CLARIFICATION MEMO #01 TO:

MATRIX-007

Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)

Cooperative Agreement #7200AA22CA00002

A Non-IND Study

Version 1.0 / July 3, 2024

Clarification Memo Date: October 4, 2024

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the MATRIX Prime-Clinical Trials Hub and MATRIX-007 Protocol Co-Chairs and are to be implemented immediately upon issuance. IRB/IEC approval of this CM is not required by MATRIX prior to implementation; however, investigators may submit the CM to the IRB/IEC overseeing the study at their site for the IRB/IEC's notification. This CM is official MATRIX-007 documentation and is effective immediately. A copy of this CM must be retained in each study country's Essential Documents file for MATRIX-007. No changes in the sample informed consent form or schedule of visits/procedures are included in this CM.

This document clarifies Enrollment Visit procedures related to review of ultrasound results and gestational age, clarifies that HIV testing would be omitted from study visits for participants who seroconvert and agree to remain on study, clarifies that syphilis testing would be omitted at the Enrollment Visit for participants with a documented recent result from a MATRIX-approved test and for participants currently being treated for syphilis, corrects a typo in an Appendix I footnote, and updates the Protocol Team Roster.

Section 2: Implementation

With the exception of updates to the protocol team roster, text to be deleted is noted below with a ~~strikethrough~~, text to be added is in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question. This information will be included in the protocol the next time the protocol is updated.

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1. The following clarification applies to Section 7.2 (Enrollment Visit), which states that "potential participants will be instructed to bring antenatal records (e.g., ANC card) with them to the

Enrollment Visit, if they have them", "participants who meet eligibility criteria and consent to participate in the study will be referred for an obstetric ultrasound to confirm gestational age, if adequate results are not available", and that study staff will "collect/update/review maternal pregnancy history" at this visit.

Although "Review available obstetric ultrasound results" is not explicitly listed as an "if indicated" visit procedure at the Enrollment Visit, Section 7.2 language cited above implies that obstetric ultrasound results will be reviewed at this visit if the participant has an ultrasound from ANC available. Therefore, ultrasound results will be reviewed with the participant if they are available at the Enrollment Visit.

2. The following clarification applies to Section 7.2 (Enrollment Visit), which states that study staff will "assess/confirm eligibility" at this visit, and that "participants who meet eligibility criteria and consent to participate in the study will be referred for an obstetric ultrasound to confirm gestational age, if adequate results are not available. Ideally, the ultrasound will take place between 8 and 24 weeks estimated gestation and before the first antenatal quarterly visit".

   Although "Review/confirm gestational age" is not explicitly listed as a required visit procedure at the Enrollment Visit, gestational age estimation is part of eligibility criteria determination per inclusion criterion #3 in Section 5.2 (Inclusion Criteria): "Estimated to be less than 34 weeks gestation (≤33 weeks and 6 days) at time of Enrollment". Section 7.2 language cited above implies that gestational age is first determined at the Enrollment visit and then confirmed/reviewed at antenatal visits. Therefore, gestational age will be reviewed/determined at Enrollment and confirmed via ultrasound prior to 1st antenatal quarterly visit, unless adequate ultrasound results are available at Enrollment.

3. The following clarification applies to Section 7.7.1 (Participants Who Become Infected With HIV), which states that "If a participant tests positive for HIV after the Enrollment Visit, the participant will be referred back to the CATALYST study site or to a public health sector clinic for confirmatory testing per the national testing algorithm in each study country and for referral for treatment. The participant will continue study follow-up, if willing. Please reference the MATRIX-007 SSP Manual for additional details".

   Although not explicitly stated in the protocol, HIV testing will be omitted from all follow-up visits for participants who seroconvert and agree to continue study follow-up. Instruction to refrain from testing participants who seroconvert during the study will be included in the SSP Manual, per Section 7.7.1 language cited above.

4. The following clarification applies to footnote #3 in Section 7.2 (Enrollment Visit) and in Appendix I (Schedule of Study Visits and Evaluations), which states that "Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual".

   Per local standard of testing and as outlined in the MATRIX-007 SSP Manual, syphilis rapid tests will be omitted from the Enrollment Visit for participants currently undergoing treatment for syphilis and for participants with a verifiable and

documented result, regardless if it is negative or positive, performed with a MATRIX-approved test during pregnancy and in the prior 3 months.

5. The following correction applies to footnote #2 in Appendix I (Schedule of Study Visits and Evaluations). The inclusion of pregnancy testing in this footnote is a typo only found in Appendix I and is inconsistent with language elsewhere in the protocol.

   [2] = HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from study visits if HIV ~~or pregnancy~~ testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual

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7. Protocol Team Roster – Additions:

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The above information will be incorporated into the next version of the protocol at a later time if it is amended.