MATRIX-003 Study-Specific Procedures (SSP) Manual
Section 1 – Introduction

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1 Introduction

This section specifies the sources of procedural information available to study staff, the responsibilities of Investigators of Record (IoR), and the process by which each site will be approved to initiate implementation of MATRIX-003.

1.1 Current Protocol Specifications

Table 1 below documents the history of the MATRIX-003 protocol, along with any Clarification Memos (CM) and Full Protocol Amendments, if applicable, all of which are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in the site essential files. It is not necessary for sites to file copies of the protocol documents mentioned below in the SSP Manual itself.

Table 1: MATRIX-003 Protocol History

Document	Date
MATRIX-003 Protocol, Version 1.0	29Jun2023
MATRIX-003 Protocol Version 1.0 Clarification Memo #01	21Aug2024
MATRIX-003 South African Protocol*, Version 1.1	19Feb2024
MATRIX-003 South African Protocol*, Version 1.2	16May2024

Document	Date
MATRIX-003 Protocol Version 1.2 Clarification Memo #01	21Aug2024

*To be implemented only by South African Sites. References to protocol specified abstinence and vaginal product use restrictions throughout the SSP manual are based on protocol version 1.0. For SA sites operating under SA protocol version 1.2, these references/details may be not applicable. Refer to local IRB/IEC approved protocol.

Sites are expected to operate under the protocol version that is currently approved by the local institutional review board/independent ethics committee (IRB/IEC) and other applicable regulatory bodies, and associated CMs. To ensure this section reflects the current specifications of the protocol, upon issuance of any future protocol Clarification Memo (CM) or Full Protocol Amendment, specifications listed above will be updated accordingly.

These documents are available on the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).

In order to respond to emerging public health emergencies like the COVID-19 pandemic, sites may need to rapidly implement practices and procedures that are not in line with the protocol or SSP Manual (e.g., modified visit procedures in the interest of staff/participant safety, conduct of remote visits, etc.). Sites should communicate with the MATRIX-003 Management Team and document contingency plans related to the public health emergency proactively, to the best of their ability (and retrospectively, as needed).

For each visit where modifications due to public health considerations result in a deviation from the protocol, a single protocol deviation should be reported with the underlying reason (e.g., "COVID-19") written in the description field, followed by what was modified during the visit. As required, sites should communicate contingency plans and protocol deviations related to COVID-19 or other emerging public health emergencies to IRBs/IECs and other applicable regulatory bodies. Sites should keep all communications and documentation in the site essential document file.

1.2 Sources of Procedural Information

The Study Specific Procedures (SSP) Manual serves to supplement the protocol. It does not replace or substitute the protocol or its contents. In the event this manual is inconsistent with the information and guidance provided in the protocol, the specifications in the protocol will take precedence. In the event study implementation questions are not adequately addressed by the study protocol or this manual or if any inconsistencies between the two documents are identified, please notify the MATRIX-003 Study Management Team at matrix003mgmtteam@lists.matrix4prevention.org. The Management Team should also be consulted for general questions on protocol implementation or study procedures, including clinical, lab, product, behavioral assessments, and/or data or case report form (CRF) completion procedures.

This group consists of the Protocol Chair(s) and representatives from the study sites, MATRIX Prime/Clinical Trials Hub (CTH), Design to Delivery (D2D) Hub Pillar 2, USAID, and Oak Crest Institute of Science (OCIS).

1.3 Investigator Responsibilities

MATRIX-003 must be conducted in accordance with the relevant United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (GCP). MATRIX-003 must be implemented in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular.

Each site IoR must sign an Investigator Signature Form (protocol signature page; PSP) and a MATRIX IoR Form to formally indicate his/her agreement to conduct MATRIX-003 in accordance with the study protocol, applicable US regulations and MATRIX policies. A copy of the PSP can be found in the MATRIX-003 protocol. A PSP must be signed by the IoR and sent to the MATRIX Prime/CTH Regulatory (matrixregulatory@lists.matrix4prevention.org) for all initial protocol versions and full protocol amendments. The site will keep copies of the PSP and MATRIX IoR Form(s) on site with their essential documents. The obligations and responsibilities assumed by the IoR when signing the MATRIX IoR Form and PSP are listed on the forms themselves. Updates to the MATRIX IoR Form should be submitted to the MATRIX Prime/CTH Regulatory (matrixregulatory@lists.matrix4prevention.org), with a short summary of any updates that were made.

The IoR may delegate his/her obligations and responsibilities for conducting MATRIX-003 to other qualified study staff members; however, delegation does not relieve the IoR of his/her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented on the site's Delegation of Duties (DoD) Log throughout study implementation.

NOTE: No staff member should fulfill the IoR role in the IoR's absence. Except in case of emergency, full responsibility and authority over the protocol by anyone other than the IoR may only take place if an additional MATRIX IoR Form that lists another person as the IoR is completed and submitted to the MATRIX Prime/CTH Regulatory (matrixregulatory@lists.matrix4prevention.org). This new IoR will be required to undergo the appropriate training and sign the PSP in the current version of the MATRIX-003 protocol and to update the site's DoD Log. In case of sudden and/or unplanned IoR absence, the IoR's designee(s) may temporarily fulfill the IoR role while the documentation described above is completed.

Staff regularly involved in the source documentation of safety data or those who are delegated to perform critical trial related procedures should be included on the MATRIX IoR Form as a sub-investigator. Such components may include, but are not limited to, adverse event (AE) assessment, collection of participant safety information, confirmation of participant eligibility, or prescription of study product. For MATRIX studies, this will typically mean the site IoR and study clinicians; lab, pharmacy, site coordinators and/or other site staff would only need to be added to the IoR Form if they will regularly conduct one or more of the critical trial related procedures listed above.

Consistent with the regulations, guidelines, and policies cited above, the site IoR must obtain and maintain IRB/IEC (and if applicable, drug regulatory authority [DRA]) approval of MATRIX-003 throughout the period of study implementation. All sites are strongly encouraged to request an acknowledgement of receipt for all documents submitted to their IRBs/IECs/DRAs and to request that IRBs/IECs/DRAs note the effective and expiry dates of all approvals. Documentation of all

correspondence to and from all responsible IRBs/IECs/DRAs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. Documentation of all IRB/IEC/DRA approvals will also be requested by the MATRIX Prime/CTH.

1.4 Study Activation Process

Prior to undertaking any study procedures, the study site must obtain approval to conduct MATRIX-003 from all required regulatory authorities and IRBs/IECs. The site also must complete study activation procedures with the MATRIX Study Management Team.

The MATRIX Prime/CTH will issue a Site-Specific Study Activation Notice to each site when all study activation requirements have been met. No protocol-specified study procedures may be undertaken at a site prior to receipt of the Site-Specific Study Activation Notice.