Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

28th March 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
6. Pregnancy update

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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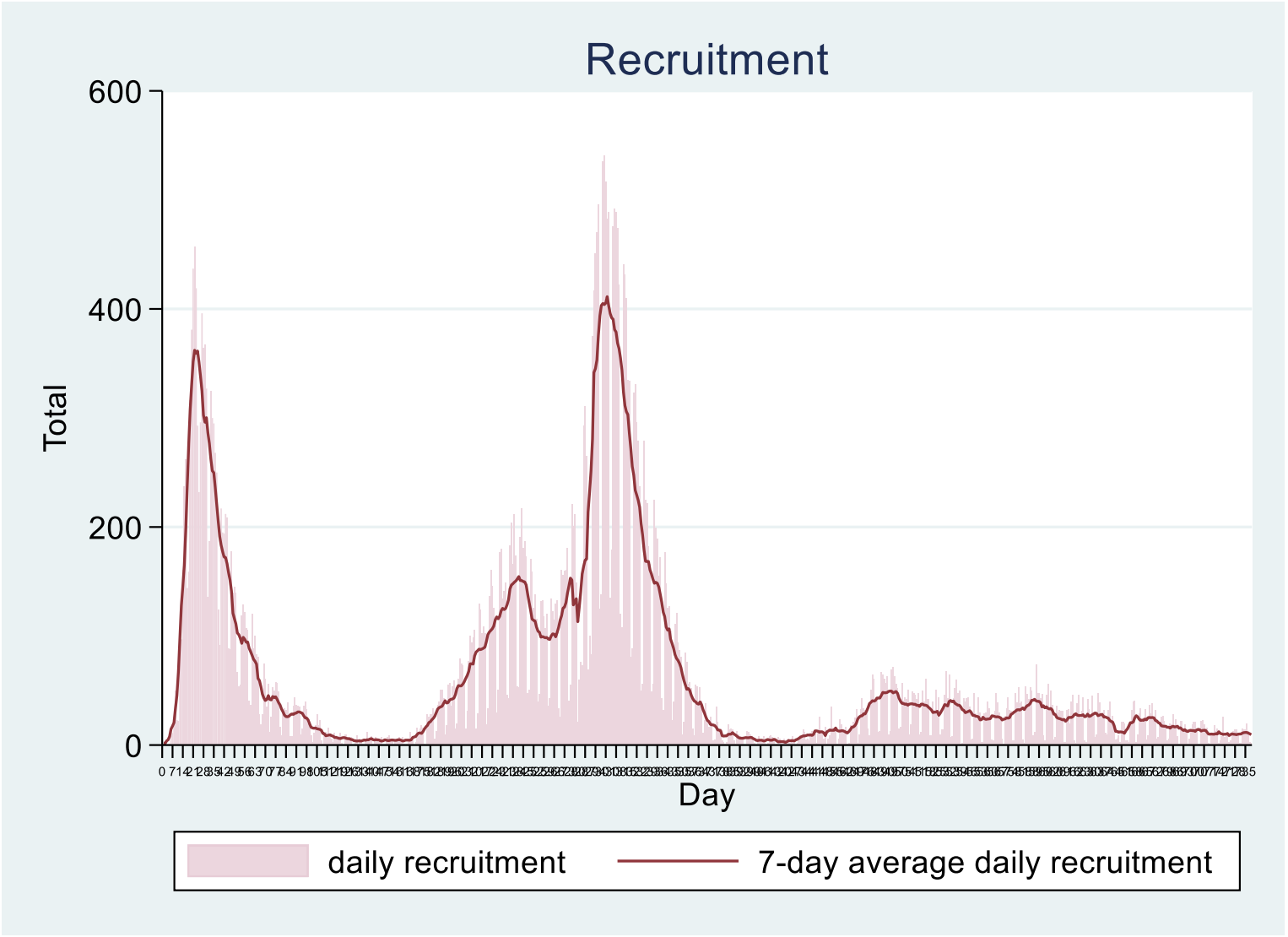

Current numbers in comparisons

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- Empagliflozin: ~3600
- High-dose corticosteroids: ~1600
- Sotrovimab: ~800
- Molnupiravir: ~350

Recruitment

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- We recognise up to ½ 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

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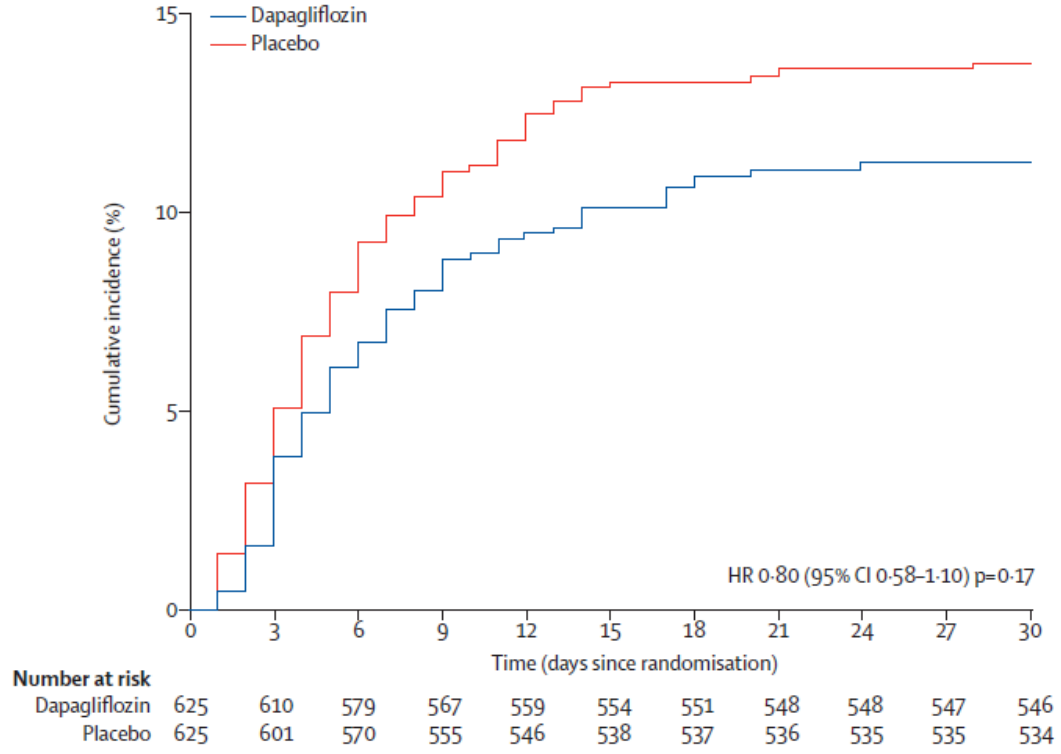
- Empagliflozin is an SGLT-2 inhibitor (SGLT-2i)

- 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

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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 methylprednisolone/prednisolone/hydrocortisone

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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

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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

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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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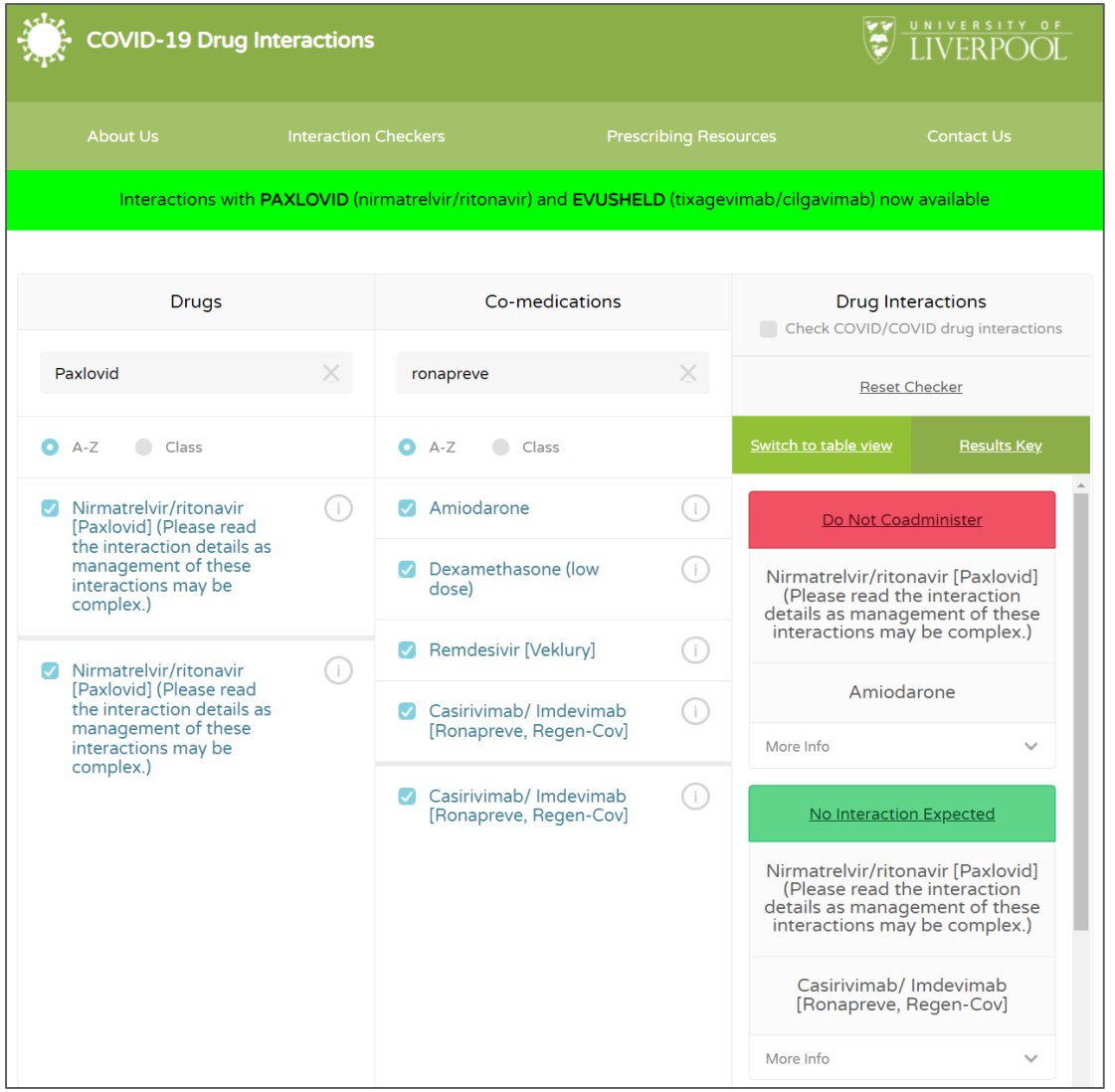
- Ritonavir interacts with many drugs, including statins, anticoagulants, antiarrhythmics, antipsychotics, benzodiazepines, immunosuppressants
- The Liverpool COVID-19 therapies interaction checker incudes Paxlovid (www.covid19-druginteractions.org)
- Contraindicated medications are listed in the protocol appendix
- Dexamethasone levels are increased, so patients cannot also be randomised to the high-dose dexamethasone comparison
- No significant interaction with standard dose (6mg) dexamethasone, tocilizumab, baricitinib, remdesivir, Ronapreve, sotrovimab, molnupiravir, or empagliflozin



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

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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)

- 96 sites have returned information on 2508 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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- Forms could not be found
  - These will be followed up with sites eg, was whole volume of notes lost, was there other documentation to confirm consent was obtained
- Forms signed by staff who have not completed training
  - Remember: **All staff** who will continue to obtain consent for RECOVERY and PIs are required to complete new training (and online confirmation form)
- Forms used incorrect version of PIS
  - Remember: please remove all old copies of PIS/ICF <u>today</u> as new protocol has been implemented

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

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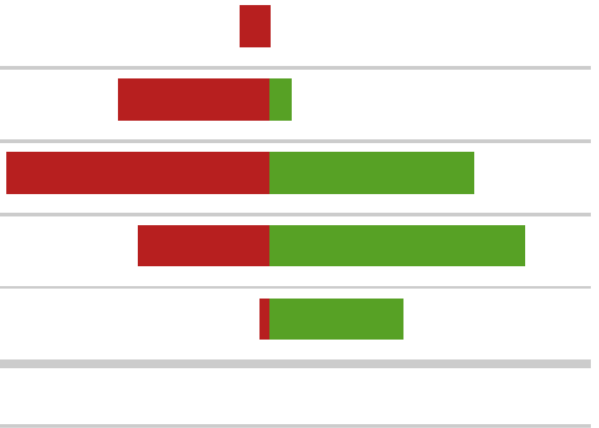
- Weekly reminders highlighting participants randomised >28 days ago without complete form

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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- 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

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators Meeting for Pregnancy

28 March 2022

RECOVERY for pregnant women

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1. Update on covid-19 and pregnancy
2. Update on new arms and adaptations
3. Q&A

Covid-19 and pregnancy

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RESEARCH

OPEN ACCESS

Check for updates

Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study

Marian Knight,[1] Kathryn Bunch,[1] Nicola Vousden,[2] Edward Morris,[3] Nigel Simpson,[4] Chris Gale,[5] Patrick O'Brien,[6] Maria Quigley,[1] Peter Brocklehurst,[7] Jennifer J Kurinczuk,[1] On behalf of the UK

BMJ: first published as 10.1136/bmj.m2107 on 8 June 2020.

PLOS ONE

PUBLISH ABOUT BROWSE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS)

Nicola Vo
Peter Bro
Published

OPEN ACCESS ORIGINAL RESEARCH

bmjmedicine

Check for updates

Severity of maternal infection and perinatal outcomes during periods of SARS-CoV-2 wildtype, alpha, and delta variant dominance in the UK: prospective cohort study

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2021-000053).

For numbered affiliations see

Received: 30 September 2021 | Revised: 9 December 2021 | Accepted: 19 January 2022

DOI: 10.1111/aogs.14329

AOGS

ORIGINAL RESEARCH ARTICLE

Management and implications of severe COVID-19 in pregnancy in the UK: data from the UK Obstetric Surveillance System national cohort

Nicola Vousden[1] | Rema Ramakrishnan[1] | Kathryn Bunch[1] | Edward Morris[2] | Nigel Simpson[3] | Christopher Gale[4] | Pat O'Brien[2,5] | Maria Quigley[1] | Peter Brocklehurst[6] | Jennifer J. Kurinczuk[1] | Marian Knight[1]

Morbidity and Mortality Weekly Report

Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020

Laura D. Zambrano, PhD[1,*]; Sascha Ellington, PhD[1,*]; Penelope Strid, MPH[1]; Romeo R. Galang, MD[1]; Titilope Oduyebo, MD[1]; Van T. Tong, MPH[1]; Kate R. Woodworth, MD[1]; John F. Nahabedian III, MS[1]; Eduardo Azziz-Baumgartner, MD[1]; Suzanne M. Gilboa, PhD[1]; Dana Meaney-Delman, MD[1]; CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team

Maternal, Newborn and Infant Clinical Outcome Review Programme

MBRRACE-UK

Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Saving Lives, Improving Mothers' Ca

Rapid report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK

Maternal, Newborn and Infant Clinical Outcome Review Programme

MBRRACE-UK

Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Saving Lives, Improving Mothers' Care

Rapid report 2021: Learning from SARS-CoV-2-related and associated maternal deaths in the UK

June 2020-March 2021

RESEARCH

OPEN ACCESS

Check for updates

FAST TRACK

Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis

John Allotey,[1,2] Elena Stallings,[3,4] Mercedes Bonet,[5] Magnus Yap,[6] Shaunak Chatterjee,[6] [6] Anushka Dixit,[6] Dengyi Zhou,[6] Rishab Balaji,[6] uti Coomar,[1] Madelon van Wely,[10] e Kunst,[12,13] Asma Khalil,[14] Simon Tiberi,[12,13] Caron Rahn Kim,[5] Anna Thorson,[5] mora,[3,4,16] Shakila Thangaratinam,[2,17] tium

BMJ: first published as 10.1136/bmj.m33

EDITORIALS

Check for updates

1 National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

2 Institute of Applied Health Research, University of Birmingham, Birmingham, UK

3 UK Obstetric Surveillance System

Include pregnant women in research—particularly covid-19 research

Adapting interventions and changing attitudes will drive scientific progress

Marian Knight,[1] R Katie Morris,[2] Jenny Furniss,[3] Lucy C Chappell[4]

The UK Confidential Enquiries into Maternal Deaths have repeatedly highlighted inequities in the medical treatment of pregnant and postpartum women, noting

or breastfeeding allows safety concerns to be allayed for women, their families, and healthcare professionals.

BMJ: first published a

Omicron and pregnancy

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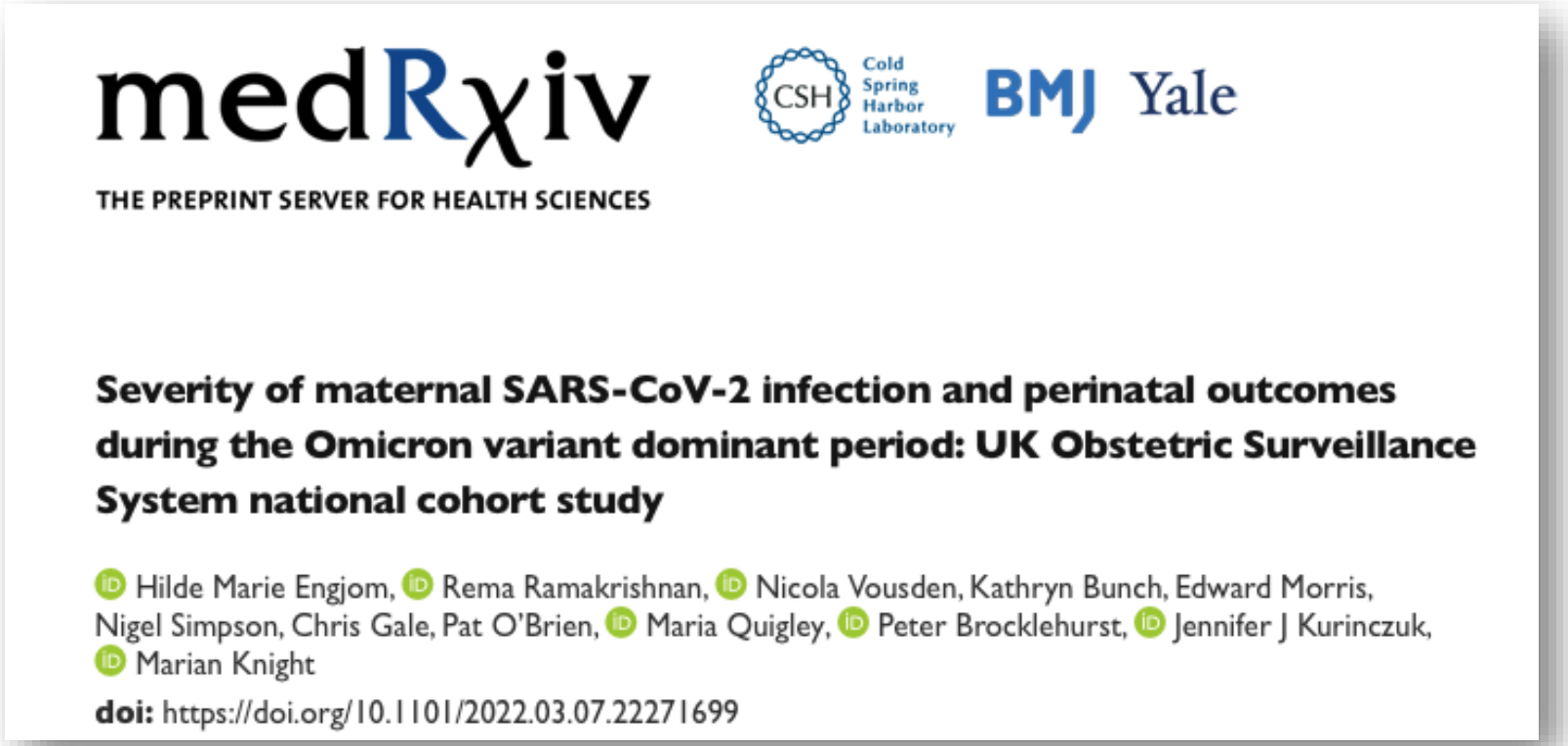

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

CSH Cold Spring Harbor Laboratory BMJ Yale

Severity of maternal SARS-CoV-2 infection and perinatal outcomes during the Omicron variant dominant period: UK Obstetric Surveillance System national cohort study

Hilde Marie Engjom, Rema Ramakrishnan, Nicola Vousden, Kathryn Bunch, Edward Morris, Nigel Simpson, Chris Gale, Pat O'Brien, Maria Quigley, Peter Brocklehurst, Jennifer J Kurinczuk, Marian Knight

doi: https://doi.org/10.1101/2022.03.07.22271699

- Pregnant women are still being assessed with NEWS
- Only around 50% of pregnant and postpartum women admitted to intensive care with covid-19 were managed with a steroid for maternal indication

Omicron period 15/12/21-14/01/22

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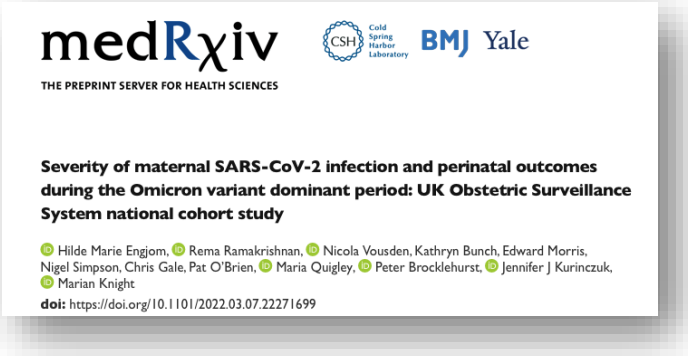
Out of 1561 women admitted to hospital with SARS-CoV-2 infection, 449 (28.8%) were symptomatic. 249/449 (65%) were unvaccinated

Among symptomatic women	Unvaccinated (n,%) (n=249)	1 dose (n,%) (n=45)	2 doses (n,%) (n=76)	3 doses (n,%) (n=13)	Vaccine status unknown (n,%) (n=66)
Composite indicator of moderate to severe infection	59 (23.7)	10 (22.2)	9 (11.8)	0 (0.0)	8 (12.1)
Intensive Care admission	14 (5.6)	3 (6.7)	1 (1.3)	0 (0.0)	1 (1.5)
Maternal Death	2 (0.8)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)

UKOSS
UK Obstetric Surveillance System


medRxiv
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Cold Spring Harbor Laboratory BMJ Yale

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doi: https://doi.org/10.1101/2022.03.07.22271699

Update from UKOSS this week

UKOSS
UK Obstetric Surveillance System

Notifications by week

Covid-19 and pregnancy: headlines

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- Covid-19 affects pregnant women – now moved into JCVI ‘at risk’ group
- Additional risk factors previously identified (ethnic minority groups, increasing gestation, higher maternal age, high BMI, pre-existing comorbidities)
- Impact on preterm birth continues to be major impact
- Ongoing evidence of increased maternal risk (ICU admission and maternal morbidity) and increased perinatal risk (stillbirth, neonatal death) – risk with omicron in unvaccinated similar to wildtype period

- RECOVERY trial is one of few trials to include pregnant women, and has changed clinical practice, including for pregnant women

PREVENT 2018

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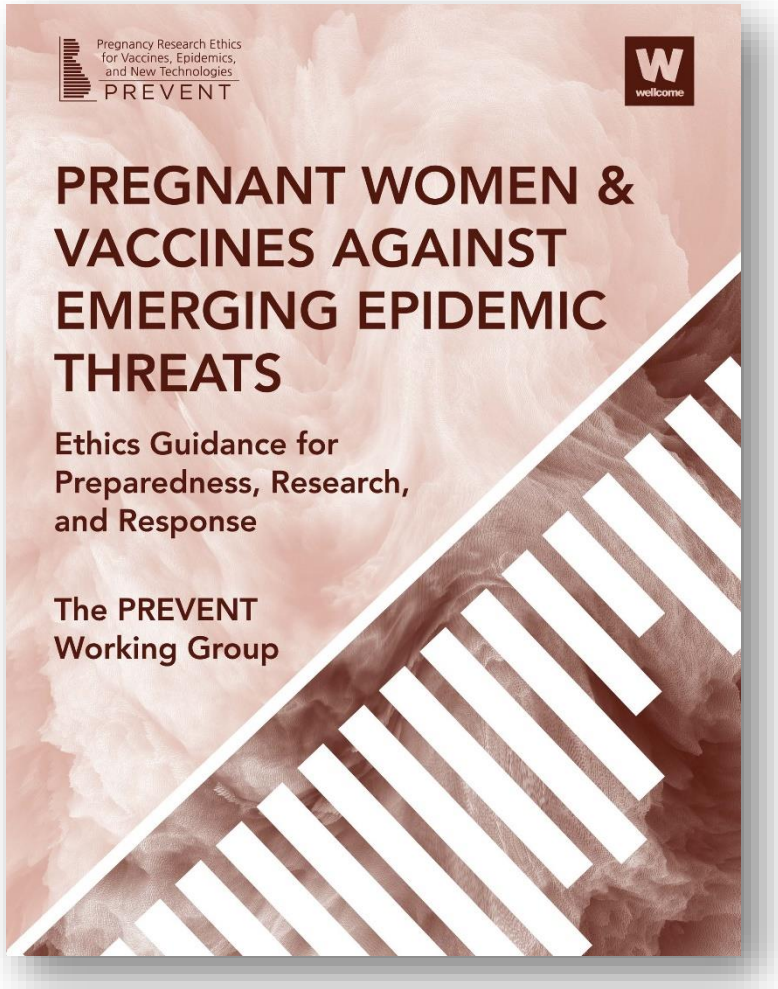

Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group guidance ethical principles state that

"Justice requires that pregnant women have fair access to research that offers the prospect of direct benefit"

PREVENT 2018

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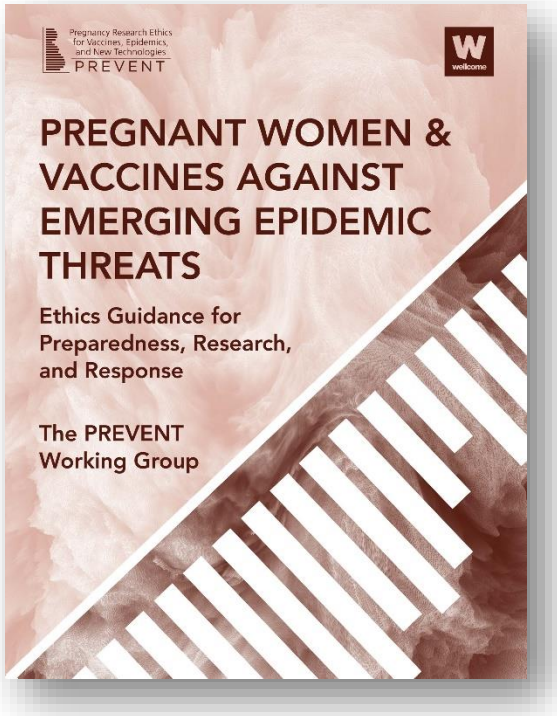
Pregnant women are autonomous human beings like most others and should have the right to choose to consent for themselves to participate in research:

"reasons that are not considered acceptable bases for exclusion from research involving prospect of direct benefit include logistical costs; liability issues; that some people would be more costly to recruit, retain, or responsibly care for or oversee; or past practices of exclusion."



Eligibility and outcomes (adults)

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Eligibility criteria:

1. Hospitalised
2. Viral pneumonia syndrome (e.g. fever, cough, or shortness of breath with compatible chest X-ray findings not thought related to another cause)
3. **Confirmed SARS-CoV-2**
4. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial

Outcomes:

1. All-cause mortality by 28 days after randomisation
2. Duration of hospitalisation; need for mechanical ventilation or death

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

Antiviral 3

L: Paxlovid *or* Usual care alone

OUTCOMES

Current comparisons for pregnant women 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 — Empagli[illegible] Usual care alone

Baseline data collected
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Outcomes collected at earliest of death, discharge or 28 days

Antiviral 1

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Antivi[illegible]

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Antiviral 3

L — Paxlovid *or* Usual care alone

OUTCOMES

Recurring message

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

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Remember the benefits of treatment

Balancing choices:

Always consider individual **benefits** and **risks** when making decisions about pregnancy

High dose steroids – pregnancy and postpartum

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Pregnant women should receive **either**

- prednisolone (130 mg) orally **or**
- hydrocortisone (540 mg in divided doses) intravenously **or**
- methylprednisolone (100 mg) intravenously for five days

- followed by **either**
  - prednisolone (65 mg) orally **or**
  - hydrocortisone (270 mg in divided doses) intravenously **or**
  - methylprednisolone (50 mg) intravenously for five days.

Postpartum women – as above **or**

- Dexamethasone may also be considered as per the adult regimen (including if breastfeeding or expressing)
  - dexamethasone 20 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days followed by dexamethasone 10 mg (base) once daily by mouth, nasogastric tube or intravenous infusion for 5 days

Sotrovimab in pregnancy and postpartum

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- As the binding target for sotrovimab is unique to COVID-19 viral proteins, it is not expected that the administration of sotrovimab in pregnancy will affect fetal development
- No binding to human embryofetal proteins in a cross-reactive binding assay
- Therefore appropriate to offer sotrovimab to pregnant women with COVID-19 in a clinical trial setting as:
  - Potential for significant maternal and fetal benefit
  - No perceived fetal risks to treatment

We will be continuing to examine pregnancy outcomes using UKOSS/UKTIS

Paxlovid (Nirmatrelvir/Ritonivir) in pregnancy and postpartum

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uktis
uk teratology information service

- No adverse effects on fetal morphology or embryo-fetal viability with doses of nirmatrelvir up to 12x human dose in rat/rabbit models.
- Offspring of pregnant rabbits administered 24x human dose of nirmatrelvir had lower fetal body weights, but evidence of maternal toxicity was described (impact on weight gain/food consumption), which is likely to explain the lower fetal weights rather than an effect of the drug itself on the fetus.
- There is a large amount of published evidence relating to the safety of ritonavir in human pregnancy, collected from antiretroviral and HIV/AIDS pregnancy registries.
- Appropriate to offer Paxlovid to pregnant women with COVID-19 in a clinical trial setting as:
  - Potential for significant maternal and fetal benefit
  - No perceived fetal risks to treatment, women in 1st trimester excluded out of caution

We will be continuing to examine pregnancy outcomes using UKOSS/UKTIS

Paxlovid guidance

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Royal College of Obstetricians and Gynaecologists (RCOG) guideline:

- Other therapies (e.g. antivirals such as Paxlovid [PF-07321332/ritonavir]) are being investigated for the management of COVID-19, and pregnant women should be offered the opportunity to enrol, if they are eligible, in clinical trials (such as the RECOVERY trial).

December 22, 2021 – Today the U.S. Food and Drug Administration issued an Emergency Use Authorization (EUA) for Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and some pediatric patients. In response, the Society for Maternal-Fetal Medicine (SMFM) issued the following statement.

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

"SMFM supports the use of Paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) for treatment of pregnant patients with COVID-19 who meet clinical qualifications. Any therapy that would otherwise be given should not be withheld specifically due to pregnancy or lactation."

Note on consent documentation

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- Many medications are used in standard clinical practice ‘off-label’ i.e. without a license for use in pregnancy based on benefit to mother
  - Trials rarely include pregnant women
  - Evidence is very slowly built up ad hoc through these uses, often over many years
- Discussions with pregnant women around such medications in situations where the benefits are likely to outweigh any theoretical risks are part of usual clinical practice
- Documentation of these discussions will also be usual clinical practice
- In order to maintain insurance for the trial we have been asked to obtain copies of the medical records documenting these discussions and we will be asking for these

RECOVERY for pregnant women

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Site teams

This page contains additional information for RECOVERY site team members. Follow these links for guidance on randomisation and how to collect follow-up data.

RECOVERY Privacy Notice for Trial Staff

INTERVENTION INFORMATION

RECOVERY intervention sheet - empagliflozin

RECOVERY intervention sheet - baricitinib

RECOVERY intervention sheet - tocilizumab

RECOVERY intervention sheet - dimethyl fumarate

RECOVERY position statement on baricitinib and tocilizumab

Measurement of additional early phase assessment outcomes SOP v1.3

GUIDES FOR SPECIFIC PATIENT GROUPS

RECOVERY for paediatric patients

RECOVERY for patients with chronic kidney disease

RECOVERY for pregnant and breastfeeding women

RECOVERY and remdesivir

COLLABORATORS' MEETINGS SLIDES

We apologise if you were unable to join the meetings.

26 April 2021	27 April 2021
22 February 2021	23 February 2021
25 January 2021	26 January 2021
4 January 2021	5 January 2021
7 December 2020	8 December 2020
16 November 2020	17 November 2020

Pregnancy information document

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RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)
for pregnant and breastfeeding women
Pregnancy lead: Prof Marian Knight
With support of UK Teratology Information Service (Dr Ken Hodson, Medical Director)

	RECOVERY trial protocol	**Adaption for pregnancy**
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. Confirmed SARS-CoV-2 iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Same eligibility
Interventions	**First randomisation part E** • High-dose corticosteroids **First randomisation part F** • Empagliflozin **First randomisation part J** • Sotrovimab **First randomisation part K** • Molnupiravir **First randomisation part I** • Paxlovid	Interventions for pregnant women • Substitution of corticosteroid (part E) iv hydrocortisone/iv methylprednisolone/ oral prednisolone (in place of dexamethasone) • Sotrovimab • Paxlovid (2nd/3rd trimester only) *Not recommended in pregnancy* • *Empagliflozin* • *Molnupiravir*
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ Vital status (alive/ dead, with date and presumed cause of death, if appropriate) ➢ Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) ➢ Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) ➢ Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same follow-up and outcomes, with **addition of UKOSS case number** (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		Dexamethasone may be considered, otherwise the same interventions as in pregnancy should be used. UKOSS case number added if available.

Follow-up = the same, + linkage

- UKOSS covid-19 in pregnancy study finishes at end of March 2022
- **EXCEPT** for women recruited to RECOVERY, who should continue to be reported via usual reporting processes
- Women and infants randomised to sotrovimab or Paxlovid will also be followed up through UKTIS

Update on progress

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- 160 pregnancy leads identified, supported by research midwives
- Midwife champions on board

- 135 pregnant or postpartum women recruited*
  - *5 with pregnancy/postpartum status to be confirmed

- 4 recruited in the Delta wave, 1 in Omicron

Thank you

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Ashford and St Peter's Hospitals NHS Foundation Trust	Leeds Teaching Hospitals NHS Trust	Oxford University Hospitals NHS Foundation Trust
Barts Health NHS Trust	Liverpool University Hospitals NHS Foundation Trust	Pennine Acute Hospitals NHS Trust
Bolton NHS Foundation Trust	Liverpool Women's NHS Foundation Trust	Royal Berkshire NHS Foundation Trust
Bradford Teaching Hospitals NHS Foundation Trust	Luton and Dunstable University Hospital NHS Foundation Trust	Royal Free London NHS Foundation Trust
Cambridge University Hospitals NHS Foundation Trust	Manchester University NHS Foundation Trust	Sheffield Teaching Hospitals NHS Foundation Trust
Chelsea and Westminster Hospital NHS Foundation Trust	Medway NHS Foundation Trust	Sherwood Forest Hospitals NHS Foundation Trust
Chesterfield Royal Hospital NHS Foundation Trust	Milton Keynes University Hospital NHS Foundation Trust	Shrewsbury and Telford Hospital NHS Trust
Croydon Health Services NHS Trust	NHS Greater Glasgow and Clyde: Glasgow Royal Infirmary	St George's University Hospitals NHS Foundation Trust
Epsom and St Helier University Hospitals NHS Trust	NHS Greater Glasgow and Clyde: Queen Elizabeth University Hospital	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Frimley Health NHS Foundation Trust	NHS Lothian: Royal Infirmary of Edinburgh	United Lincolnshire Hospitals NHS Trust
Guy's and St Thomas' NHS Foundation Trust	North Cumbria Integrated Care NHS Foundation Trust	University College London Hospitals NHS Foundation Trust
Imperial College Healthcare NHS Trust	North Tees and Hartlepool NHS Foundation Trust	University Hospitals Of Leicester NHS Trust
James Paget University Hospitals NHS Foundation Trust	North West Anglia NHS Foundation Trust	Western Sussex Hospitals NHS Foundation Trust
Kettering General Hospital NHS Foundation Trust	Northampton General Hospital NHS Trust	Worcestershire Acute Hospitals NHS Trust
King's College Hospital NHS Foundation Trust	Northumbria Healthcare NHS Foundation Trust	Wye Valley NHS Trust
Kingston Hospital NHS Foundation Trust	Nottingham University Hospitals NHS Trust	

Q&A

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