STANDARD OPERATING PROCEDURE

SOP TITLE: RANDOMISATION: PREPARATION, BLISTER AND BOX (DRUG KIT) PACKING AND DRUG KIT MANAGEMENT INSTRUCTIONS

Study Title: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

Internal Reference Number / Short title: COPCOV

RANDOMISATION: PREPARATION, BLISTER AND BOX (DRUG KIT) PACKING AND DRUG KIT MANAGEMENT INSTRUCTIONS

Version 3, dated 01 Mar, 2021

Prepared by the Trial Statistician

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STUDY: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)
1. PURPOSE
This is a trial specific SOP that applies to the COPCOV trial. This SOP is based on the main general MORU CTSG SOP. The SOP focusses on the preparation of the randomisation list, the packaging and labelling of drug kits at the pharmaceutical company, implementation of the randomisation at the site and procedures for unblinding.

2. SCOPE
This study specific document describes the randomisation scheme and the instructions for the preparation of the drugs; packaging and management for the COPCOV Trial and applies to all trial sites.

Where there are some site specific deviations in procedures, these will be detailed in site specific guidelines which will be available to the affected sites and the sites will be trained in such variations

3. TRIAL DESIGN
The COPCOV trial is a double-blind, randomised, controlled, superiority trial to determine if chloroquine/ hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in healthcare workers or other groups at high risk and if chloroquine/ hydroxychloroquine attenuates COVID-19 infections compared to placebo.

4. PROCEDURE

4.1 DRUG KITS/BOXES (DESCRIPTION & COMPOSITION)

Drug kits, also known as drug boxes, are boxes containing the blister packed chloroquine/ hydroxychloroquine or placebo that will be prepared by the pharmaceutical company. Each drug kit will be labelled with a unique drug kit number (Kit ID), which is pre-assigned to a corresponding randomisation number prepared by the trial statistician and supplied directly to the company.

Each drug kit will contain 10 blister packs each containing 10 chloroquine/ hydroxychloroquine or placebo tablets, according to the computer-generated randomisation list provided by the trial statistician.

4.2 PREPARATION OF RANDOMISATION LIST, BLINDING AND STUDY OVERSIGHT

Chloroquine/ hydroxychloroquine tablets containing 155mg base equivalent and identical placebo pills will be packed in opaque blister packs containing 10 tablets. Each participant will be allocated a drug kit containing 10 blister packs of 10 tablets for the chloroquine/ hydroxychloroquine or matching placebos. The initial dose to be taken from the chloroquine starter blister pack is 10mg/kg. Further information is available in the relevant SOP.
A randomisation list will be prepared by a Statistician using block randomisation in a 1:1 ratio for the chloroquine/ hydroxychloroquine arm versus the placebo. The randomisation will be computer-generated and programmed in Stata 15. The randomisation procedure has been stratified by site. An appropriate computer seed will be used to allow reproducibility of the randomisation list. The randomisation list will be done in blocks with the block size known and kept by the statistician only and is documented in the Stata do-files for reference purposes. The block size will not be revealed to maximise double blinding.

The list will be provided directly to the pharmaceutical company by the trial statistician so each drug kit and each blister pack are labelled correctly (detailed below). Each drug kit will thus contain a drug kit number stickered on top of the drug kit. This number will also be stickered on each monthly bag dispensed to the participant. The drug kit will contain stickers with the drug kit number, meant to be stuck on the subject information card and on the first page of the paper screening form and subsequent pages of the CRF (these will be handwritten in pen where extra stickers are not available). The number will also be entered in the electronic data capturing tool. This number will also be written on every page of the CRF using a pen. In situations where many stickers may be produced quickly, drug kit number labels will be stuck on every page of the CRF.

The labelling of drug kits will be performed by independent staff at the pharmaceutical company and will follow the computer-generated randomisation list provided by the statistician. One drug kit will be allocated to one participant. Should the company not have capacity to pack treatment, the packing and labelling of drug kits will be performed by independent staff at MORU, supervised by the trial statistician.

At enrolment, the subject’s kit number (Kit ID) will be on the drug kit (and on each blister pack only if possible). The participant will write their date of birth and initials on the drug box at the beginning of the study and each occasion they collect further blister packs (i.e. on three occasions. Day 0, day 30 and day 60). Upon opening the drug kit, if the blister pack does not have a kit number affixed, the investigator will transcribe the drug kit number onto all blister packs. The investigator will hold on to the drug kit which contains the 100 tablets and dispensation from the drug kit will be done on a monthly basis by the investigator. The starter blister pack and first 30 tablets (3 blister packs of 10 tablets each) dispensed to the participant at enrolment.

The kit number determines drug allocation but the study staff and subjects will both be blinded.

The drug kit will be kept securely by the study staff. Subsequent 30 tablets (3 blister packs) will be dispensed at each monthly check with the study manager.

Individual unblinding will be done only on consultation with the study/site PI. Only the study statistician/designate will have the drug allocation list.

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4.3 PACKAGING INSTRUCTIONS FOR DRUG KITS (BOXES)

1. The randomisation list will be provided by the Trial Statistician to the company.
2. The randomisation lists are provided for 50 sites for Chloroquine based and 50 sites for Hydroxychloroquine based (also called 50 sets of 400 participants for each base).
3. At the pharmaceutical company, each site (set) will be allocating 200 participants allocated to either chloroquine/ hydroxychloroquine or placebo based on the randomisation list giving a total of 400 drug kits for both treatments per site (set).
4. Sites (sets) have been denoted as A001, A002, A003, ..., A050 for Asian based sites and denoted as E001, E002, E003, ..., E050 for the European based sites. The actual site name will be recorded on the data collection tools and transferred into the database when the sites are identified. We also refer to the site allocation as a “SET” because bigger sites will be given more than one site allocation. For example a site enrolling 800 participants will be assigned consignments for two sites.
5. Each site will have a pre-determined order of allocation according to randomisation schedule. However, for packaging purposes, the randomisation list for each site will comprise of two separate sheets: one for chloroquine/ hydroxychloroquine and another for placebo.
6. Figure 1 below summarises the processes of the randomisation list from MORU and the packaging at the pharmaceutical company

Figure 1 Randomisaton list from MORU and packaging logistics at the company
As illustrated in the figure 1 above:

7. When packing into drug kits, packing staff MUST use SEPARATE rooms/locations for chloroquine/hydroxychloroquine and placebo to avoid accidental mixing up of the chloroquine/hydroxychloroquine and placebo blister packs in the same drug kit.
8. When packing one drug, for example chloroquine/hydroxychloroquine, 10 blister packs each containing 10 tablets will be put in one a drug kit.
9. Similarly, when packing Placebo, 10 blister packs each containing 10 tablets will be put in a drug kit.
10. A sticker label for a Kit number (Kit ID) will be placed on each box and this will be a unique number for all sites.
11. Stickers will be prepared SEPARATELY for the chloroquine/hydroxychloroquine arm and the placebo arm in a definite order provided by the Trial Statistician.
12. NO treatment details will be shown on the drug kit or inside the box. It will be blinded.
13. The treatment details shown in the dummy randomisation list above are only for assisting the packaging staff to pack appropriately without mixing up the placebos and chloroquine/hydroxychloroquine. The documents sent to pharmaceutical company for packaging remains confidential documents and will be provided directly to the company as a password protected documents.
14. As shown in Figure 2a and 2b, each drug kit MUST be SEALED to avoid accidental opening of the drug kits.

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15. Once the 200 chloroquine/ hydroxychloroquine and 200 placebo drug kits have been labelled using kit numbers for EACH SITE, the drug kits will then be arranged in a sequential order as shown below:

16. For Asia the 400 drug kits will packed in two BIG BOXES each containing 200 sequentially numbered drug kits for a site and clearly labelled with site number as shown in the dummy randomisation (i.e. the BIG BOX for European site 1 should be labelled 001, while for Asia it should be labelled A001). For each site number, e.g. A001, the first box MUST contain 200 sequential numbers A001-001 to A001-200. The second box MUST contain 200 sequential numbers A001-201 to A001-400.

The figure 2a below summarises how packaging and labelling should be prepared by the drug manufacturer in Asia:

17. For Europe the 400 drug kits will packed in 8 BIG BOXES each containing 50 sequentially numbered drug kits for each site and clearly labelled with site number as shown in the dummy randomisation (i.e. the BIG BOX for European site 1 should be labelled E001, while for Asia it should be labelled A001). For each site number, e.g. E001, the first box MUST contain 50 sequential numbers E001-001 to E001-50. The second box MUST contain 50 sequential numbers E001-51 to E001-100. The third box MUST contain 50 sequential numbers E001-101.

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to E001-150 and so on until the eighth big box that MUST contain 50 sequential numbers E001-351 to E001-400. The figure 2b below summarises how packaging and labelling should be prepared by the drug manufacturer in Europe.

18. The BIG BOXES that contains the drug kits assigned to the site will be labelled on all sides with the site name e.g. SITE: E001 or SITE: E002 until SITE E050 for European sites and SITE: A001 or SITE: A002 until SITE A050 for Asian sites.

19. The BIG BOX MUST also indicate the range of kit numbers in that box e.g. E001-001 to E001-50

20. In the kit number, for example “E001-015”, E001 is code for site 1 (or set 1 for sites that will get BIG BOXES for more than one site in Europe); and 015 is the randomisation number for that site (or for the first set).

21. When sites are ready to start, the trial coordinator will be liaising with the trial statistician to get advice on which BIG BOXES containing the 400 drug kits should be used.

22. At the drug company, the big box will contain a maximum of 200 kits in Asia and maximum of 50 kits in Europe. Thus, two boxes will be used to contain all the 400 kits for Asian sites and 8 big boxes will be used to contain all the 400 kits for European sites. In this case, the company should label Box 1 as follows (e.g. site 1): A001 to A200. Box 2 should be labelled: A201 to

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A400. The site label for both boxes should be A001 in this case. The company staff MUST make sure that the kit number (Kit ID) range matches the kit numbers (Kit IDs) inside the box.

4.4 DRUG KIT MANAGEMENT INSTRUCTIONS AT THE RESEARCH SITE

4.4.1 How to implement randomisation during enrolment at the site

1. Since the drug kits are in sequence of randomisation, there is no need to use envelopes as they do not provide extra information to that of the kit number (Kit ID) ordering.
2. All 400 SEQUENTIALLY numbered drug kits in two BIG BOXES (each containing 200 kits) will be transferred to the site in Asia. If there will be larger sites, those sites will receive additional BIG BOXES from the other sites (sets). For example, 3 site pairs of BIG BOXES of size 200 drug kits each will be sent to a site that is expected to enrol between 800 and 1200 participants. All 400 SEQUENTIALLY numbered drug kits in 8 BIG BOXES (each containing 50 kits) will be transferred to the site in Europe.
3. Administration of the drug kits at the site will be done only by designated trial staff.
4. Prior to onset of recruitment in ASIA, trial staff MUST check that the first BIG BOX labelled EXXX-001 to EXXX-200 (containing 200 kits) contains all SEQUENTIALLY NUMBERED drug kits e.g. A001-001, A001-002, A001-003, A001-004 .... A001-200 for Asia. THE SECOND BOX MUST NOT BE CHECKED until the first box has been randomised to participants. When starting the second BIG BOX labelled EXXX-201 to EXXX-400 (containing 200 kits), trial staff MUST check that it contains all SEQUENTIALLY NUMBERED drug kits eg. Axxx-201, Axxx-202, Axxx-203, Axxx-204 .... Axxx-400 for Asia. The order of randomising boxes for Asia MUST be strictly: box Axxx-001 to Axxx-200; box Axxx-201 to Axxx-400.
5. Prior to onset of recruitment in EUROPE, trial staff MUST check that the first BIG BOX labelled EXXX-001 to EXXX-50 (containing 50 kits) contains all SEQUENTIALLY NUMBERED drug kits e.g. E001-001, E001-002 E001-003, E001-004 .... E001-50 for Europe. THE SECOND BOX MUST NOT BE CHECKED until the first box has been randomised to participants. When starting the second BIG BOX labelled EXXX-051 to EXXX-100 (containing 50 kits), trial staff MUST check that it contains all SEQUENTIALLY NUMBERED drug kits eg. Exxx-051, Exxx-052 Exxx-053, E001-054 .... Exxx-100 for Europe. The same procedure should continue for the next set of boxes. The order of randomising boxes MUST be strictly: box EXXX-001 to EXXX-050; box EXXX-051 to EXXX-100; box Exxx-101 to Exxx-150; box Exxx-151 to Exxx-200; box Exxx-201 to Exxx-250; box Exxx-251 to Exxx-300; box Exxx-301 to Exxx-350; box Exxx-351 to Exxx-400.
6. The trial staff should immediately contact the trial coordinator and statistician should there be a missing drug kit in the sequence. The coordinator and the statistician will advise how to proceed.
7. The subject’s kit number (Kit ID) will be on the drug kit.
8. The trial staff will be allocating the drug kits SEQUENTIALLY to eligible trial participants. That is, for site 1 in Europe, the first enrolled participant will be allocated drug kit number “E001-001”, the second participant will be allocated drug kit number “E001-002”, the third participant will be allocated drug kit number “E001-003”, ..., sequentially until participant 50 who will be allocated kit number “E001-50” from the first BIG BOX and then continue with the second BIG BOX allocated drug kit number “E001-051”, the next participant will be allocated drug kit number “E001-052”, the next participant will be allocated drug kit number “E001-053”, ..., sequentially moving across boxes until participant 400 who will be allocated kit number “E001-400”. For site 1 in Asia, the first enrolled participant will be allocated drug kit number “A001-001”, the second participant will be allocated drug kit number “A001-002”, the third participant will be allocated drug kit number “A001-003”, ..., sequentially until participant 200 who will be allocated kit number “A001-200” from the first BIG BOX and then continue with the second BIG BOX allocated drug kit number “A001-201”, the next participant will be allocated drug kit number “A001-202”, the next participant will be allocated drug kit number “A001-203”, ..., sequentially until participant 400 who will be allocated kit number “A001-400”.

9. When the eligible participant is randomised, the site staff will select the relevant drug kit that is labelled the same as the kit number / Kit ID assigned to the enrolled participant.

10. The site staff will then label the drug kit box with the participant’s name, date of birth and the date of randomisation prior to opening. This will help in situations where the participant may have forgotten his/her kit number during follow-up.

11. If the drug kit number is not affixed to the blister packs then this will be transcribed on to these by the site staff.

12. After opening the kit number sticker label will be placed on the first page of the paper CRF (recorded electronically otherwise) and will be recorded in pen on all other pages of the CRF/ the data capturing tool as an identifier unless further stickers are available for these pages.

13. Then the site staff will pick out the required number of tablets/ blister packs for that visit and administer/ give to the enrolled participant for that visit. The participant will be advised of the next visit date.

14. The remaining kits/ tablets will remain at the site in the same drug kit and securely kept by the site staff.

15. At the participant’s next visit, the site staff will open the corresponding drug kit and pick out the next set of blister packs. This procedure will continue and the full required number of blisters/ tablets are administered to the participant.

16. In the unfortunate scenario that a kit out of sequence within the BIG BOX has been assigned, the trial staff should immediately contact the trial coordinator and the statistician to advise how to proceed. As much as possible recruiting participants out of sequence within the BIG BOX MUST be avoided.

Figure 3 below summarises the randomisation of participants, documentation and how to capture drug Kit number into the electronic data capturing tool at enrolment for Asia.

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procedure is similar for Europe, the only difference is that boxes will be containing 50 drug kits instead 200 kits.

**Drug kits Received at the Sites**

The site will receive TWO big boxes, each containing 200 drug kits (total 400 drug kits in the two boxes)

- **Box 1**
  - 200 drug kits - labelled "A001-001" to "A001-200" for site 1 (i.e., site A001)

- **Box 2**
  - 200 drug kits - labelled "A003-201" to "A003-400" for site 1 (i.e., site A001)

**Note:** The labels would be "A002-001" to "A002-200" for site 2 boxes (i.e., site A002) and so on.

**Note:**
Bigger sites may get more boxes, but will need to liaise with the coordinator and statistician on how to proceed.
Which Box to start using?

1. Start with kit labelled: “A001-001” to “A001-200” for site1 boxes i.e. site A001

2. Do not open the second large box under any circumstances until all kits in the first box have been distributed to participants.

3. Once the first big box has been randomised, then open the second big box.

4. Continue with box labelled: “A001-201” to “A001-400” for site1 i.e. site A001

How to randomise kits?

1. After opening the relevant box, arrange drugs sequentially according to Drug kit number in each box. E.g. box 1.

2. Verify - All 200 drug kits sequentially according to Drug kit number in each box.

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Participant enrolment

1. Assign a Sequential eligible participant to a sequential Drug kit number (labelled on the box)

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4.4.2 Study number vs. randomisation number/ kit number/Kit ID

The study number/ kit number / kit ID/ randomisation number mean the same thing in this trial. Thus, only kit number will be used as an identifier. Once the participant is eligible and randomised to the kit (in sequence), the corresponding kit number will be recorded manually on to the CRF/ data correction tools. Care must be taken to make sure that the number written in the CRF is an exact match with the kit number on the kit.

4.4.3 Unblinding

1. Unnecessary or unintentional unblinding will not be possible as only the Statistician will have the randomisation list.
2. In the case of an emergency at the site prompting unblinding, the site staff will immediately communicate to the country PI/ coordinators.
3. Once unblinding is confirmed, the trial statistician/designate will be contacted by the country PI/ coordinators and will unblind the particular participant that had an issue. Where the country PI is unsure, s/he will contact the MORU Co-PIs.
4. The original plan is that the Trial Statistician and his team statistician will be the primary contact for unblinding by site Pls/coordinators and will be available 24/7. However, if there will be need for some delegation in the Europe due to time differences, then a responsible person will be identified within DTU to assist in managing unblinding. In that case the designate will be reporting regularly to the Trial Statistician for documentation purposes.
5. All unblinded participants will be documented with reasons for unblinding and the unblinding processes that were taken will also be documented.
6. These event must be fully documented in the Trial Master File and in the relevant statistical report

5. SOP VERSION HISTORY

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<td>“Patient” changed to “participant”</td>
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STUDY: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) In the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

SOP Version: V3
SOP Date: 03 Mar 2021
[SOP template V2/22 July 2020]
**STANDARD OPERATING PROCEDURE**

**SOP TITLE:** RANDOMISATION: PREPARATION, BLISTER AND BOX (DRUG KIT) PACKING AND DRUG KIT MANAGEMENT INSTRUCTIONS

### 6. SOP SIGNOFF

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