Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Local Clinical Centre Principal Investigator training materials

V1.0 2022-06-29

Topics

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. Role of local principal investigator
2. Training and delegation
3. Identification and invitation of potential participants
4. Informed consent
5. Randomisation
6. Follow-up
7. Safety reporting
8. Protocol violations

Role of Local Clinical Centre PI

- Needs to be qualified by education, training and experience to assume responsibility for the proper conduct of the trial
- Is responsible for conduct of the trial in compliance with the protocol at their site, including oversight of other members of trial team
- Should be aware of, and comply with, good clinical practice and applicable regulations (in UK: The Medicines for Human Use (Clinical Trials) Regulations, as amended)
- As specified in the protocol, RECOVERY is being conducted in accordance with the principles of ICH-GCP

Principles of ICH-GCP

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

Training and delegation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- PI is required to be trained in relevant aspects of GCP

- Trial requires PI to complete training on the following topics:
  - Background and rationale of trial
  - Obtaining informed consent
  - Randomisation
  - IMP-specific training modules

- PI is responsible for ensuring that members of his/her research team have completed training relevant to their role

Delegation of duties

- Although PI is responsible for all trial-related activities at his/her site, they do not have to deliver all such activities

- At beginning of trial, a formal delegation of duties log was not required by the sponsor because of challenging clinical environment and need to start trial at speed. This does not remove obligation from PI to retain oversight of his/her team.

- Delegation logs (based on trial training records) will be distributed to sites during Q2 2022 to formalise this process. Instructions will accompany the logs.

Identification and invitation

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- PI should ensure that there is a process at their site to identify potential participants
  - For example, regular review of admission wards or link with microbiology laboratory SARS-CoV-2 PCR testing

- Maintaining recruitment is good way to ensure quality at sites, as staff familiarity with procedures will improve and errors will be reduced

Informed consent

- Written informed consent is required for all patients prior to any trial-specific procedures
  - May be given in person by patient after discussion with member of research team and review of Participant Information Sheet
  - If patient unable to sign form (but has capacity), a witness (independent of research team) can sign on their behalf
  - If patient lacks capacity, consent may be obtained from a legal representative (either family member or friend, or professional legal representative). In such cases, participant must be informed about trial if they regain capacity and such information documented
- Site PIs should ensure there is a small group of doctors willing to act as professional legal representatives for the trial, who have no other role in the trial.

Randomisation

- Eligibility assessment should be made by medically-qualified person with appropriate training and knowledge of IMPs (and contraindications). This assessment should be documented in the medical records.
- Randomisation may be conducted by member of research team (not necessarily the person who obtained consent or assessed eligibility).
- The individual who completes the randomisation form must have completed the trial-specific training on this topic and confirm that consent has been obtained.
- A reliable method of informing the participant's treating clinicians of the randomised allocation(s) must be developed
- PI is responsible for sharing the site's password for the online randomisatoin system with appropriate staff. If they have concerns that inappropriate staff know it, they can contact CCO to request a new one.

Follow-up

- PI must nominate individuals with appropriate training (including trial-specific training on this topic) to sponsor who will provide accounts on OpenClinica system to complete relevant case report forms

- PI is responsible for ensuring they have access to relevant medical records to use when completing such forms

Safety reporting

- RECOVERY protocol requires that Serious Adverse Events (SAEs) believed by the PI to be related "with reasonable probability" to study treatment(s) should be reported
  - Other SAEs do not require reporting (in UK)

- Definition of "serious" adverse event:
  - Fatal or life-threatening
  - Requires or prolongs hospitalisation
  - Results in persistent or significant disability or incapacity
  - Results in congenital anomaly or birth defect
  - Other important medical event in opinion of the PI

Safety reporting

- For an adverse event to be considered an adverse reaction requires (according to 'CT-3' guidance from European Commission) *"a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship."*

- SAEs believed to be related to study treatment (suspected serious adverse reactions, SSARs) should be reported within 24 hours of PI becoming aware
  - Maybe helpful to discuss adverse event with CCO to ensure sufficient information provided to support onward reporting (to regulators, ethics committee etc.)

Safety reporting

- CCO will assess ‘expectedness’ of event against reference safety information for the IMP(s)
- If ‘unexpected’, CCO will report SUSAR
- All information on SUSARs in RECOVERY is made available to PIs on trial website (updated every quarter)

Protocol violations

- PI may become aware of potential protocol violation or CCO may identify them from information received from site

- All potential protocol violations should be reported to the CCO (e-mail recoverytrial@ndph.ox.ac.uk) where they will be recorded and reviewed to determine further actions

- PI may be asked to complete a filenote to document protocol violation and any corrective and preventative actions

Thank you!

- Thank you very much for all your help with RECOVERY! With your help, the trial has changed the treatment of patients with COVID-19 around the world so thank you!