Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meetings

6 & 7 April 2020

Agenda

1. Introductions
2. Trial design
3. Frequently asked questions
   a) Informed consent
   b) Study treatments
4. Update on progress
5. Ideas on site organisation
6. Follow-up
7. Q&A

Introductions

- One of the central study team will talk to the agenda
- If you have questions about that particular topic please enter them into the “chat”
- Please save other questions for the general Q&A at the end

RECOVERY trial design

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ELIGIBLE PATIENTS

1. Age ≥18 years
2. Admitted to hospital
3. Proven SARS-CoV-2 infection

R

No additional treatment

Lopinavir-ritonavir
400/100 mg bd PO for 10 days

Dexamethasone
6 mg od PO/IV for 10 days

Hydroxychloroquine
See protocol for dosing

Interferon-β1a
6 MIU od via nebuliser for 10 days

OUTCOMES

Primary: in-hospital death

Secondary:
- Duration of hospitalisation
- Need for ventilation
- Need for renal replacement therapy

Informed consent

- Can be obtained in one of three ways:
  1. Directly with participant
  2. Witnessed (if participant has capacity but unable to read/sign)
  3. Legal representative (if participant lacks capacity)

- What do with paper consent form if participant has signed it?
  - NHS England Infection Control guidance would allow fresh ICF to be taken into room, signed by participant (with clean hands) and immediately removed
  - May not comply with local infection control guidance
    - Capture image digitally and store in electronic health record (or print)
    - Use witness

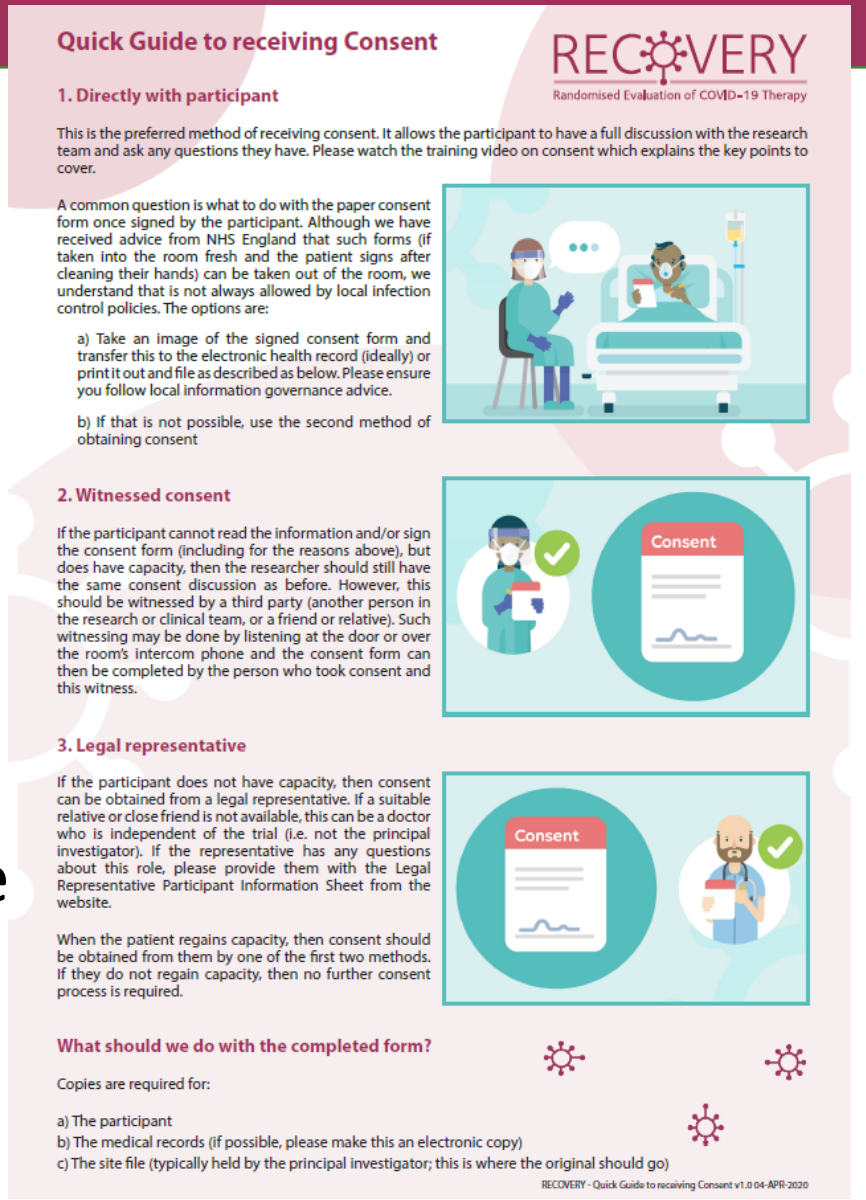
Informed consent

- Witnessed consent can be used if participant cannot read or sign for themselves (but has capacity to give consent)
  - May be used in situations when infection control procedures do not allow ICF out of the ‘red zone’

- Legal representative (either family or other doctor [not PI]) may provide consent if patient lacks capacity
  - If patient regains capacity, their consent should be sought
  - No need to involve relatives in consent process (but good practice to inform them)

Informed consent

- Other situations
  - eg, non-English speaking patient with capacity
- What copies are required?
  - One for site file (ideally original)
  - One for patient
  - One for medical notes
- Quick reference guide soon to be available online



Quick Guide to receiving Consent

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1. Directly with participant

This is the preferred method of receiving consent. It allows the participant to have a full discussion with the research team and ask any questions they have. Please watch the training video on consent which explains the key points to cover.

A common question is what to do with the paper consent form once signed by the participant. Although we have received advice from NHS England that such forms (if taken into the room fresh and the patient signs after cleaning their hands) can be taken out of the room, we understand that is not always allowed by local infection control policies. The options are:

a) Take an image of the signed consent form and transfer this to the electronic health record (ideally) or print it out and file as described as below. Please ensure you follow local information governance advice.

b) If that is not possible, use the second method of obtaining consent

2. Witnessed consent

If the participant cannot read the information and/or sign the consent form (including for the reasons above), but does have capacity, then the researcher should still have the same consent discussion as before. However, this should be witnessed by a third party (another person in the research or clinical team, or a friend or relative). Such witnessing may be done by listening at the door or over the room's intercom phone and the consent form can then be completed by the person who took consent and this witness.

3. Legal representative

If the participant does not have capacity, then consent can be obtained from a legal representative. If a suitable relative or close friend is not available, this can be a doctor who is independent of the trial (i.e. not the principal investigator). If the representative has any questions about this role, please provide them with the Legal Representative Participant Information Sheet from the website.

When the patient regains capacity, then consent should be obtained from them by one of the first two methods. If they do not regain capacity, then no further consent process is required.

What should we do with the completed form?

Copies are required for:

a) The participant
b) The medical records (if possible, please make this an electronic copy)
c) The site file (typically held by the principal investigator; this is where the original should go)

Study treatments: Lopinavir-Ritonavir

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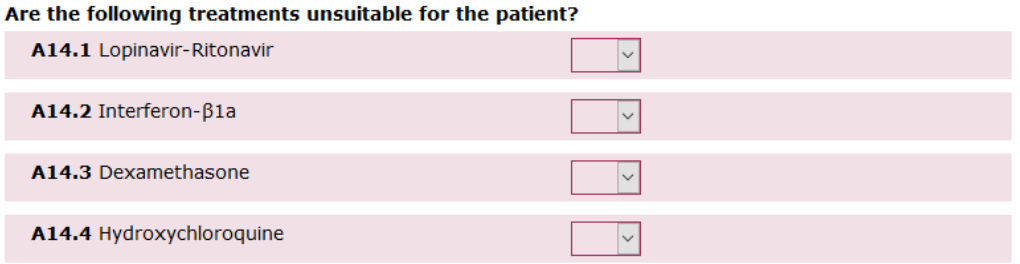
- Licensed for treatment of HIV
- **Issues:**

1. Interactions with other medications:

Alfuzosin, amiodarone, dronaderone, colchicine, quetiapine, simvastatin, sildenafil, **midazolam** and more.

Can the interaction medication be withheld for 10 days?

If not, then exclude lopinavir-ritonavir from randomisation



2. Limited availability of liquid form

Even if available, not compatible with polyurethane nasogastric tubes. NB tablets should <u>not</u> be crushed.

- Therefore <u>not</u> suitable for most patients on ICU
  - If randomised before ICU, can be discontinued if necessary after sedation/intubation
  - NEVER re-randomise a patient

Study treatments: Dexamethasone

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- 6 mg daily is equivalent to 40 mg prednisolone

- Genuine equipoise in clinical community about risks and benefits
  - WHO recommend testing in RCTs
  - ICU guidelines recommend corticosteroids for ARDS (on basis of weak evidence)

- Should be excluded from randomisation for certain patients
  - Those who require high-dose corticosteroids for concomitant condition (eg asthma)
  - Those with poorly-controlled diabetes

Study treatments: Hydroxychloroquine

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- Very unusual pharmacokinetics
- In acute administration, main determinant of blood concentration is distribution, not excretion
- After ingestion, HCQ is rapidly distributed to tissues where it binds, causing huge (100 litres) volume of distribution
- Hence large loading doses are required to saturate tissues and achieve blood concentration sufficient to kill SARS-CoV-2
- Renal excretion much less relevant so no dose modification required for CKD
- More information available on website: hydroxychloroquine intervention sheet

Study treatments: Interferon-β1a

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- Interferons are cytokines known to have antiviral and immunomodulatory properties
- Used in treatment of multiple sclerosis, haematological diseases and some viral illnesses
- Shown to have *in vitro* activity against SARS and MERS viruses

- **Contraindications:** severe hepatic insufficiency
- **Side effects:** 'flu-like symptoms, chest pain, leucopaenia

Update on progress

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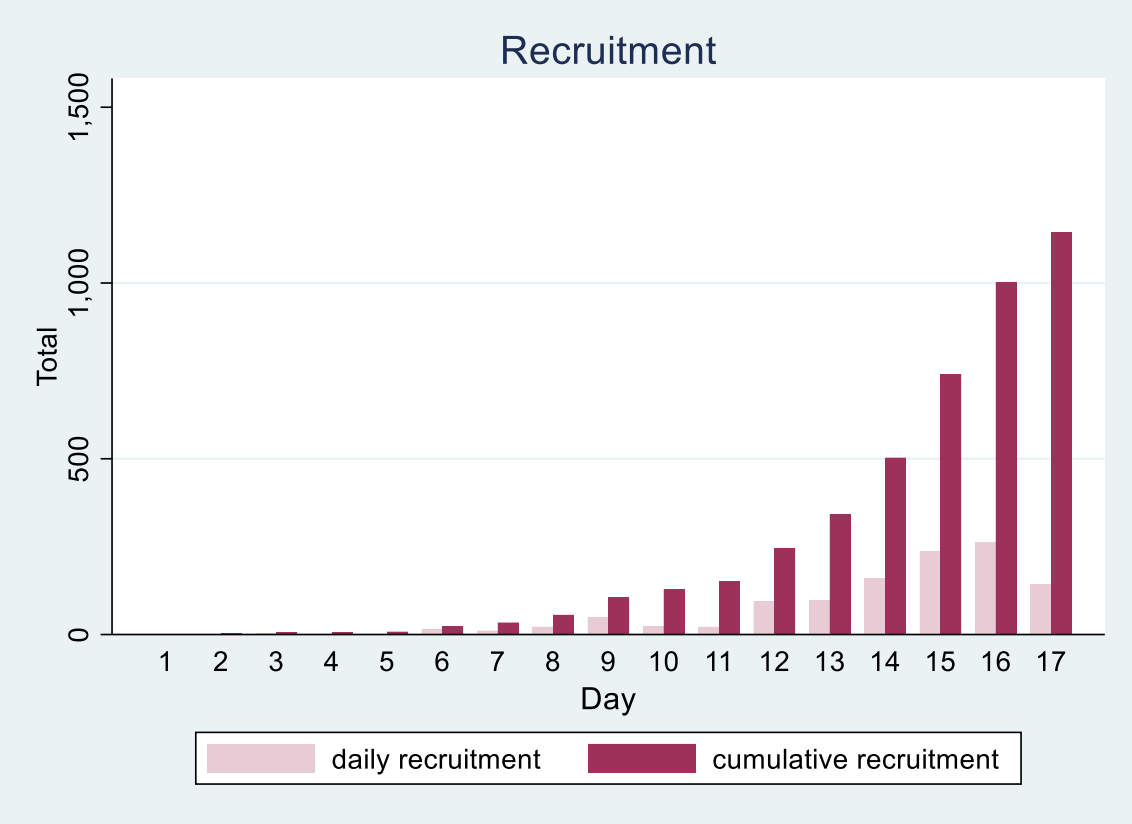
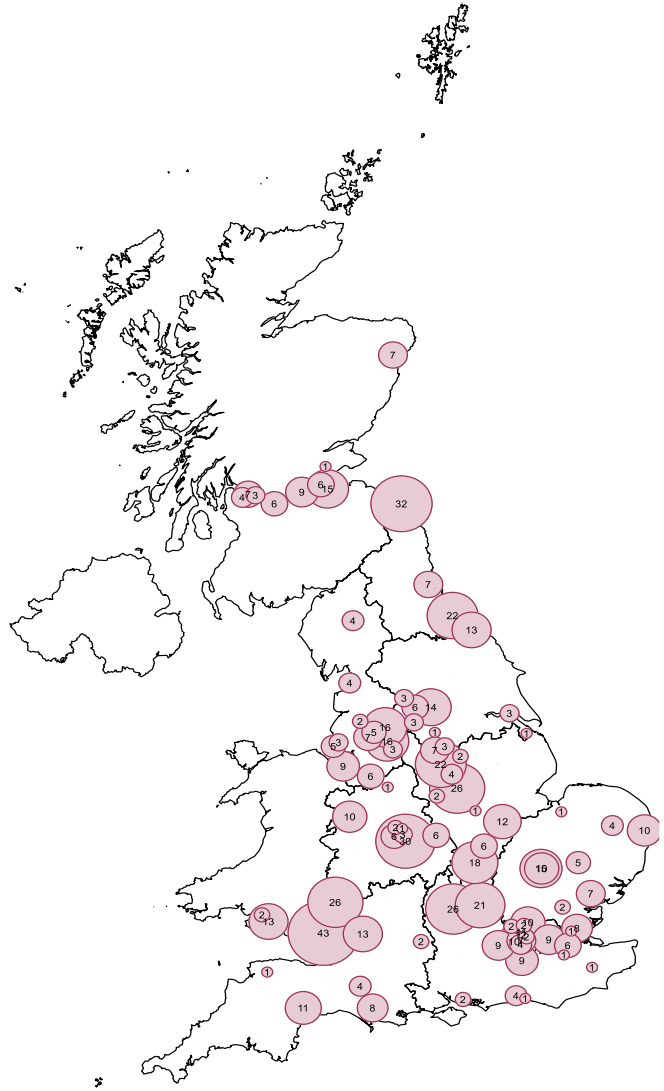
- Amazing start to recruitment!





Characteristics at randomisation (n=1002)

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Characteristic		N (%), mean (SD) or median (IQR)
Male sex		681 (68%)
Age		65 (15)
Days since symptom onset		9 (6-13)
Days since hospitalisation		3 (2-6)
Severity of disease	No oxygen required	181 (18%)
	Supplemental oxygen only	604 (60%)
	Ventilation/ECMO	217 (22%)
Prior disease	Diabetes	270 (27%)
	Cardiovascular disease	255 (25%)
	Chronic lung disease	212 (21%)

Site organisation

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- Systematic identification of new cases
  - Electronic laboratory alerts
  - Medical teams discuss and document decision about eligibility (and which arms)
- Clear line of responsibility of roles for consent and randomisation
- Electronic prescribing systems for prescribing allocated treatment

Follow-up

- Follow-up methods being released

- Team required to take responsibility
  - LCRN will be contacting you to identify individuals
  - Local PI will assent to their role
  - Training provided online and confirmation form completed
  - Log-in to OpenClinica-based Follow-up provided

- Supplemented by real-time linkage with NHS Digital and equivalent bodies in Scotland and Wales

Any questions?

Thank you!

- Thank you very much for your collaboration in these uniquely challenging circumstances

- RECOVERY will provide reliable information on treatments for COVID-19 in the coming weeks to months which could influence management both in the UK and globally

- And a challenge…