WHAT TO REPORT ON THE EDC

As the Ambition study recruits cryptococcal meningitis (CM) patients often acutely ill and/or presenting with co-morbidities, it is expected that the incidence of adverse events will be high. The purpose of this document is to differentiate between events that are symptoms and signs of the underlying disease (HIV-associated CM) and thus not reportable as adverse events (AEs), and those AEs that should be reported.

The list below must be consulted prior to recording an adverse event onto the Ambition EDC. Where an adverse event meets the reporting criteria (i.e. grade 3 and above), the EDC will prompt the user to complete an Adverse Event CRF. This CRF must be completed onto the Ambition EDC within 24 hours of becoming aware of the event to comply with the Sponsor's pharmacovigilance requirements.

It is important to note that national regulatory bodies may have different expectations for adverse event reporting, therefore teams are advised to seek advice from their local standard procedures or consult with the Trial Manager, Dr Nabila Youssouf, by emailing **Nabila.Youssouf@lshtm.ac.uk or ambition@lshtm.ac.uk**

DO REPORT:

- All grade III/IV laboratory values – including those captured in the EDC and those not routinely requested as part of monitoring, apart from those detected on baseline bloods
- An abnormal grade III baseline blood which worsens to grade IV after day one
- Any abnormal baseline blood which subsequently falls into the grade III or IV category
- Grade III/IV clinical syndromes outlined in DAIDS v2.1 which are not associated with CM (as specified below) and are not present at baseline
- Vomiting causing hypotension requiring additional intravenous therapy
- The development of seizures which were not present upon enrolment
- A change in seizure character either in duration or quality (e.g. severity or focality)
- Grade III/IV visual loss which was not present upon enrolment
- Amphotericin induced rigors causing severe symptoms and requiring the infusion to be stopped indefinitely
- Thrombophlebitis requiring antibiotic therapy (oral or intravenous)
- Prolonged hospitalisation – on the 17th day of an initial admission submit a report
- Re-hospitalisation after discharge for any reason

DO NOT REPORT:

- An abnormal laboratory parameter detected on baseline bloods (but be aware of early withdrawal criteria)
- General symptoms of cryptococcal meningitis, either present at baseline or occurring during treatment, such as
    - Headache
    - Dizziness
    - Nausea
    - Confusion
    - Generalised weakness

- Increased frequency of seizures from previous level without change in seizure character
- Amphotericin induced-rigors that do not cause severe symptoms and only require modification of the infusion rate and/or administration of paracetamol
- Elevated CSF pressure: do not report as an AE, but record on the relevant CRF.

A RECURRENCE

IS:
Return of symptoms (headache, diplopia) consistent with CM after returning to full or near-full health for at least a week, but often longer

IS NOT:
Ongoing symptoms which fluctuate from day to day for example, a headache coming back after a few days without an LP

Reportable adverse events must be entered on the Ambition EDC, using the Adverse Event CRF, within 24 hours of becoming aware of the event.