1. PURPOSE

The purpose of this SOP is to describe the process to allocate study drug (investigational medicinal product, IMP) to enrolled participants in the COPCOV study, and procedures to manage accountability and compliance during the study.

This procedure also describes steps for a site in the case that a site investigator deems an emergency need to unblind treatment for a study participant during study conduct.

2. PROCEDURE

2.1. GENERAL POINTS

1. Administration and accountability of IMP is only to be done by designated pharmacy staff.
2. This is a double blinded trial, neither site staff nor participant will be aware of the assigned IMP arm for each participant.
3. IMP should be maintained in a secure and temperature monitored location within pharmacy departments. Temperature logs should be retained for the duration of the trial.
4. All drug kits contain one large sticker that can be cut into 6 patient ID stickers; one should be adhered to the prescription or other pharmacy records if e-prescriptions are being used.
5. Pharmacies may use their own template documents provided they meet the trial requirements. Please send to copcov@dtu.ox.ac.uk for review.
6. The E0## numbers are European site numbers that form part of the drug kit numbers, which are also the participant ID numbers *e.g.* E001-001. The GB0## numbers are your site number to be used on all documentation where site number is required.

2.2. INITIAL DRUG RECEIPT

1. IMP has been pre-packed at the pharmaceutical company in sequential (pre-defined) order based on the study randomisation schedule.
2. Sites will receive an initial shipment of 400 drug kits. All 400 drug kits will be SEQUENTIALLY numbered and arrive in 8 BIG BOXES (50 kits per box) and will be shipped to the local site pharmacy.
    - If a local site expects to recruit more than 400 participants they can liaise with the Diabetes Trials Unit (DTU) trial team to request additional kits.
    - Local sites can run clinics at two hospitals with two pharmacies with prior agreement from DTU if this will facilitate recruitment. IMP will be shipped to

one pharmacy in the first instance and specific boxes can then be shipped on to the second pharmacy with DTU approval.

- Box dimensions: 353mm X 400mm X 236mm (50 kits in each)

3. Upon receipt of IMP, pharmacy staff should confirm the shipment has been received in good condition without any damage or temperature excursions (if temperature monitor included).
4. Pharmacy staff are to verify all kits are correct as per the expected sequence and review the provided inventory to ensure accuracy.
5. Pharmacy staff MUST check that each BIG BOX (containing 50 kits) contains all SEQUENTIALLY NUMBERED drug kits e.g. for site number 1 E001-001, E001-002, E001-003, E001-004 … to E001-050 in box 1, E001-051 to E001-100 in box 2, E001-101 to E001-150 in box 3, etc.
6. Complete the Drug Receipt Acknowledgement enclosed with the IMP delivery and return this to the email addresses indicated on the form.
7. Complete the details of shipment on the drug accountability log and file all shipment documentation in the pharmacy file.
8. Individual drug kits should not be opened until assigned to a participant on the day of their randomisation.

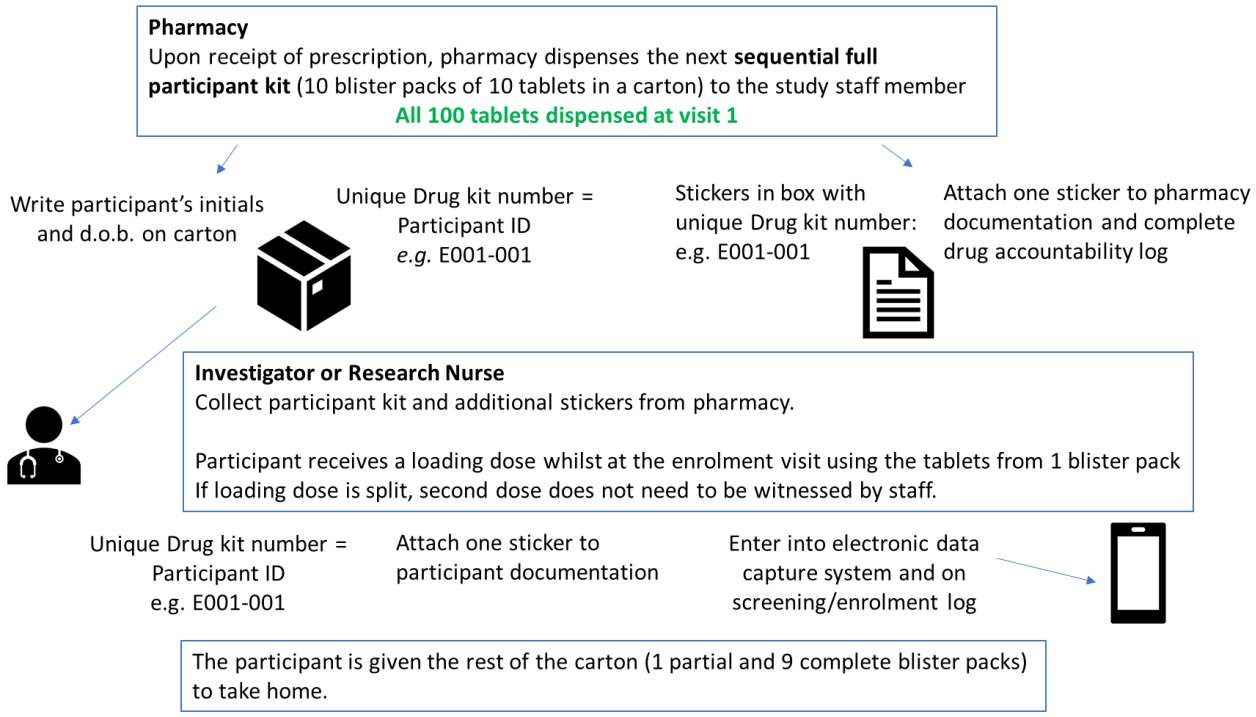
2.3. ENROLMENT AND KIT ALLOCATION

1. A delegated and appropriate member of site staff will complete a prescription for eligible trial participants and provide this to pharmacy.
2. Pharmacy staff will allocate 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 400 who will be allocated kit number "E001-400". Refer to Figure 1 for description of the overall process.
3. Upon allocation of participant ID the designated pharmacy staff member will obtain the drug kit which contains the matching ID.
4. IMPORTANT: The pharmacy staff member should handwrite the following information on the drug kit outer box:
    a. *Participant's initials*
    b. *Participant's date of birth*
5. Site staff will collect the participant drug kit from pharmacy.
6. Site staff will affix one participant ID sticker to be affixed to a participant document (*e.g.* informed consent form).
7. Site staff will dispense the participant the "loading dose" and witness administration, obtaining the pills from one of the blister packs. If the loading dose is 'split' then only the first dose needs to be witnessed.

8. Site staff will give the participant the remaining drug kit (i.e., carton containing 1 partial and 9 complete blister packs).

Note: Randomising participants out of sequence MUST be avoided.
In the unfortunate scenario that a kit is assigned out of sequence or a kit is wrongly allocated, the pharmacy/trial staff should immediately contact the Diabetes Trials Unit (DTU) to be advised how to proceed.

Figure 1. Summary of enrolment and kit assignment process



2.4. IMP ACCOUNTABILITY

1. Participants will enter daily verification of dosing via the electronic patient reported outcomes (ePRO) application.
2. Participants are to be instructed to bring their used blister packs to follow-up study visits for verification. The site will review and note missed doses and discrepancies in reported dosing vs remaining pills within the electronic case report form (eCRF).
3. All participant identifiers should be re-confirmed upon return of any IMP.
4. Following the final visit, pharmacy staff will record all returned pills on the IMP accountability log.
5. If any blister pack is accidentally misplaced by a participant it should be considered lost, this should be noted in site records. The site should contact the DTU for further guidance regarding replacement or further dosing instructions.

2.5. IMP DESTRUCTION

All IMP is to be destroyed at the local/site facility following their procedures, after final site reconciliation and check at study closeout by the monitor.

The site will file and provide DTU with documented evidence of destruction.

2.6. UNBLINDING

1. The site staff will not have a copy of the randomisation list as this is maintained centrally by the MORU trial statistician.
2. If the site investigator considers knowledge of assigned study drug necessary for medical management of a participant, they should immediately contact the:

    - UK Chief Investigator during working hours (08.00 to 18.00) 7 days/week

      Tel: 01273 876671

    - MORU Chief Investigators at all other times (18.01-07.59)

      Tel: 07380 327900

3. RELATED DOCUMENTATION

- COPCOV UK CRF Completion Guidelines
- COPCOV UK Temperature Log for Study Drug
- COPCOV UK Drug Accountability Log
- COPCOV UK Prescription
- COPCOV UK HCQ Dosing SOP