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CLARIFICATION MEMO

DATE: September 7, 2023

TO: A5418 CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5418 Protocol Team

SUBJECT: Clarification Memo #2 for Protocol A5418 Version 3.0

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately.

The following are clarifications (noted in bold or strikethrough) to Protocol A5418, Version 3.0, 08Nov2022, titled, "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease." These clarifications will be included in the next version of the A5418 protocol if it is amended at a future date.

1. The team would like to clarify that drug interactions will be assessed for participants taking ARVs for pre-exposure prophylaxis, not just participants living with HIV.

   Section 1.4.10
   To assess the potential for drug interactions between tecovirimat and antiretrovirals among persons on ARVs ~~living with HIV (PLWH)~~.

   Section 11.1.2
   To assess the potential for drug interactions between tecovirimat and antiretrovirals ~~among PWH~~.

2. The only people who should cross over to Arm C are those who develop severe disease (as defined in the five bullet points in 4.3.2).

   Section 6.2.3

   Confirmation of Disease Progression
   Participants in Arms A or B who develop severe disease (as defined in the first five bullets in section 4.3.2) should be seen in person or through telemedicine for a confirmation of disease progression visit. This can occur at any point after randomization. If severe disease is confirmed by study personnel, participants should stop blinded study treatment and start a 14-day course of open-label tecovirimat. Participants should continue to be followed according to the SOE. Participants do not change to Arm C.

3. The dose of tecovirimat for participants <3 kg is listed as 33.3 mg, or 3.3 mL. The preparation instructions in Table A of the MOPS indicate that the contents of a 200 mg capsule are mixed with 20 mL water, which yields a 10 mg/mL solution, and then 3.3 mL is given to the participant. 3.3 mL of a

10 mg/mL solution will only be 33 mg and not 33.3 mg. The volume of the mixture given to participants <3 kg is revised to 3.33 mL of the prepared mixture.

Table 5.1-2: Initial Treatment Regimens for Participants <6 kg

Weight	Dose	Duration
<3 kg	Tecovirimat 33.3 mg (~~3.3~~ **3.33** mL) every 12 hours	14 days
3 to <6 kg	Tecovirimat 50 mg (5 mL) every 12 hours	14 days

5.1.1 Dispensing
Tecovirimat 33.3 mg: Administer as 33.3 mg/~~3.3~~ **3.33** mL – 200 mg capsule (20 mg total dose) orally every 12 hours.

4. Section 6.4.2, Oral, Rectal, Vaginal, and Index Lesion Swabs

   The protocol states that swabs will be self-collected by the participants as instructed per the SOE. This means that the index lesion should be swabbed at the follow-up visits indicated in the SOE even if it is healed, crusted, or scabbed over, or the scabs have fallen off and new skin has grown in.

5. Section 6.3.6, Swabs, Rectal Swabs, and/or Skin Lesion Swabs

   The protocol states that the index lesion will be swabbed throughout study follow-up. This means that the index lesion should be swabbed at the follow-up visits per the SOE even if it is healed, crusted, or scabbed over, or the scabs have fallen off and new skin has grown in. Additionally, this section states that any new skin lesion that has appeared since the participant's last study visit should be swabbed. Swabbing of a new skin lesion is in addition to the swabs required for the index lesion at follow-up visits per the SOE.

6. Given the changing nomenclature of the monkeypox virus, the protocol title is updated to, "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human ~~Monkeypox Virus~~ **Mpox** Disease."