Good Clinical Practices (GCP) principles & Key responsibilities of the investigators in the context of the WHO Solidarity trial
The main learning objective of this training course is that at the end of this course, the participants should:

understand how to comply with key GCP requirements when conducting the WHO Covid-19 Solidarity trial
Content

▪ GCP principles

▪ Role and responsibilities at trial site
  Qualification
  Patient protection
  Compliance
  Documentation

▪ Conclusion
Good Clinical Practice (GCP) ≠ Good Medical Practices
GCP

2 basic principles of GCP:

1. Protection of rights, safety and well-being of trial participants
2. Credible clinical trial data

This presentation explains what the trial site team needs to do to comply with these 2 principles in the Solidarity Trial.
Roles and responsibilities of the trial site team

4 main components

- Qualification
- Patient protection
- Compliance
- Documentation
Qualification of the trial site (adequate resources)

Trial requirements for the hospitals involved:

- Potential to recruit patients
- Have enough staff and ensure all trial staff are adequately trained about the study
- Have study drugs available
- Have adequate facilities for
  - recruitment (definite confirmation of COVID-19 and informed consent),
  - randomisation,
  - medical care,
  - study drug management,
  - reporting of study data into the electronic data base,
  - archiving of study documentation

- All steps to set up the study and ensure adequate resources for conducting the Solidarity trial are described in SOP-1 and are the responsibility of the lead doctor at each site

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**WHO COVID-19 SOPs**

**SOP-1 Approval of hospitals to join the trial and access trial drugs**

If the WHO Director-General asks the Minister of Health of a seriously affected country, and the Minister decides the country should join the trial, two high-level representatives are chosen, one of the Health Ministry (or Medical Research Council) and one of the leading clinical investigators. These two National Representatives will work together to get all necessary approvals rapidly, to select as potential collaborating centres major hospitals that already have, or are expected soon to have, substantial numbers of inpatient admissions for COVID, and to facilitate local ethical approval on behalf of willing local collaborators. The following steps should ensure the trial can start promptly in each collaborating hospital. They should happen in parallel, and not in sequential fashion.

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<tbody>
<tr>
<td>1</td>
<td>Officially confirm interest to participate</td>
<td>Minister of Health or authorised Delegate of the Minister of Health</td>
<td>Communication to WHO Secretariat</td>
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Qualification of trial site team staff

The lead doctor at each hospital has to

- select a trial site team which has the necessary:
  - Medical / scientific knowledge
  - Technical knowledge
- ensure training on the protocol, procedures and GCP of the trial site team
Patient protection
Patients protection

Based on the following fundamental principles:

1. Approval of the protocol by independent ethics committee
2. Patient's informed consent before any study procedure
3. Medical care
4. Safety reporting
5. Respect of confidentiality of patient data
1. Approval of the Solidarity trial protocol by independent ethics committee

**WHO COVID-19 SOPs**

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<tr>
<td>1</td>
<td>Approval of the Solidarity trial protocol</td>
<td>Minister of Health or authorized Delegate of the Minister of Health</td>
<td>Communication to WHO Regional Solidarity Trial Unit</td>
<td>These two National Representatives should both be senior within their Ministry or institution</td>
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<tr>
<td>2</td>
<td>Appoint two National Representatives, one Governmental and one Clinical</td>
<td>W.H.O. or other body responsible for health</td>
<td>Communication to WHO Regional Solidarity Trial Unit</td>
<td>Selected nephrologists should have basic SOP knowledge</td>
</tr>
<tr>
<td>3</td>
<td>Identify which hospitals will have substantial numbers and will collaborate</td>
<td>The two National Representatives, with one lead doctor per selected hospital</td>
<td>Communication to WHO Regional Solidarity Trial Unit</td>
<td>No modification of the protocol is possible, as very large numbers of hospitals are involved</td>
</tr>
<tr>
<td>4</td>
<td>Facilitate approval - or not - by national authority and local ethics committee</td>
<td>The two National Representatives</td>
<td>High-level national support, but local application by each collaborator</td>
<td>No modification of the protocol is possible, as very large numbers of hospitals are involved</td>
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<tr>
<td>5</td>
<td>Select which study drugs are available in each location</td>
<td>Clinical National Representative, helped by WHO focal point</td>
<td>Biological Interactions</td>
<td>WHO will facilitate study drug (or drugs) where this is needed</td>
</tr>
<tr>
<td>6</td>
<td>Facilitate import permits for study drug, as needed</td>
<td>The two National Representatives</td>
<td>Depends on national guidelines and regulations</td>
<td>After permits for initial amount, supply will depend on analytics</td>
</tr>
<tr>
<td>7</td>
<td>Set up personnel and equipment for study implementation</td>
<td>Appoint small central administrative support to the Clinical National Representative</td>
<td>Make use of existing p. &amp; u. and some staff of known validity to downscale study</td>
<td>Local centres will need help in approaches, drug supply, fighting going, and monitoring process</td>
</tr>
<tr>
<td>8</td>
<td>When local hospitals move quickly into rapid recruitment</td>
<td>Lead doctor and local pharmacist motivate and train colleagues</td>
<td>Local leaders select and discuss study with colleagues</td>
<td>Local lead motivates &amp; ensures full compliance, rapid entry and discipline</td>
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**Procedure SOP-1**

For the Solidarity trial, two National Representatives have the responsibility to ensure approval by relevant national authorities and ethical committees (National and local EC if relevant).
2. Informed consent of the patient

The patient has to agree (consent) to participate in the study

- Fully informed on key aspects of the trial
- Having understood the information provided
- Without their consent having been coerced (through undue influence or intimidation)
- Patient or a next of kin, a relative, or a legally acceptable representative if a patient is not able to agree at the time
Informed consent by the patient - Process

Procedure SOP-3

How?

- The information text approved by the EC should be read by the patient or to the patient
- A health care worker has to be available to answer any questions about the trial the patient may have
- Enough time has to be given to the patient to consider whether to participate or not
- When answering patient questions, it is important to remember:
  - At this stage, no drugs are of proven value against Covid-19
  - the patient cannot chose his/her treatment because of the random allocation of the drugs under investigation
  - In any case, all patients will receive the standard of care for COVID-19 infection offered in the hospital but depending on the randomization an additional treatment may or not be added
Informed consent by the patient - Process

**Procedure SOP-3**

**Who is responsible for obtaining informed consent?**

- Health care worker from the trial site team trained to do so

**When?**

Before any procedure is done for the study (i.e. a procedure that would not be done if the patient was not participating in the study)
Informed consent by the patient - Documentation

Procedure SOP-3

The informed consent is documented by:

- the signature of the patient

The original copy of the signed form is given to the patient and a picture is taken by the investigator to document the process.

Statement by the researcher/person taking consent

I accurately read the information sheet to the participant and made sure they understand what the study entails. The participant could ask questions about the study, and all questions asked were answered correctly to the best of my ability. Consent was given freely and voluntarily, and a copy of this form has been given to the participant.

This study has been reviewed by ethics experts at the World Health Organization (WHO), which is co-sponsoring it. The study has been reviewed and approved locally by . This committee exists to make sure research participants are protected from harm. If you want to contact them about it, now or later, their contact details are .

- the signature of the person who informed the patient (‘took consent’)
Informed consent of the patient - Documentation

**Procedure SOP-3**

<table>
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<tr>
<th>WHO COVID-19 SOPs</th>
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<tr>
<td><strong>PART 1: Certificate of consent</strong></td>
</tr>
<tr>
<td><strong>Clinic/Hospital:</strong></td>
</tr>
<tr>
<td><strong>Province/Region:</strong></td>
</tr>
<tr>
<td><strong>Participant:</strong></td>
</tr>
<tr>
<td>I read the information, or had it read to me.</td>
</tr>
<tr>
<td>I could ask any questions I wanted, and had any questions answered satisfactorily.</td>
</tr>
<tr>
<td>I consent voluntarily to participate in this study.</td>
</tr>
<tr>
<td><strong>First &amp; last name</strong></td>
</tr>
<tr>
<td><strong>Signature</strong></td>
</tr>
<tr>
<td><strong>Date</strong></td>
</tr>
<tr>
<td><strong>Thumb-print (if illiterate)</strong></td>
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</table>

Informed consent of the patient - Documentation

**If the patient is unable to read (illiterate subjects)**

- An impartial witness should be present during the reading and discussion of the information

- Witness should sign & date the consent form to attest
  - information was read
  - accurately explained to
  - understood by the patient
  - consent was freely given

- The patient should put their thumbprint on the form
3. Medical Care and Safety Reporting

- The responsible trial team members have to
  - Assure adequate medical care for the patients
  - Assure appropriate management of adverse events
  - Document as much as possible the reason for withdrawal
Safety Reporting – SAE reporting

- GCP requirement
- Secondary Solidarity trial objective: identify any **serious adverse reactions**

Each adverse event needs to be characterized as

- **Serious** Adverse Event or not
- **Causally** related to treatment or not

The trial site team needs to determine who has final responsibility for this characterization
Safety Reporting – SERIOUS vs SEVERE

Serious ≠ Severe

- Severity or toxicity refers to the intensity of an event (e.g. mild, moderate or severe)

- The seriousness of an event refers to the regulatory definition of Serious Adverse Events (SAE) and imposes special reporting procedures
Safety Reporting – GCP Definition of AEs and SAE

An Adverse Event (AE) is any ‘untoward medical occurrence’ (unfavourable sign, symptom, laboratory finding, disease) in a patient administered a pharmaceutical product whether related to the product or not.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
The causal relationship between the SAE and the study drug has to be evaluated.

Categories vary between protocols (e.g. related or unrelated, e.g. probably related/possibly related/unlikely related/unrelated).

The Solidarity protocols requires categorization between related and unrelated SAEs.

Factors to be considered for determining causal relationship are:

- Temporal relationship between the study drug and the AE
- Dechallenge and rechallenge
- Biologic plausibility of relationship
- Patient’s underlying clinical state
- Known side effects of concomitant agents/therapies the patient receives

A drug related SAE is called Serious Adverse Drug Reaction (SADR).
**Safety Reporting - Procedure**

**Procedure SOP-9**

**WHO COVID-19 SOPs**

**SOP-9  Reporting SUSARS and major protocol violations**

SUSARS are Suspected Unexpected Serious Adverse Reactions that are fatal or life-threatening, such as Stevens-Johnson syndrome, anaphylaxis, aplastic anaemia, or anything comparably uncommon. Major protocol deviations could be largely or wholly substantial over-dosing with a study drug that had a seriously detrimental effect (because the protocol leaves the local doctor fully responsible for all decisions about patient care, including discontinuing study medication if considered appropriate).

SUSARS and major protocol deviations should be uncommon, but must be reported promptly by logging into the study website [www.who.int/COVIDcore](http://www.who.int/COVIDcore). The local doctor reporting the event then enters a narrative description of the event and its seriousness that includes the patient’s trial identification number.

All such events entered onto the study website are reviewed promptly and, unless refuted, will be reported by the trial centre to the Global Data and Safety Monitoring Committee (Appendix 1), the appropriate National Regulatory Agency and the local Ethics Review Committee within 24 hours of having been entered.

**Solidarity trial – WHO COVID-19**
Safety Reporting – Suspected Unexpected SADRs

Based on the SAEs reported as caused by the study drugs by the site trial team, i.e. SADRs, the COUNTRY SPONSOR will decide whether a SADR is a SUSAR.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SADR considered ‘unexpected because its nature or severity is not consistent with the applicable product information’.

All SUSARs will be reported by the country sponsor to:
- the Global Data Safety Monitoring Board,
- the appropriate National Regulatory Agency and
- local Ethics Review Committee

within 24 hours
4. Confidentiality

- Confidentiality of participation and data from patients must be ensured:
  - In WHO Castor database, patients are identified via a patient ID, not their name, WHO Castor database access is password protected
  - A ‘screening and enrolment log’ needs to be generated and maintained to link a patient to the patient ID
  - Study Documents have to be kept in a safe and secure place
Compliance

1. Screening and recruitment of study participants
2. Informed consent
3. Compliance with all protocol procedures
4. Randomisation procedures
5. Provision of medical care to trial participants
6. Safety reporting
7. Entry of data on to the WHO Castor database website
8. Study drug storage, dispensation, administration and accountability
Documentation

Solidarity trial – WHO COVID-19
In the Solidarity trial, an electronic CRF accessible on the COVIDcore website is used to collect data at:

- Patient enrolment
- Patient discharge

Data entered need to be consistent with those in the hospital records (source documents)

The lead doctor should determine who is authorized to enter data onto the website.

The trial site team has to keep all standard hospital record of the patients and other records on the trial in a safe place.
As per GCP, on site monitoring visits should be done to make sure the study is conducted in accordance with the protocol and GCP requirements.

In the Solidarity trial external monitoring will be avoided partly to limit virus spread.

But a degree of **internal monitoring** could be put in place by the lead doctor of the trial site team to check key elements such as:

1. The compliance with informed consent process
2. The accuracy of key information entered into the WHO Castor database i.e. treatment arm and status at discharge
1. Subject screening and enrolment log
2. Identification of enrolled participants (‘screening and enrolment log’)
3. Signed informed consent and related documents
4. EC communications, approvals
5. Product management and accountability
6. Trial team training records and assigned responsibilities

For the Solidarity trial this should be for at least 5 years after the study is discontinued or for at least 5 years after a marketing application for the drug for COVID-19 has been approved or rejected.
Conclusion

The trial site team members are key players for ensuring:

- The well-being, safety & protection of the rights of subjects engaged in the RCT
- The credibility of the Data

That are the 2 principles of the GCP
To know more and references


- International Conference of Harmonisation (ICH) ([www.ich.org](http://www.ich.org))
  - E2A: Clinical safety data management
  - E6: Guidelines for Good Clinical Practice


- Public health emergency solidarity trial (WHO)
  - COVID-19 core protocol “an international randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care” (Version 10.0 March 22, 2020)
  - Standard Operating Procedures and Appendixes (Version 10.0 22 March 2020)