Working Instructions

Reporting Adverse Events and Serious Adverse Events

Adverse Event (AE)

Definition

- Adverse events include any possible side effect to taking medication as part of the trial (i.e. if the drug is reintroduced), listed in the study drug SmPC.
  OR
- Any event the PI deems clinically significant occurring as a result of participation in the trial.

Procedure for Recording Adverse Events

- Complete the AE form with the following information:
  - **Description**
  - **Date of onset**
  - **Outcome** (1 = resolved, 2 = resolving, 3 = not resolved, 4 = resolving with sequelae, 5 = unknown, 6 = Fatal)
  - **Severity** (1 = mild, 2 = moderate, 3 = severe)
  - **Relationship to study drug** (1 = not related, 2 = possibly related, 3 = probably related, 4 = definitely related)
  - **Date of resolution**
  - **Is the AE serious?** (1 = NO, 2 = results in death, 3 = is life-threatening, 4 = requires inpatient hospitalisation or prolongation of existing hospitalisation, 5 = results in persistent or significant disability / incapacity, 6 = is a congenital anomaly / birth defect, 7 = other important medical event)

- **The severity of events, and the relationship of AEs to the study medication, will be assessed by the local medically qualified investigator or a medically qualified member of the research team.**

- Relatedness:
  - Related: The adverse event follows a reasonable temporal sequence from trial medication withdrawal. It cannot reasonably be attributed to any other cause.
  - Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

Follow-up of Adverse Events

- Follow-up will continue until resolution or the event is considered stable, clinically insignificant or asymptomatic in the following cases:
    - AEs considered related to the withdrawal of medication (the intervention).
    - All related AEs that result in a participant's withdrawal from the study or are present at the end of the study.

Re-introduction of the Participant's Withdrawn treatment

- The recruiting physician will decide whether or not an AE is of sufficient severity to require re-introduction of the participant's withdrawn treatment and the reason will be recorded (on study discontinuation form).
- A participant may also decide to have treatment re-introduced due to what he or she perceives as an intolerable AE.

If either of these occurs, the participant must be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Serious Adverse Event (SAE)

Definition

- A serious adverse event is any untoward medical occurrence that:
  - results in death
  - is life-threatening
  - requires inpatient hospitalisation or prolongation of existing hospitalisation
  - results in persistent or significant disability/incapacity
  - Other 'important medical events' if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Expected Adverse Events

- **Expected** adverse events related to reintroduction of antihypertensive medication are given in the IMP dossier (section 4.8 of the SmPC for each drug class). There are no sections of the SmPC, or previous clinical studies which detail expected adverse events as a result of medication withdrawal and therefore all SAEs at least possibly related to the study IMP will be considered unexpected and reported as SUSARs.

Procedure for Recording Serious Adverse Events

- All SAEs occurring during the study either observed by the recruiting GP or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF.

General Instructions

- SAEs must be reported to the PC-CTU within 24 hours of discovery or notification of the event.

- Refer to the trial protocol for definitions of Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARs).

- SAEs are forwarded by the site GP to PC-CTU using the PC-CTU SAE Report Form, following assessment for seriousness and relatedness.

- Report Form must be:
    - Faxed to the PC-CTU using the number quoted on the report form – **01865 289412**.
    - Emailed to the PC-CTU using the email address quoted on the form – **optimise@phc.ox.ac.uk**.

- The PC-CTU will acknowledge receipt of the SAE Report Form. This receipt will be emailed and faxed to the site physician.

- If the site physician does not receive a receipt within 24hrs of them sending the report (during office hours), they should re-send the SAE Report Form to the PC-CTU by email or fax and telephone ahead.

- Follow-up information should be provided as necessary. Additional information, as it becomes available, will also be reported on the SAE Report Form (i.e. updating the original form) and returned to the PC-CTU by email or fax as above.

- File a copy of the completed SAE Reporting Form in your Investigator Site File / Study File.

- If you have any questions regarding the classification of an adverse event or form completion then please call your Trial Manager.

- Ensure ALL details of the SAE are documented in the participant's medical records including the Investigator's assessment of causality, which the study physician must document in the medical records.

- Record 'NK' for any data that is not known.

Instructions for completing the SAE form (also on SAE form):

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Q1. If this is the first time the SAE has been reported then please tick "initial". If you are submitting new, updated or corrected information for a previously reported SAE then please tick "follow-up information".

Q3. Record the unique trial number assigned to the participant. Enter the participant's weight in grams **OR** kilograms and delete the unit which is not applicable.

Q5. Enter date and time that the adverse event became serious.

Q6. Enter date and time that the adverse event stopped being serious (for example, if a participant has a life-threatening condition which was resolved by surgery then the date and time for end of surgery would be entered).

Q7. Enter the time and date that a member of the site trial/study team became aware of the SAE.

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Q8. Choose **one** of the severity options to describe the intensity of the event.

Q9. Choose **one** of the reasons why the adverse event has been classified as serious. If there is more than one reason which applies then choose the more/most significant one and document other reason(s) in the AE description.

Q10. Provide a full description of any medical history which could be relevant to this SAE and which may need to be considered by the individual reviewing the event.

Q12. Record details of study drug(s). This section must be completed regardless of whether there is a causal relationship with the study drug(s).

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Q13. Use the table to list all concomitant medications and use additional pages (P3a section 13a) if required.

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Q14. Select **one** of the outcome options. If the outcome is "Resolving" or "Not Resolved" then complete a follow-up report when the status of the SAE changes.

Q16. Include a telephone number for the person reporting the SAE so that the individual assessing the event can contact them in case of queries or if clarifications are needed.

Q17. A medically qualified individual is responsible for reviewing the SAE and considering whether the event was related to the study drug(s).

If a medically qualified individual is not available to make the causality assessment send in the SAE Reporting Form without this information and re-send the form as soon as this assessment has been made.

	Name	Title	Signature	Date
Written by:				
Approved by:				

Effective Date:	