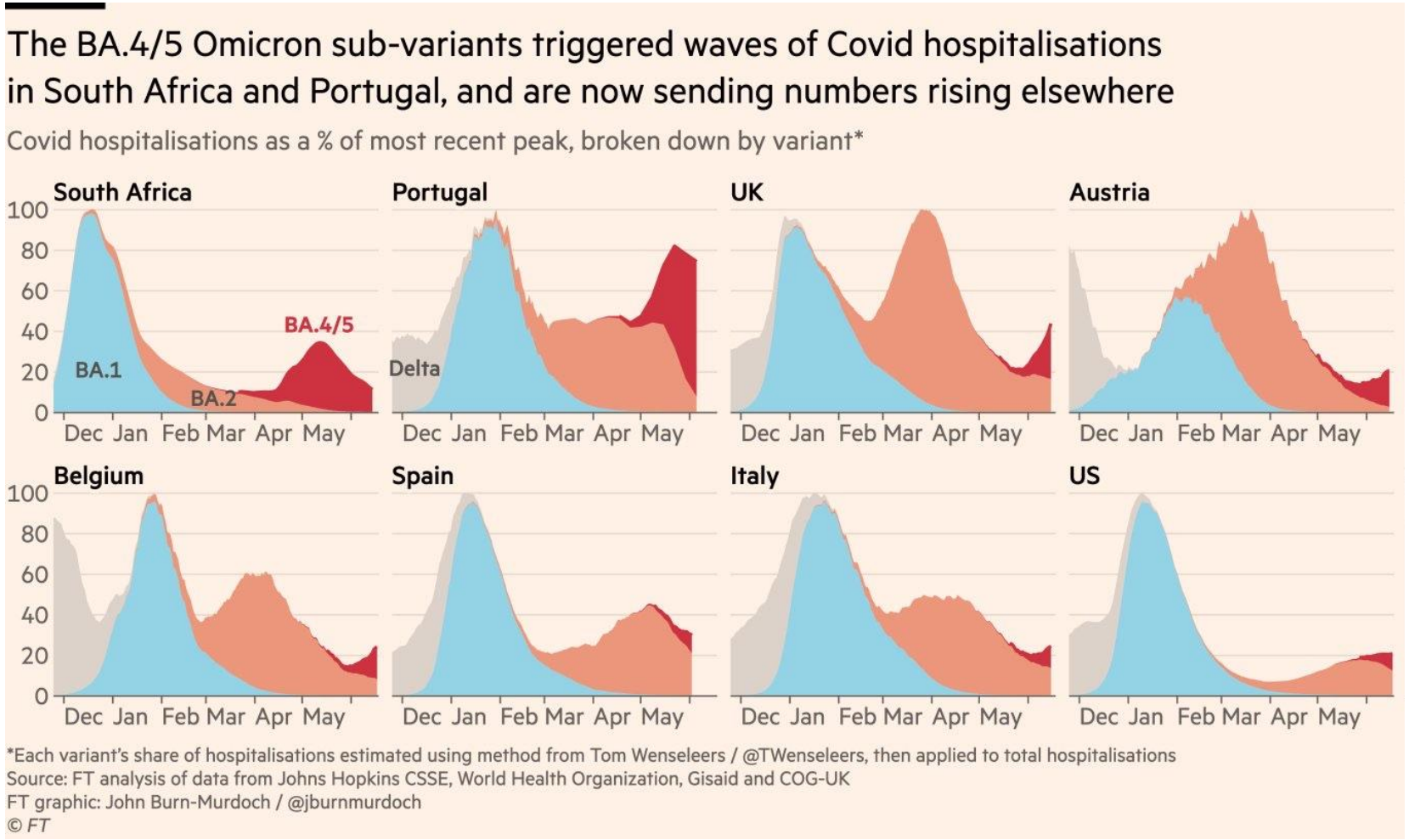

State of the pandemic

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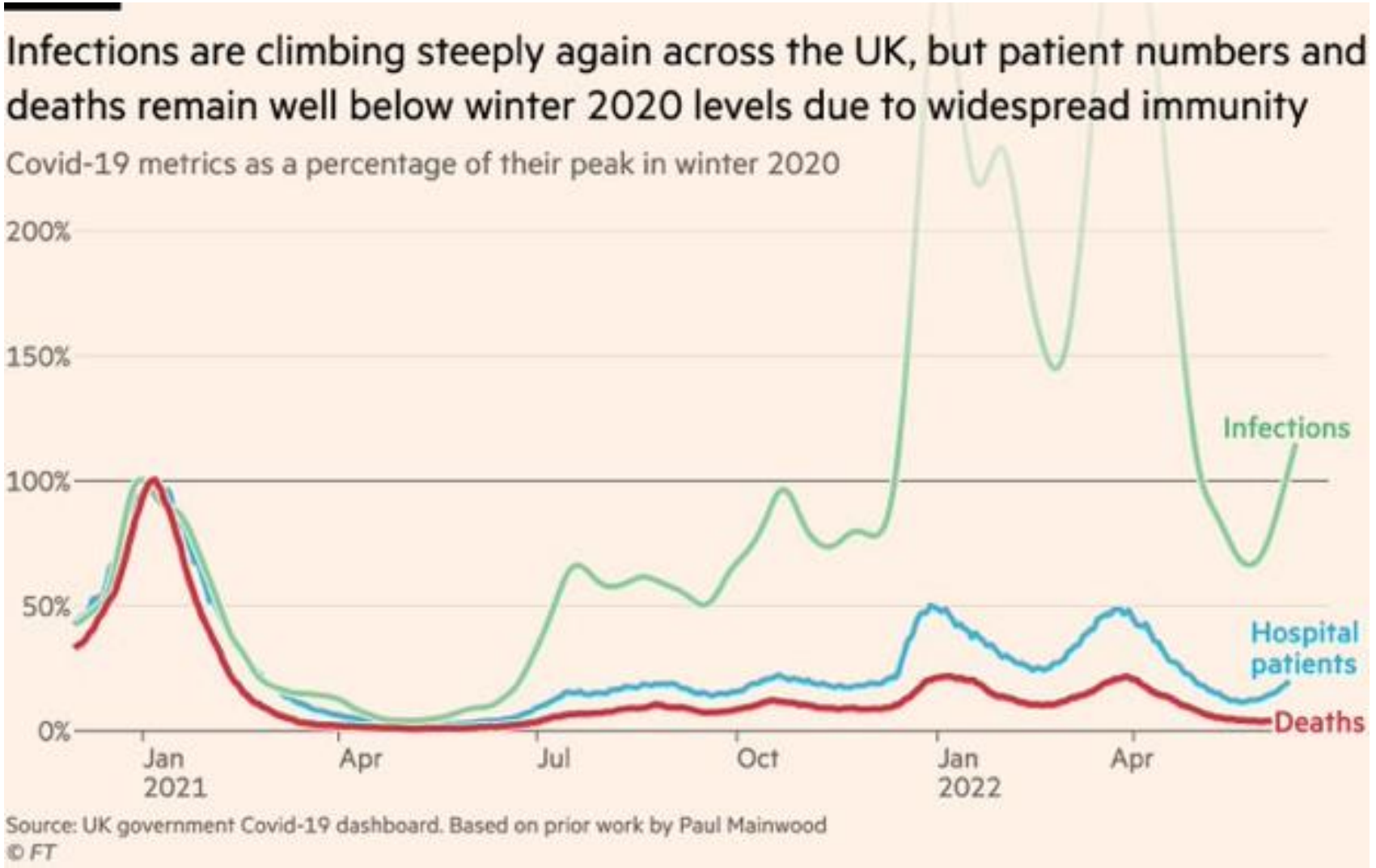

Recruitment by time

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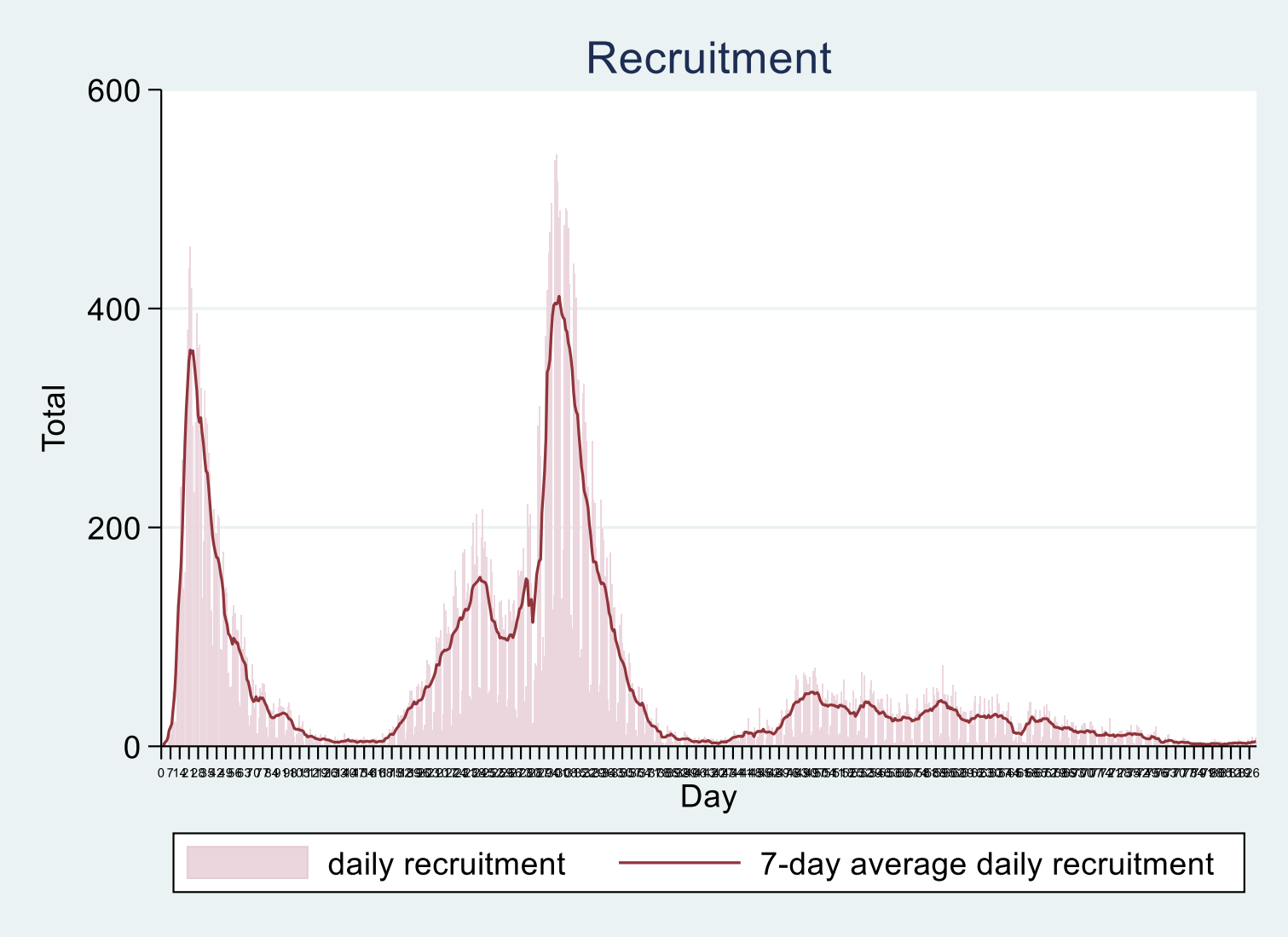

Recruitment challenges

- NIHR ‘Research Reset’ processes have meant RECOVERY has been de-prioritised at some hospitals
- Staff absences with COVID-19 exacerbate this situation
- 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 (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

OUTCOMES

Eligibility

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1. Hospitalised

2. Viral pneumonia syndrome

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

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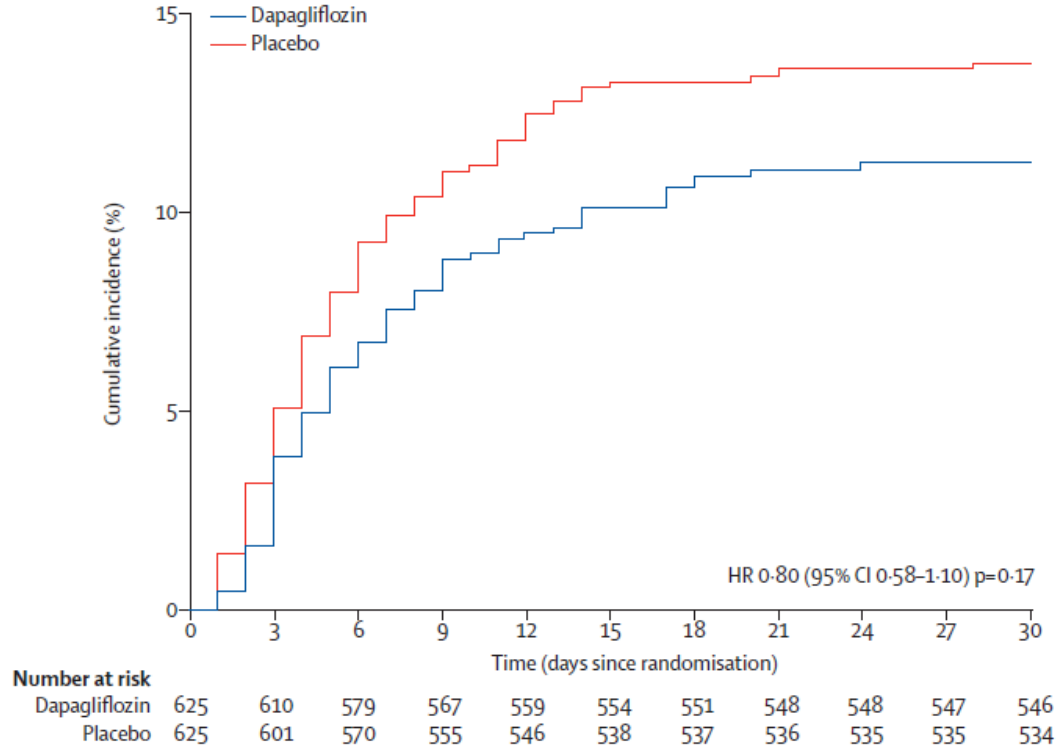
- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- 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

Empagliflozin in RECOVERY

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- 3800 participants in the comparison to date
- Recruiting in UK, Vietnam, Indonesia and Nepal
  - Other countries to start soon
- 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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- 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: Urgent Safety Measure

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- Data Monitoring Committee recommended that recruitment of patients on no oxygen or simple oxygen was stopped due to hazard in this subgroup (based on 1272 participants)

- Urgent Safety Measure implemented on 13 May 2022 and now formalised in V25.0 of the protocol

- Results of this subgroup will be reported

High-dose corticosteroids

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- **Eligibility:** adult patients <u>on ventilatory support</u>
  - 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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- 414 participants currently in active comparison (ie, not counting the subgroup excluded by the Urgent Safety Measure)
- Recruiting in all countries in RECOVERY
- Blinded mortality rate ~30% so 3-4000 participants required

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SOTROVIMAB

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

Sotrovimab in RECOVERY

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- 1120 participants to date
- Blinded mortality rate is about 20%
- Key importance of subgroups defined by serostatus

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MOLNUPIRAVIR

Molnupiravir

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- Molnupiravir is a prodrug of the ribonucleoside analogue N-hydroxycytidine (NHC), being rapidly converted into this form in plasma after absorption

- The SARS-CoV-2 RNA polymerase incorporates NHC into its RNA when creating copies inside human cells, thereby introducing errors into its genetic code

- Eventually these errors are too great and replication is blocked

Molnupiravir

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- Molnupiravir is licensed in the UK for treatment of mild-moderate COVID-19 in outpatients. (Also being tested by PANORAMIC trial.)

- Based on data from 1433 participants in MOVe-OUT trial which showed it reduced risk of hospitalisation or death by ~30% (from 9.7% to 6.8%)

- Evidence in hospitalised patients is limited: MOVe-IN trial assessed 3 different doses vs placebo in 300 hospitalised patients, so only 75 patients received preferred dose

Eligibility for molnupiravir

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- Protocol currently excludes use for:
  - Patients with known hypersensitivity to molnupiravir
  - 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 Ronapreve

Safety assessments

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- Known adverse effects include:
  - Headache, dizziness
  - GI upset: nausea, vomiting, diarrhoea
  - Rash

- All usual outcomes will be collected along with Suspected Serious Adverse Reactions

Use in RECOVERY

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- Dose is **800 mg twice daily for 5 days**
- Capsules must be swallowed whole and should not be opened
- Course **should be completed** at home if discharged before completing it

Requirements for participation

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- Site PI must complete online training
  - Cascade to other relevant staff

- CCO will inform NHS England to ensure supply is available

Molnupiravir in RECOVERY

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- 575 participants to date

- Blinded mortality rate is about 14%

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PAXLOVID

Paxlovid

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- Paxlovid is a combination of nirmatrelvir (PF-07321332) and ritonavir
- Nirmatrelvir is an inhibitor of the SARS-CoV-2 main protease, and stops viral replication by preventing cleavage of the viral polypeptide
- Ritonavir inhibits CYP3A mediated metabolism, resulting in higher concentrations of nirmatrelvir
- The viral protease is a conserved target, so Paxlovid retains activity against Omicron (and hopefully future variants)
- Because Paxlovid, molnupiravir and sotrovimab have distinct viral targets, they may have additive antiviral effects

Efficacy of Paxlovid

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- Paxlovid is approved for use in early COVID-19, but there is no data from hospitalised patients
- In the EPIC-HR trial, 2,085 patients with COVID-19 symptoms starting in the past 5 days were given Paxlovid or placebo
- Hospitalisation or death occurred in 8/1039 (1%) allocated Paxlovid versus 66/1046 (6%) allocated placebo (a reduction of 88%)
- Adverse effects included altered taste (6%) and diarrhoea (3%). Treatment was discontinued due to adverse events in 2% allocated Paxlovid and 4% allocated placebo

Eligibility for Paxlovid

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Contraindications

- Patients aged < 18 years
- Severe liver impairment (Child-Pugh class C)
- Severe renal impairment (eGFR <30 mL/min/1.73m^2)
- Concomitant medication that may have dangerous interactions with ritonavir (if this cannot be withheld)
- 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)

- Pregnant women in the 2nd & 3rd trimester, and breast-feeding women *are* potentially eligible after individualised discussion of risks & benefits - see protocol appendix for more information.

Paxlovid drug interactions

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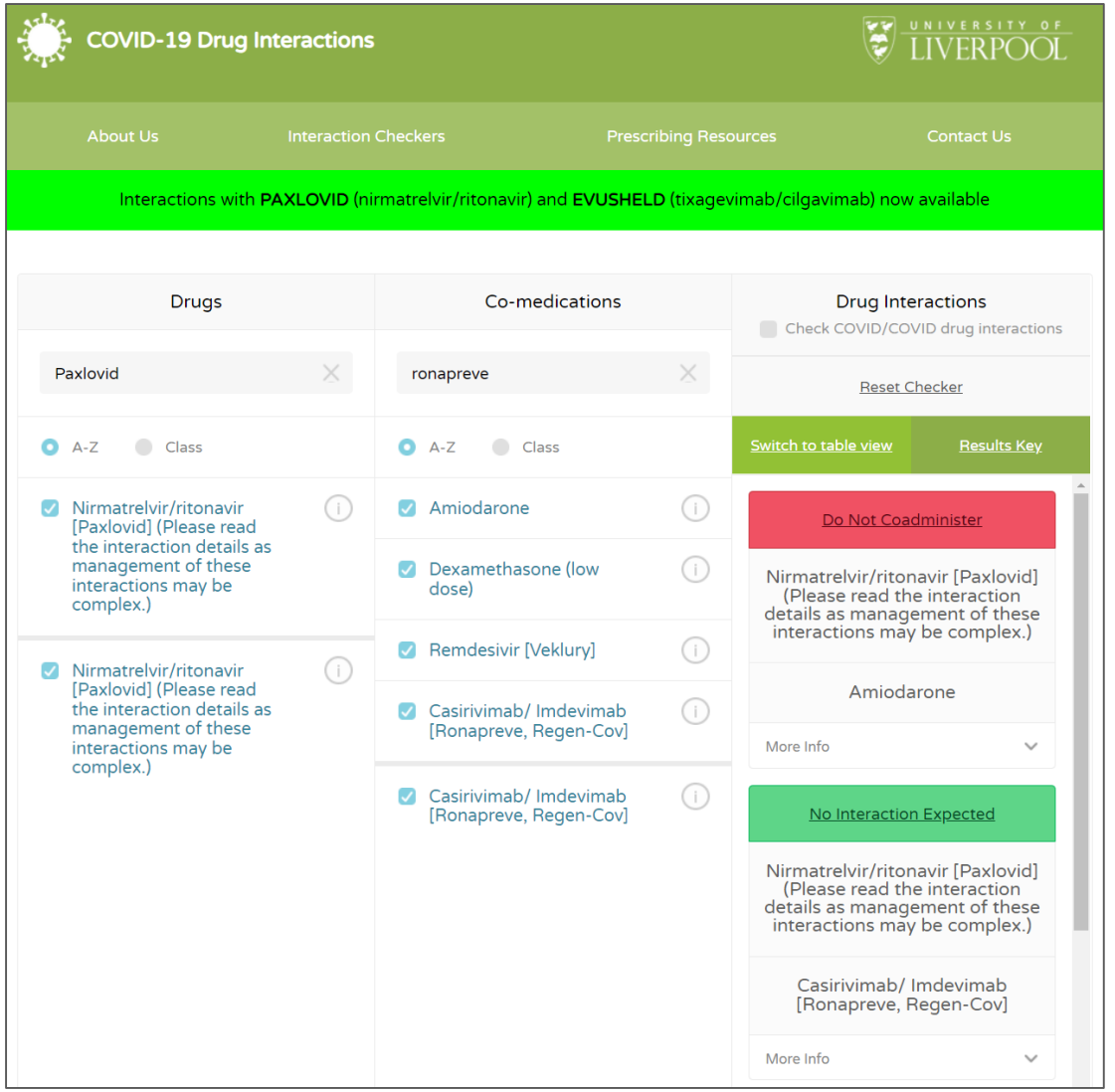
- Ritonavir interacts with many drugs, including statins, anticoagulants, antiarrhythmics, antipsychotics, benzodiazepines, immunosuppressants
- The Liverpool COVID-19 therapies interaction checker incudes Paxlovid (www.covid19-druginteractions.org)
- Contraindicated medications are listed in the protocol 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 in Paxlovid comparison already automatically unsuitable for high-dose dexamethasone comparison
- Following Urgent Safety Measure, Paxlovid should not be given with low-dose dexamethasone to people not on oxygen or just on simple oxygen
- Prednisolone or hydrocortisone should be used instead (as no important interaction with these) for all participants receiving Paxlovid

Paxlovid in RECOVERY

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- Dose is **Paxlovid 300/100 twice daily for 5 days (two nirmatrelvir 150mg tablets plus one ritonavir 100mg tablet)**
- Reduce dose to 150/100 twice daily in moderate renal impairment (eGFR 30-59 mL/min/1.73m^2).
- The course should be completed at home if participants are discharged before it is finished
- Please try to ensure that provision of drug to take home does not delay discharge
- May affect combined oral contraceptives, so women of child-bearing potential should use an effective alternative for one complete menstrual cycle after stopping
- Biological sampling will be <u>crucial</u> to assessments

Access to molnupiravir and Paxlovid

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- In England, if your trust has a COVID-19 Medicines Delivery Unit (CMDU) you will be able to use stock from this for RECOVERY

- Other trusts in England are also being provided with stock by NHSE for use in RECOVERY

- In Devolved Nations, we understand that stock is provided to acute hospitals and can be used for RECOVERY

Omicron and Pregnancy

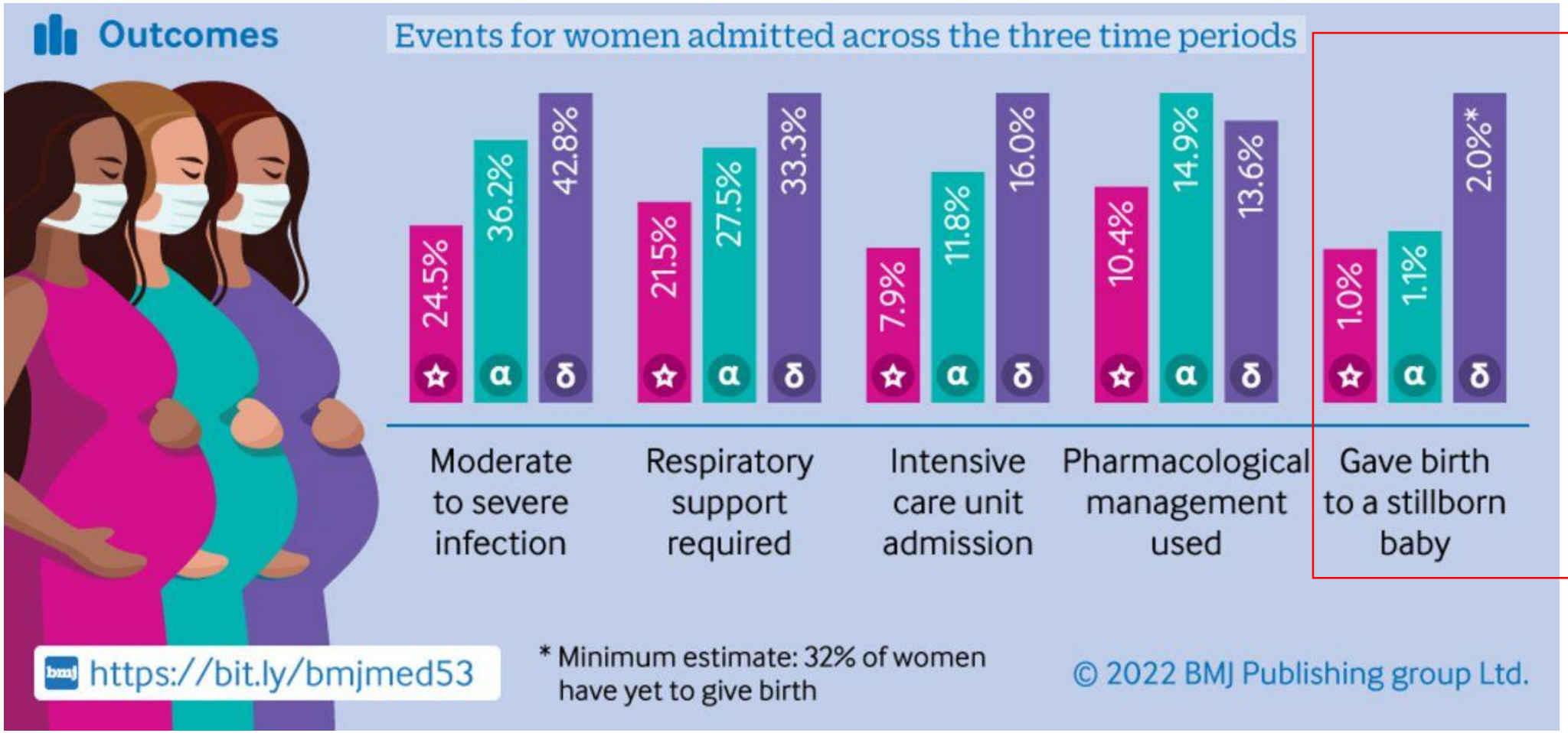
- 3,699 women admitted with confirmed SARS-CoV-2 infection 15/12/21-14/03/22
- 986 (27%) had symptomatic infection (59% unvaccinated)

	Number of symptomatic women N=986	% (95% CI)
Composite indicator of moderate to severe infection	144	14.6 (12.5, 17.0)
Oxygen saturation <95%	31	4.2 (2.9, 5.9)
Evidence of pneumonia on imaging	72	7.3 (5.8, 9.1)
Respiratory support required	99	10.4 (8.6, 12.5)
Invasive Ventilation or ECMO	12	13.3 (6.1, 27.6)
Intensive Care Unit admission	30	3.0 (2.1, 4.3)
Maternal Death	4	0.4 (0.1, 1.1)
Pharmacological Management Total	50	5.1 (3.9, 6.6)

Omicron and vaccination status

	Unvaccinated n (%) N=489	1 dose n (%) N=107	2 doses n (%) N=194	3 doses n (%) N=55	Unknown n (%) N=141
Composite indicator of moderate to severe infection	93 (19.0)	14 (13.1)	19 (9.8)	3 (5.5)	15 (10.6)
Intensive Care admission	23 (4.7)	3 (2.8)	2 (1.0)	0 (0.0)	2 (1.4)
Maternal Death	3 (0.6)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Stillbirth	5/291 (1.7) (1.0)	1/70 (1.4) (0.9)	3/101 (3.0) (1.5)	0/27 (0.0) (0.0)	1/70 (1.4) (0.7)

Covid-19 and baby



Omicron Minimum estimate 1.0% (may be higher in unvaccinated)

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TRIAL PROCEDURES

Biological sampling in RECOVERY

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

- 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 have now 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)
- In the new protocol, **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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- Many thanks to sites which have returned consent monitoring tools
  - If your site has not yet, please do so (and ask if you're not sure)

- 147 sites have returned information on 3894 consent forms
  - 70% consent obtained from participant directly
  - 15% consent obtained from participant via witness
  - 15% consent obtained from legal representative
    - Remember: in these cases participant **must** be informed about participation prior to discharge and this should be documented in notes

Consent monitoring

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- We need to finish current round of monitoring so please complete the tool if your site has not already done so

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

- **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.)

Delegation of duties logs

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- The CCO team have distributed draft delegation of duties logs to sites
- Please check these and indicate to CCO if anyone has left trial team so they can be removed
- Please return to CCO asap
- We will also publish some training materials for PIs – more details to follow

Completeness of follow-up

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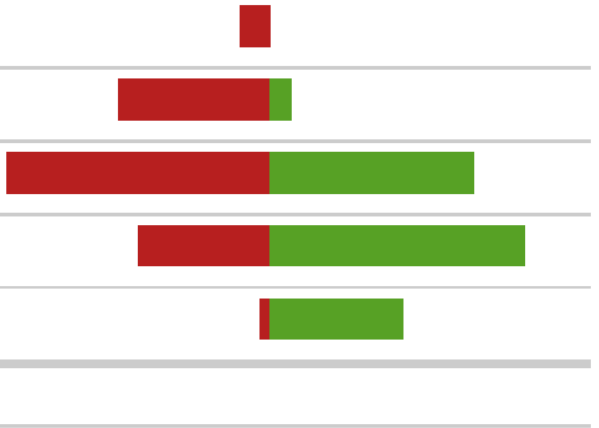
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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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- COVID-19 will be ongoing problem for some time. 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 as part of the clinical care pathway and help us identify new treatments as we care for patients with COVID-19

Request for ‘ephemera’

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We are looking for:

- photos
- video footage
- treatment packaging
- posters
- presentations
- anything else that will help tell the RECOVERY story (physical or digital)

All materials can be credited and/ or placed under time limited embargoes, if needed

For the **Collecting COVID project**
https://www.hsm.ox.ac.uk/collecting-covid and our own archive