# MATRIX Clinical Trials Hub Procedure: Protocol Development and Review

## Standard Operating Procedure (SOP)#: CTH002, Version 1
## Effective Date: 03/23/2023

### 1.0 Purpose:

**1.1** To establish and describe the procedures for development, review and modification of all clinical research protocols conducted as part of the MATRIX (Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence) Collaborative, from concept to Version 1.0 and beyond.

**1.1.1** As appropriate, protocols will integrate social and behavioral research (SBR) components developed by the Design to Delivery (D2D) Hub into placebo studies and early phase studies of investigational products.

### 2.0 Scope:

**2.1** This procedure is applicable to all clinical research protocols (active and/or placebo product) implemented within MATRIX.

### 3.0 Authority:

U.S. Agency for International Development (USAID)
U.S. President's Emergency Plan for AIDS Relief (PEPFAR)
U.S. Food & Drug Administration (FDA)
Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence (MATRIX)

### 4.0 References: (Check for the most up-to-date version of the following)

**4.1** 2 CFR Part 200 ..... *Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards*
**4.2** 22 CFR Part 225 ..... *Protection of Human Subjects*
**4.3** USAID Automated Directives System (ADS) Chapter 201 ... *Program Cycle Operational Policy*
**4.4** USAID ADS Chapter 303 ..... *Grants and Cooperative Agreements to Non-*

*Governmental Organizations*
**4.5** ICH E6 Standard ..... *Good Clinical Practice (GCP)*
**4.6** MATRIX Policy ..... *Good Documentation Practice (GDP)*
**4.7** MATRIX Policy ..... *Human Subjects Research*
**4.8** MATRIX Protocol Template
**4.9** MATRIX List of Definitions
**4.10** MATRIX Clinical Trials Hub Study Activation SOP
**4.11** Attachment #1 ..... *Protocol Concept Template*
**4.12** Attachment #2 ..... *Protocol Version 0.1 Template Distribution Email (sample)*
**4.13** Attachment #3 ..... *Protocol Development Team Call Agenda Email (sample)*
**4.14** Attachment #4 ..... *Final Protocol Review Checklist (template)*
**4.15** Attachment #5 ..... *USAID Comments Response Document (template)*
**4.16** Attachment #6 ..... *Clarification Memo (template)*
**4.17** Attachment #7 ..... *Summary of Changes Document (template)*

## 5.0 Definitions:

See *MATRIX List of Definitions*.

## 6.0 Responsibilities:

### 6.1 Clinical Trials Hub Co-lead Principal Investigators (PI)

**6.1.1** Provide general oversight of development/updating of the study-specific template protocol version 0.1 template and Final Protocol Review Checklist documents.

**6.1.2** Provide general oversight of protocol development process.

**6.1.3** Provide general oversight of protocol review process prior to Version 1.0.

**6.1.4** Provide general oversight of protocol revision, version amendment, and clarification memo processes after Version 1.0.

### 6.2 MATRIX Prime Program Manager

**6.2.1** In collaboration with the Clinical Trials Hub Co-lead PIs, develop the study-specific protocol version 0.1 template document based on the MATRIX Protocol Template and the protocol concept (see Attachment 1 for Protocol Concept Template).

**6.2.2** Manage communications/logistics related to protocol development process:

**6.2.2.1** Following the MATRIX Steering Committee (SC) site selection vote, request that a study-specific Protocol Team email group be created in the MATRIX website.

**6.2.2.1.1** Protocol Teams initially consist of Product Developer and USAID representatives, investigators and study coordinators from the newly selected sites, and members of the Clinical Trials and D2D Hubs.

**6.2.2.2** Distribute study-specific protocol version 0.1 template to the Protocol Team (see Attachment 2 for sample distribution email).

**6.2.2.3** Schedule a 1-hour weekly Protocol Development Team call to coordinate protocol development and review processes through Version 1.0.

**6.2.2.4** Manage the Protocol Development Team calls, including creation of call agendas and moderation of Protocol Team discussions (see Attachment 3 for sample call agenda email).

**6.2.2.5** Collate content/comments/edits received from Protocol Team members (via email or on a call) and incorporate in subsequent versions (i.e., 0.2, 0.3, etc.) of the protocol draft document.

**6.2.2.6** Distribute subsequent versions of the protocol draft document to the Protocol Team, including document review timelines and specific instructions as needed.

**6.2.3** Develop the study-specific Final Protocol Review Checklist based on the Final Protocol Review Checklist template (see Attachment 4 for checklist template).

**6.2.4** Manage communications/logistics related to protocol review process prior to Version 1.0:

**6.2.4.1** Once the protocol document is ready for submission to USAID, typically at version 0.4 or higher, review the draft protocol document against the study-specific Final Protocol Review Checklist.

**6.2.4.2** Email the completed Final Protocol Review Checklist to the Product Developer, Protocol Chair/Co-Chairs and Clinical Trials Hub Co-lead PIs.

**6.2.4.2.1** If protocol document does not initially meet review criteria, make necessary edits and include revised protocol document (with revised version date and/or number as needed) along with completed checklist.

**6.2.4.3** Submit the final draft of the protocol document to USAID via email for their review and approval.

**6.2.4.4** In collaboration with Protocol Team members, respond to USAID comments received and revise the protocol document as needed (see Attachment 5 for USAID Comments Response Document template).

**6.2.4.4.1** Repeat 6.2.4.3-6.2.4.4 as needed until USAID approval is received.

**6.2.4.5** Distribute the final protocol Version 1.0 document to the Protocol Team and request the document be posted on the MATRIX website.

**6.2.5** Coordinate the transition from protocol development to study activation preparations:

**6.2.5.1** Request that the Protocol Team email group be renamed in the MATRIX website (from "Protocol Development Team" to "Protocol Team") and that a separate study-specific email group be created in the MATRIX website for the Management Team.

**6.2.5.2** Cancel the weekly Protocol Development Team calls and schedule a 1-hour bi-weekly Management Team call to coordinate study activation processes through site activation at the African study sites.

**6.2.6** Manage communications/logistics related to protocol revision, version amendment, and clarification memo processes after Version 1.0:

**6.2.6.1** In collaboration with other Management Team members as needed, determine the extent of protocol and/or consent form changes necessary (if any) when a section(s) of the protocol and/or consent form(s) is(are) identified as needing modification or clarification after Version 1.0 (e.g., during development of study activation materials).

**6.2.6.1.1** If the identified section(s) of the protocol and/or consent form(s) do not require modification or clarification, the Management Team may opt to modify or clarify the relevant section(s) in the Study-Specific Procedures (SSP) Manual.

**6.2.6.1.2** If the identified section(s) of the protocol and/or consent form(s) requires clarification but the protocol and/or consent form(s) do not need to be modified, the Management Team may opt to issue a Clarification Memo.

**6.2.6.1.3** If the identified section(s) of the protocol and/or consent form(s) require the text of the protocol and/or consent form(s) to be modified but the USAID-approved protocol Version 1.0 document has yet to be included in any regulatory submissions by the Product Developer or study sites, the Management Team may opt to incorporate these changes in a revised protocol Version 1.0 document with updated version date.

**6.2.6.1.4** If the identified section(s) of the protocol and/or consent form(s) require the text of the protocol and/or consent form(s) to be modified and the USAID-approved protocol Version 1.0 document has already been included in regulatory submissions by the Product Developer or study sites, the Management Team will incorporate these changes in an amended protocol version with updated version number and date.

**6.2.6.2** Draft the Clarification Memo or Summary of Changes Document, as applicable (see Attachments 6 and 7 for Clarification Memo and Summary of Changes Document templates, respectively).

**6.2.6.3** Distribute Clarification Memo, or Summary of Changes Document and clean and tracked changes versions of the revised protocol, as applicable, to the Protocol Team, including document review timelines and specific instructions as needed.

**6.2.6.3.1** Document review may be limited to select Protocol Team members depending on the extent and scope of identified changes.

**6.2.6.4** Collate content/comments/edits received from Protocol Team members (via email or on a call) and incorporate in subsequent versions of the draft document(s).

**6.2.6.5** Distribute subsequent versions of the draft document(s) to the Protocol Team, including document review timelines and specific instructions as needed.

**6.2.6.5.1** Repeat 6.2.6.3-6.2.6.5 as needed until document(s) is(are) ready for submission to USAID.

**6.2.6.6** Submit the final draft document(s) to USAID via email for their review and approval.

**6.2.6.6.1** Clarification Memos are submitted to USAID for informational purposes only.

**6.2.6.6.2** In collaboration with Protocol Team members, respond to USAID comments received for protocol revisions or amendments and revise the submitted document(s) as needed (see Attachment 5 for USAID Comments Response Document template).

**6.2.6.6.3** Repeat 6.2.6.3-6.2.6.6 as needed for protocol revisions or amendments until USAID approval is received.

**6.2.6.7** Distribute the final document(s) to the Protocol Team and request they be posted on the MATRIX website.

**6.2.7** Update MATRIX Protocol Template and/or Final Protocol Review Checklist template as needed, in collaboration with Clinical Trials Hub Co-lead PIs.

**6.2.8** Save protocol development, review and modification materials/communications, checklists, and other relevant documentation according to MATRIX's Good Documentation Practice (GDP) Policy.

## 6.3 MATRIX Protocol Team Members

**6.3.1** Prior to site selection, Product Developers provide MATRIX Prime and/or Clinical Trials Hub staff with a protocol concept document that gives a brief synopsis of their planned clinical research protocol (see Attachment 1 for Protocol Concept Template).

**6.3.2** Once the initial Protocol Team is formed, members actively participate in calls, communications, discussions, and decisions related to protocol development, review, and modification.

**6.3.2.1** Discussions and decisions may be limited to select Protocol Team members as needed depending on topic scope (e.g., clinical vs. behavioral) and member role (e.g., safety physician vs. SBR experts).

**6.3.3** Review distributed draft document(s) and provide feedback as needed either in writing or on a call.

**6.3.4** Product Developers save protocol development, review and modification materials/communications, checklists, and other relevant documentation according to MATRIX's GDP Policy.

### 6.4 USAID Representatives

**6.4.1** USAID representatives embedded in the Protocol Team actively participate in calls, communications, discussions, and decisions related to protocol development, review, and modification.

**6.4.2** Review near-final draft document(s) and provide feedback either in writing or on a call.

**6.4.3** Provide final approval of protocol Version 1.0 and subsequent revision and/or amendment documents prior to inclusion in any regulatory submission by the Product Developers or study sties.

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## 7.0 Procedure:

**NOTE:** All MATRIX clinical research plans, including all clinical research protocol concepts, are pre-approved by USAID through their Workplan approval process. However, USAID will review protocol concepts and any feedback provided will be incorporated into the protocol as appropriate. Furthermore, USAID will provide final approval of the protocol Version 1.0 document and subsequent Version 1.0 revisions/amendments prior to inclusion in any regulatory submission by the Product Developers or study sites.

**NOTE:** USAID will also embed a technical area expert in all Protocol teams to aid with timely provision of feedback and resolution of queries as needed.

**NOTE:** Other Clinical Trials Hub staff may fulfill the MATRIX Prime Program Manager tasks described herein as needed should the MATRIX Prime Program Manager be unable or unavailable.

**NOTE:** Frequency of Protocol Development Team calls, Management Team calls and/or Protocol Team calls may differ from the descriptions herein if study leadership agrees to hold the calls at more or less frequent intervals (e.g., bi-weekly rather than weekly, or vice-versa).

### 7.1 Develop Protocol Version 0.1 Template Document

**7.1.1** Once a protocol concept is received from a MATRIX Product Developer partner (see Attachment 1 for Protocol Concept Template), the MATRIX Prime Program Manager, in collaboration with the Clinical Trials Hub co-lead Pis, develops the study-specific protocol version 0.1 template document.

**7.1.2** The protocol version 0.1 template document follows all MATRIX formatting and quality control (QC) requirements (e.g., document structure, cover page, table of contents, section headings, etc.) and includes recommended language (e.g., regulatory oversight, data management, clinical management, informed consent form, etc.) to ensure:

**7.1.2.1** Consistency across all MATRIX clinical research protocols, including as relates to social and behavioral research (SBR) in the context of early phase trials and placebo studies.

**7.1.2.2** Inclusion of all necessary components to facilitate local institutional review board (IRB)/independent ethics committee (IEC) approvals.

**7.1.3** Formatting and QC requirements are listed in detail in the Final Protocol Review Checklist (see Attachment 4 for template checklist).

## 7.2 Distribute Protocol Version 0.1 Template Document to Protocol Team

**7.2.1** Following the MATRIX SC site selection vote, the MATRIX Prime Program Manager emails the MATRIX website manager to request they create a study-specific Protocol Team email group in the MATRIX website named "Protocol Development Team".

**7.2.1.1** Protocol Teams initially consist of Product Developer and USAID representatives, investigators and study coordinators from the newly selected sites, and members of the Clinical Trials and D2D Hubs.

**7.2.2** The MATRIX Prime Program Manager sends the study-specific protocol version 0.1 template document to the Protocol Team via email (see Attachment 2 for sample distribution email).

**7.2.2.1** The email includes instructions that Protocol Team members use the provided document and email group address when drafting the protocol document and distributing materials to other Protocol Team members.

**7.2.3** The MATRIX Prime Program Manager or designee saves the protocol concept, study-specific protocol version 0.1 template document, and all relevant communications and documentation according to MATRIX's GDP Policy.

## 7.3 Schedule and Manage Protocol Development Team Calls

**7.3.1** Following the MATRIX SC site selection vote, the MATRIX Prime Program Manager emails the MATRIX Prime staff assigned to schedule calls to request they solicit Protocol Team members' availability for a 1-hour weekly Protocol Development Team call to coordinate protocol development and review processes through Version 1.0.

**7.3.1.1** These calls will be recorded and made available to Protocol Team members via the MATRIX website.

**7.3.1.2** These calls should begin as soon as possible after site selection to allow adequate time to work through the protocol document while staying within expected timelines for protocol submission to USAID (i.e., within 6 months of receiving the protocol concept from the Product Developer).

**7.3.1.3** Protocol Team members required to be on these calls include the MATRIX Prime Program Manager, Product Developer and site PIs (or designees), Clinical Trials Hub co-lead PIs (or designees), MATRIX Clinical Research Manager(s) (CRM), MATRIX Laboratory Manager(s), MATRIX Data Manager(s) (if applicable), D2D Hub Pillar 2 co-lead PIs (or designees), and USAID representative(s).

**7.3.2** After Protocol Team members respond and a day and time are selected, the MATRIX Prime staff assigned to schedule calls sends a calendar invite to the Protocol Team, including call details and URL link(s).

**7.3.3** The MATRIX Prime Program Manager drafts the call agendas for the weekly Protocol Development Team calls and emails them to the Protocol Team no later than the day before each call, including relevant updates and topics for discussion during the call, and inviting call attendees to send items for addition to the agenda (see Attachment 3 for sample call agenda email).

**7.3.4** The MATRIX Prime Program Manager, in collaboration with the Protocol Chair/Co-Chairs (once selected), Product Developer PIs and Clinical Trials Hub co-lead PIs, disseminates updates/tasks and moderates team discussions during the weekly Protocol Development Team calls to work through unresolved protocol sections and protocol-related queries, compare notes/lessons learned/best practices, and discuss any other topics of interest to the Protocol Team.

## 7.4 Incorporate Protocol Team Comments in Subsequent Protocol Drafts

**7.4.1** Beginning with the protocol version 0.1 template document, the MATRIX Prime Program Manager requests (via email or on a call) that Protocol Team members review each version (i.e., 0.1, 0.2, 0.3, etc.) of the protocol draft document and provide additions, revisions and/or comments as needed.

**7.4.1.1** Subsequent versions of the protocol draft document are distributed to the Protocol Team via email, including document review timelines and specific instructions as needed.

**7.4.1.2** Document review may be limited to select Protocol Team members as needed depending on topic scope (e.g., clinical vs. behavioral), member role (e.g., safety physician vs. SBR experts), and/or document development stage (e.g., early vs. near-final).

**7.4.2** Protocol Team members provide their additions, revisions and/or comments (ideally) as tracked changes in the protocol draft document and send the revised document via email to the MATRIX Prime Program Manager.

**7.4.2.1** Comments and queries raised by Protocol Team members may be included in subsequent call agendas for team discussion as needed.

**7.4.2.2** Protocol-related decisions and queries resolved during a call will be summarized and listed in the agenda for the next scheduled team call.

**7.4.3** The MATRIX Prime Program Manager collates all additions, revisions and/or comments received (via email or on a call) from Protocol Team members and incorporates them in subsequent versions (i.e., 0.2, 0.3, etc.) of the protocol draft document.

**7.4.3.1** Repeat steps 7.4.1-7.4.3 as needed until the protocol document is ready for submission to USAID for final review and approval, typically at version 0.4 or higher.

**7.4.4** Product Developers save all protocol document versions, relevant call agendas/minutes/ transcripts and email discussions, and other relevant documentation according to MATRIX's GDP Policy.

**7.4.5** The MATRIX Prime Program Manager or designee saves all protocol document versions, relevant call agendas/minutes/transcripts and email discussions, and other relevant documentation according to MATRIX's GDP Policy.

### 7.5 Review Protocol Document prior to USAID Submission

**7.5.1** Prior to submission of the study protocol document to USAID for final review and approval, the MATRIX Prime Program Manager creates the study-specific Final Protocol Review Checklist based on the Final Protocol Review Checklist template (see Attachment 4 for checklist template).

**7.5.2** The MATRIX Prime Program Manager performs the QC checks detailed in the study-specific Final Protocol Review Checklist, then signs and dates the checklist.

**7.5.2.1** If the protocol document does not initially meet review criteria, the MATRIX Prime Program Manager makes any necessary edits to the protocol and includes the revised protocol document (with revised version date and/or number as needed) when distributing the completed checklist to study leadership.

**7.5.3** The MATRIX Prime Program Manager sends the signed/dated, study-specific Final Protocol Review Checklist (and revised protocol document if applicable) via email to the Product Developer, Protocol Chair/Co-Chairs, and Clinical Trials Hub co-lead PIs, and notifies them that submission of the protocol document to USAID is forthcoming.

## 7.6 Submit Protocol Document to USAID for Final Review and Approval

**7.6.1** The MATRIX Prime Program Manager submits the final, QC'd draft of the protocol document to the USAID representative(s) on the Protocol Team and USAID's core Project Management Team.

**7.6.1.1** May request Medium Priority review timeline for 7-14 business day turnaround of USAID comments, if needed.

**7.6.2** The MATRIX Prime Program Manager forwards the protocol document submission email to the Protocol Team, including expected review timelines if known.

**7.6.3** The MATRIX Prime Program Manager or designee saves the signed/dated, study-specific Final Protocol Review Checklist(s), all protocol document versions and relevant email communications, and other relevant documentation according to MATRIX's GDP Policy.

## 7.7 Respond to USAID Reviewer Comments

**7.7.1** Upon receiving USAID reviewers' comments (typically via email), the MATRIX Prime Program Manager forwards them to the Protocol Team, including response/review timelines and specific instructions as needed.

**7.7.1.1** If USAID approves the protocol document as is, skip to step 7.8.

**7.7.2** In collaboration with Protocol Team members, the MATRIX Prime Program Manager drafts responses to each individual comment received and revises the protocol document as needed (see Attachment 5 for USAID Comments Response Document template).

**7.7.2.1** See step 7.4 for guidance regarding iterative Protocol Team review process for the protocol and USAID Comments Response documents.

**7.7.3** Repeat steps 7.6-7.7.2 as needed until USAID approval of the protocol and response documents is received (typically via email).

## 7.8 Distribute USAID-approved Protocol Version 1.0 Document to Protocol Team

**7.8.1** Upon receiving USAID approval of the protocol and response documents, the MATRIX Prime Program Manager revises the version number and date throughout the protocol document to reflect achievement of Version 1.0.

**7.8.2** The MATRIX Prime Program Manager distributes both Word and PDF versions of the USAID-approved protocol Version 1.0 document to the Protocol Team via email.

**7.8.3** The MATRIX Prime Program Manager emails the MATRIX website manager and requests that the USAID-approved protocol Version 1.0 document be posted on the website.

**7.8.4** Product Developers save the signed/dated, study-specific Final Protocol Review Checklist(s), all protocol and response document versions, relevant email communications, the USAID-approved protocol Version 1.0 document, and other relevant documentation according to MATRIX's GDP Policy.

**7.8.5** The MATRIX Prime Program Manager or designee saves all protocol and response document versions, relevant email communications, the USAID-approved protocol Version 1.0 document, and other relevant documentation according to MATRIX's GDP Policy.

## 7.9 Coordinate Transition from Protocol Development to Study Activation Preparations

**7.9.1** The MATRIX Prime Program Manager emails the MATRIX website manager to request they rename the Protocol Team email group in the MATRIX website (from "Protocol Development Team" to "Protocol Team") and that a separate study-specific email group be created for the Management Team in the MATRIX website named "Management Team".

**7.9.1.1** Management Teams are initially limited to the Product Developer PIs, USAID representatives, site PIs and study coordinators, members of the Clinical Trials and D2D Hubs, and other Product Developer and/or site staff the PIs have identified as being significantly involved in development and/or coordination of study activation and/or implementation materials and/or processes.

**7.9.2** Once the Protocol Team and Management Team email groups are created, the MATRIX Prime Program Manager notifies the Protocol Team (via email or on a call) of the change, including the newly created email group addresses and instructions to use the provided email group addresses when communicating with and/or distributing materials among study team members because the previous Protocol Team email group (named "Protocol Development Team") has been deactivated.

**7.9.2.1** Product Developers and sites should also be instructed to review the email groups on the MATRIX website and notify the MATRIX Prime Program Manager of any study team member additions or removals they would like to make to either or both groups at this time, including email addresses for any additions.

**7.9.3** The MATRIX Prime Program Manager emails the MATRIX Prime staff assigned to schedule calls to request they cancel the weekly Protocol Development Team calls and solicit the Management Team members' availability for a 1-hour bi-weekly Management Team call to coordinate study activation processes through site activation at the African study sites.

**7.9.3.1** These calls will be recorded, call minutes will be created, and both recordings and minutes will be made available to Protocol Team members via the MATRIX website.

**7.9.3.2** These calls should begin as soon as possible after distribution of the USAID-approved protocol Version 1.0 document to allow adequate time to work through study activation preparations while staying within expected timelines for site activation at the African study sites (i.e., within 7 months of receiving USAID approval).

**7.9.3.3** Management Team members required to be on these calls include the MATRIX Prime Program Manager, Product Developer and site PIs and study coordinators (or designees), Clinical Trials Hub co-lead PIs (or designees), MATRIX Clinical Research Manager(s) (CRM), MATRIX Laboratory Manager(s), MATRIX Data Manager(s) (if applicable), D2D Hub Pillar 2 co-lead PIs (or designees), and USAID representative(s).

**7.9.4** After Management Team members respond and a day and time are selected, the MATRIX Prime staff assigned to schedule calls sends a calendar invite to the Management Team, including call details and URL link(s).

**7.9.4.1** Management Team calls are managed by the MATRIX CRM(s) in collaboration with the Protocol Chair/Co-Chairs, Product Developer PIs and Clinical Trials Hub co-lead PIs, including drafting of call agendas, dissemination of updates/tasks, and moderation of team discussions; see MATRIX Clinical Trials Hub Study Activation SOP for additional details.

## 7.10 Develop Protocol Revisions, Amendments, and/or Clarifications after Version 1.0

**7.10.1** During development of study activation and/or implementation materials and/or processes, as a result of national drug regulatory authority or site IRB/IEC recommendations and/or requirements, or due to any other circumstances (unforeseen or otherwise) at any point following distribution of the protocol Version 1.0 document to the Protocol Team, Protocol Team members may identify (via email or on a call) one or more problems with the language in the protocol and/or consent form(s) that may warrant modification and/or clarification of protocol Version 1.0.

**7.10.2** The MATRIX Prime Program Manager, in collaboration with other Management Team members as needed, determines the extent of protocol and/or consent form changes necessary (if any) to address the identified problem(s), and whether the identified

problem(s) could instead be addressed without modifying or clarifying the relevant protocol or consent form section(s).

**7.10.2.1** If the identified problem(s) can be addressed without modification or clarification of the relevant protocol and/or consent form section(s), the Management Team may opt to modify or clarify the relevant section(s) in the Study-Specific Procedures (SSP) Manual.

**7.10.2.2** If the identified problem(s) can be addressed through clarification of the relevant protocol and/or consent form section(s) but the protocol and/or consent form(s) do not need to be modified, the Management Team may opt to issue a Clarification Memo.

**7.10.2.3** If the identified problem(s) require modification of the relevant protocol and/or consent form sections(s) but the USAID-approved protocol Version 1.0 document has yet to be included in any regulatory submissions by the Product Developer or study sites, the Management Team may opt to incorporate these changes in a revised protocol Version 1.0 document with updated version date.

**7.10.2.4** If the identified problem(s) require modification of the relevant protocol and/or consent form sections(s) and the USAID-approved protocol Version 1.0 document has already been included in any regulatory submissions by the Product Developer or study sites, the Management Team will incorporate these changes in an amended protocol version with updated version number and date.

**7.10.3** The MATRIX Prime Program Manager drafts the Clarification Memo (for protocol and/or consent form clarifications) or Summary of Changes Document (for protocol and/or consent form modifications) as applicable (see Attachments 6 and 7 for Clarification Memo and Summary of Changes Document templates, respectively).

**7.10.3.1** Clarification Memos and Summary of Changes Documents include a listing of the identified problem(s) along with the proposed protocol and/or consent form clarifications/modifications proposed to address each.

**7.10.3.2** For protocol and/or consent form modifications, the MATRIX Prime Program Manager also revises the USAID-approved protocol Version 1.0 document to incorporate the modifications listed in the Summary of Changes Document.

**7.10.4** The MATRIX Prime Program Manager distributes the draft Clarification Memo (for protocol and/or consent form clarifications) or draft Summary of Changes Document and clean and tracked changes versions of the revised/amended protocol (for protocol

and/or consent form modifications) to the Protocol Team, including document review timelines and specific instructions as needed.

**7.10.4.1** Document review may be limited to the Management Team or select Protocol Team members depending on the extent and scope of proposed protocol and/or consent form clarifications or modifications.

**7.10.4.2** See step 7.4 for guidance regarding iterative Protocol Team review process for the Clarification Memo (for protocol and/or consent form clarifications) or Summary of Changes and revised/amended protocol documents (for protocol and/or consent form modifications) until ready for submission to USAID.

**7.10.4.3** See step 7.5 for guidance regarding QC of revised/amended protocol documents (for protocol and/or consent form modifications) prior to submission to USAID.

**7.10.5** Once the draft Clarification Memo (for protocol and/or consent form clarifications) or draft Summary of Changes and revised/amended protocol documents (for protocol and/or consent form modifications) are ready for submission to USAID, the MATRIX Prime Program Manager sends the document(s) via email to the USAID representative(s) on the Protocol Team and USAID's core Project Management Team.

**7.10.5.1** If needed, may request High or Medium Priority review timeline for 3-7 or 7-14 business day turnaround of USAID comments, respectively.

**7.10.5.2** Clarification Memos are submitted to USAID for informational purposes only and may be implemented immediately upon submission to USAID.

**7.10.5.3** Summary of Changes and revised/amended protocol documents are subject to USAID review and approval and may be implemented only after final USAID approval is received.

**7.10.6** The MATRIX Prime Program Manager forwards the document submission email to the Protocol Team, including expected review timelines if known for protocol and/or consent form modifications.

**7.10.6.1** For Clarification Memos, skip to step 7.10.9.

**7.10.7** Upon receiving USAID reviewers' comments (typically via email) and in collaboration with Protocol Team members as needed, the MATRIX Prime Program Manager responds to USAID comments received and revises the submitted document(s) as needed (see Attachment 5 for USAID Comments Response Document template).

**7.10.7.1** See step 7.7 for guidance regarding iterative Protocol Team review process for protocol revision/amendment and USAID Comments Response documents until USAID approval is received.

**7.10.8** Upon receiving USAID approval of the protocol and response documents, the MATRIX Prime Program Manager revises the version date and (for protocol amendments) version number throughout the protocol document and distributes both Word and PDF versions of the USAID-approved protocol revision/amendment document to the Protocol Team via email.

**7.10.8.1** See step 7.8 for additional guidance regarding distribution of the USAID-approved protocol revision/amendment document to the Protocol Team.

**7.10.9** Product Developers save all protocol clarification/revision/amendment and response document versions, relevant call agendas/minutes/transcripts and email communications, the signed/dated, study-specific Final Protocol Review Checklist and USAID-approved protocol revision/amendment documents (for protocol modifications), and other relevant documentation according to MATRIX's GDP Policy.

**7.10.10** The MATRIX Prime Program Manager or designee saves all protocol clarification/revision/amendment and response document versions, relevant call agendas/minutes/transcripts and email communications, the signed/dated, study-specific Final Protocol Review Checklist and USAID-approved protocol revision/amendment documents (for protocol modifications), and other relevant documentation according to MATRIX's GDP Policy.

### 7.11 Update MATRIX Protocol Template and Final Protocol Review Checklist Template

**7.11.1** The MATRIX Prime Program Manager, in collaboration with the Clinical Trials Hub co-lead PIs, updates the MATRIX Protocol Template and/or Final Protocol Review Checklist template, as needed, to incorporate feedback from Protocol Team members and/or updates and changes to relevant regulations, policies and procedures.

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## 8.0 Document History

| Version / Date Effective | Summary of Changes | Revised by / Approved by |
|---|---|---|
| A / [*03/23/2023*] | Original Release | L. Duran / N. Mgodi / S. Hillier |
| | | |
| | | |

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## 9.0 Approvals

DocuSigned by:
Luis Duran
Signer Name: Luis Duran
Signing Reason: I am the author of this document
Signing Time: 7/25/2023 | 8:25:15 AM PDT
4F4E4A7E27804D9387497FBC68D468A2

7/25/2023

*Prime Program Manager Signature* *Date (month/day/year)*

DocuSigned by:
Nyaradzo Mgodi
Signer Name: Nyaradzo Mgodi
Signing Reason: I approve this document
Signing Time: 7/25/2023 | 1:19:10 PM PDT
CA2EE955FFE04C83BFE4F075EC10A21E

7/25/2023

*Clinical Trials Hub Co-lead/PI Signature* *Date (month/day/year)*

DocuSigned by:
Sharon Hillier
Signer Name: Sharon Hillier
Signing Reason: I approve this document
Signing Time: 7/25/2023 | 8:28:28 AM PDT
437BF8C12B1541729992EA42A322B571

7/25/2023

*Executive Director's Signature* *Date (month/day/year)*

**MATRIX-[*XXX*]: [*Insert Study Title*]**

**[*Insert IND# or "A Non-IND Study", as applicable*]**

**Study design:**

**Study population:** Approximately [*XX*] [*Insert brief description of target study population*], with approximately [*XX*] participants each at [*XX*] sites from [*DELETE if not applicable: the United States,*] Kenya, South Africa and/or Zimbabwe.

**Study product(s):**

**Study regimen:**

**Primary Objective:**

- **Primary Endpoint(s):**
    - 

**Secondary Objective:**

- **Secondary Endpoint(s):**
    - 

**Secondary Objective:**

- **Secondary Endpoint(s):**
    - 

**Exploratory Objective:**

- **Exploratory Endpoint(s):**
    - 

**Exploratory Objective:**

- **Exploratory Endpoint(s):**
    - 

**Key inclusion criteria:**

- 

**Key exclusion criteria:**

- 

**Background and Study Rationale:**

[*Provide brief background/rationale for conducting the study, e.g., Why develop this type of HIV prevention product in general? Why this specific study product in particular? Why conduct this study at this point in R&D? Why this study design?*]

**Visits and Study Procedures:**

[*List study visits and briefly describe procedures conducted, screen-to-enrollment window and if/when randomization occurs*]

**Visit Schedule / Study Product Regimen Figure:**

[*Insert Figure illustrating study visit sequence/timeline*]

**Schedule of Study Visits and Evaluations:**

[*Insert Table illustrating schedule of study visit procedures; see example below*]

| STUDY PROCEDURES | SCREEN | ENROLL | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 |
| Day | | | | | | | | |
| Length of Visit | | | | | | | | |
| Medical History & Medication review | | | | | | | | |
| Randomization | | | | | | | | |
| Acceptability Questionnaire | | | | | | | | |
| In-depth interview | | | | | | | | |
| HIV pre- and post-test counseling | | | | | | | | |
| HIV/STI risk reduction counseling | | | | | | | | |
| HIV Rapid Test | | | | | | | | |
| HIV Confirmatory Test | | | | | | | | |
| Review Applicable Test Results | | | | | | | | |
| Protocol Counseling | | | | | | | | |
| AE assessment | | | | | | | | |
| Urine Pregnancy Test | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pelvic Exam with speculum | | | | | | | | |
| Vaginal pH | | | | | | | | |
| Gram Stain | | | | | | | | |
| Genital swab for quantitative PCR | | | | | | | | |
| GC/CT/Trich | | | | | | | | |
| Wet mount | | | | | | | | |
| Brief Physical Exam | | | | | | | | |
| Provide study product | | | | | | | | |
| Compensation | | | | | | | | |
| Collect/update/review contact/locator information | | | | | | | | |

x = Required; ^ = If indicated and/or per local standard of care

**NOTE:** A Protocol Template Distribution email should include a brief description of the study, instructions re: use of the attached template document and email group address, and re: final QC checks prior to protocol Version 1.0.

To: [*MATRIX-[XXX] Protocol Team*]
Cc: [*MATRIX Prime*]
Subject: MATRIX Protocol Template for MATRIX-[*XXX*] [*Insert Study Short Title*]

Dear MATRIX-[*XXX*] Protocol Team members,

Attached please find draft protocol version 0.1 of MATRIX-[*XXX*], [*Insert Study Title*], dated [*Insert document date*]. The study-specific protocol template(s) attached has been adapted using the MATRIX-[*XXX*] protocol concept document dated [*Insert document date*].

The MATRIX-[*XXX*] protocol is designed to [*Insert primary study objective(s)*]. [*Insert brief description of study design, product(s) studied, and product use duration; also study population if not already included in primary objective(s)*].

To ensure consistency across all MATRIX clinical research protocols, Clinical Trials Hub staff will perform a series of quality control (QC) checks on the MATRIX-[*XXX*] protocol document(s) prior to achieving Version 1.0. This is a requirement of all clinical research protocols. Submission of Version 1.0 protocol document(s) to regulatory authorities [*Insert if applicable:* or towards an IND/IDE application] prior to satisfactory completion of these QC checks will constitute a violation of MATRIX policies and procedures.

Therefore, we urge you to distribute the provided template version to all MATRIX-[*XXX*] Protocol Team members and begin using this version moving forward as you continue to draft the MATRIX-[*XXX*] protocol document(s). The attached template(s) already incorporate all QC-relevant formatting requirements (e.g., document structure, cover page, table of contents, section headings, etc.). The template(s) also include recommended language (e.g., regulatory oversight, data management, clinical management, informed consent form, etc.) to facilitate local regulatory approval requirements, including as relates to social and behavioral research in the context of early phase trials and placebo studies, without being overly prescriptive at this early stage of protocol development.

**NOTE:** Specific instructions/suggestions within the attached template document(s) are identified with [*italicized brackets*]. Specific clarification requests are identified with comments.

Lastly, Clinical Trials Hub staff would be happy to provide additional support and/or assistance with protocol writing as you continue to draft the MATRIX-[*XXX*] protocol document(s). Please accept or decline the offer by responding to me by COB [*Insert deadline date*].

Feel free to contact me if you require additional time to respond or have any questions/comments re: the attached document(s).

Best regards,

[*MATRIX Prime Program Manager*]

To: [*MATRIX-[XXX] Protocol Team*]
Cc: [*MATRIX Prime*]
Subject: MATRIX-[*XXX*] Protocol Development Team call agenda for [*Month Day*]

Dear MATRIX-[*XXX*] team,

Please see below agenda for our Protocol Development Team call scheduled for [*Month Day*] at [*Time*] EST/[*Time*] PST/[*Time*] SAST/[*Time*]KST:

- [*LIST announcements and other housekeeping items, if any*]
- [*LIST updates on protocol development, if any*]
- [*LIST presentations from Protocol Team members, if any*]
- [*LIST topics for discussion and/or questions from/to Protocol Team members*]
- [*LIST next steps in protocol development, including timelines*]
- AOB

Our next team call is scheduled for [*Month Day*] at [*Time*] EST/[*Time*] PST/[*Time*] SAST/[*Time*]KST. An agenda will be sent by email prior to the call. If you have any specific items you would like to bring up during the call, please let me know by noon on [*Day*] to ensure they are added to the call agenda.

# Protocol Document Checks Prior to Final Version(s)

**Study #: MATRIX-[XXX]** **Protocol Version #: [*Insert Number and Date*]**

In order to ensure the Protocol/Amendment document is ready for final approval(s), the following quality control checks were independently completed and hereby documented:

1. □ Check consistency of the long title and short title of the protocol within the following sections:
    - □ Cover page (Long title)
    - □ Table of Contents (Long title)
    - □ List of Abbreviations and Acronyms (Long title)
    - □ Protocol Team Roster (Long title)
    - □ Investigator Signature Form (Long title)
    - □ Protocol Summary (Long and short title)
    - □ Section 1.1, Protocol Identification (Long and short title)
    - □ Appendix IV: Sample Informed Consent (Long and short title)

2. □ Ensure that the funding agencies (USAID and any other grant/award sources as applicable), pharmaceutical collaborator, and IND holder (if applicable) are listed consistently in the following sections:
    - □ Cover Page (Funder, pharmaceutical collaborator and IND holder)
    - □ Investigator Signature Form (Funder, pharmaceutical collaborator and IND holder)
    - □ Protocol Summary (Pharmaceutical collaborator and IND holder)
    - □ Section 1.2, Funding Agencies, IND Sponsor and Monitor Identification (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 8.1, Safety Monitoring (Pharmaceutical collaborator and IND holder)
    - □ Section 8.4, Expedited Adverse Event Reporting Requirements (Pharmaceutical collaborator and IND holder)
    - □ Section 9.8, Criteria for Early Termination of Study Participation (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 11.2, Source Documents and Access to Source Data/Documents (Pharmaceutical collaborator and IND holder)
    - □ Section 12.0, Clinical Site Monitoring (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 13.0, Human Subjects Protections (Funder)
    - □ Section 13.3, Study Coordination (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 13.6, Participant Confidentiality (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 13.11, Study Discontinuation (Funder, pharmaceutical collaborator and IND holder)
    - □ Section 14.0, Publication Policy (Funder, pharmaceutical collaborator and IND holder)
    - □ Appendix IV: Sample Informed Consent (Funder, pharmaceutical collaborator and IND holder)

- Informed Consent/Introduction section
- Why You May Stop Taking the Drug Early or Be Asked to Leave the Study section
- Confidentiality section

3. □ Confirm that the USAID Cooperative Award number (and any other grant/award sources as applicable) and IND number (if applicable) are correct on the protocol cover page.

4. □ Make sure that the study designation, version number and version date are correct throughout the document. This includes:
    - □ Footer of every page except the cover page (Study designation, version number and version date)
    - □ Cover page (Study designation, version number and version date)
    - □ Table of Contents (Study designation)
    - □ List of Abbreviations (Study designation)
    - □ Protocol Team Roster (Study designation)
    - □ Investigator Signature Form (Study designation, version number and version date)
    - □ Protocol Summary (Study designation)
    - □ Section 1.1, Protocol Identification (Study designation and version date)
    - □ Appendix IV: Sample Informed Consent (Study designation, version number and version date)

5. □ Ensure that formatting is consistent throughout the document, specifically the:
    - □ Cover page, including required logos/identify marks
    - □ Page footers and headers
    - □ Page breaks
    - □ Font style, font size and alignment (Tahoma 11pt Justified, except for Main sections [12pt] and Tables [10pt])
        - Avoid "orphaned" text (apply "Window/orphan control" and/or "Keep with next" where necessary)
    - □ Table of Contents, including hyperlinks to sections/figures/tables
    - □ Protocol Team Roster
    - □ Section headings (style and structure) and spacing between sections
    - □ Tables in the document should not break across the page
        - If a table does break across the page, repeat the table header at the top

6. □ Ensure text/descriptions within the following sections are reflective of each other:
    - □ Study objectives and endpoints should be consistent
        - Protocol Summary
        - Section 3.0, Objectives
        - Section 4.2, Summary of Major Endpoints
        - Section 10.2, Study Endpoints
        - Primary endpoint in Appendix IV: Sample Informed Consent (Informed Consent/Introduction and Why Is This Research Being Done? sections)
    - □ Description of study procedures should be consistent
        - Tables within Section 7.0, Study Procedures
        - Appendix I: Schedule of Study Visits and Evaluations
        - Appendix IV: Sample Informed Consent (What Will I Be Asked To Do If I Join This Research Study? and What Will Happen During the Study Visits? sections)

- □ Text within Section 13.5, Informed Consent Process and Appendix IV: Sample Informed Consent should align
- □ Text regarding pregnancy should align
  - ■ Section 7.5.2, Participants Who Become Pregnant
  - ■ Section 8.5, Pregnancy and Infant Outcomes
  - ■ Section 9.7, Pregnancy
  - ■ Section 13.7.1, Pregnant Women
  - ■ Appendix IV: Sample Informed Consent (What If I Become Pregnant? section)
- □ Text regarding HIV-1 infections should align
  - ■ Section 7.5.1, Participants Who Become Infected with HIV-1
  - ■ Section 9.6, HIV-1 Infection
  - ■ Section 13.10, Access to HIV-related Care
  - ■ Appendix IV: Sample Informed Consent (What If I Become Infected with HIV? section)
- □ Text regarding product hold or permanent discontinuation should be consistent
  - ■ Section 7.5.3, Participants Who Temporarily Hold or Permanently Discontinue Study Product Use
  - ■ Section 9.3, General Criteria for Temporary Hold and Permanent Discontinuation of Study Product
  - ■ Section 9.4, Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events
  - ■ Section 13.11, Study Discontinuation
  - ■ Appendix IV: Sample Informed Consent (Why You May Stop Taking the Drug Early or Be Asked to Leave the Study section)
- □ Text regarding study risks should be consistent
  - ■ Section 13.4.1, Risks
  - ■ Appendix IV: Sample Informed Consent (Risks and/or Discomforts section)
- □ Text regarding study benefits should be consistent
  - ■ Section 13.4.2, Benefits
  - ■ Appendix IV: Sample Informed Consent (Benefits section)

7. □ Ensure that Section 14.0, Publication Policy includes the correct parties involved in governing publication of the study results.

8. □ Ensure contact information is up to date in the Protocol Roster.

9. □ Update Table of Contents prior to finalizing.

Reviewer: _____ Date: _____
Signature (mm/dd/yyyy)

_____ Title: _____
Printed Name

Response to USAID Comments on MATRIX-[*XXX*] Version [*X.X*] [*MM/DD/YYYY*]

**USAID Comments received [*MM/DD/YYYY*]:**

**Overarching Comments:**

- [*COPY each individual Overarching Comment from list of USAID review comments received by email; COPY all bullet points and sub-bullet points*]

  **Response:** [*ADD response to each individual Overarching Comment from list of USAID review comments received by email; One response per comment, but may answer more than one sub-bullet point with one response*]

**Specific Comments:**

- [*COPY each individual Specific Comment from list of USAID review comments received by email; COPY all bullet points and sub-bullet points*]

  **Response:** [*ADD response to each individual Specific Comment from list of USAID review comments received by email; One response per comment, but may answer more than one sub-bullet point with one response*]

**[*ADD any other categories included in USAID email*]:**

- [*COPY each individual comment from list of USAID review comments received by email; COPY all bullet points and sub-bullet points*]

  **Response:** [*ADD response to each individual comment from list of USAID review comments received by email; One response per comment, but may answer more than one sub-bullet point with one response*]

Additional minor edits and updates were made throughout the document for clarity and consistency.

**MATRIX SOP #CTH002, Version 1, Attachment 6**
**MATRIX Clarification Memo Template (Version 1)**

# CLARIFICATION MEMO #[*XX*] TO:

**MATRIX-[*XXX*]**

**[*Insert Study Title*]**

**Cooperative Agreement #7200AA22CA00002**

**IND # [*Insert if applicable; If not, replace with "A non-IND study"*]**

**Version [*1.0/2.0/X.0*] / [*Month Day, Year*]**

**Clarification Memo Date: [*Month Day, Year*]**

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## Section 1: Summary of Clarifications and Rationale

The procedures clarified in this Clarification Memorandum (CM) have been approved by the MATRIX Clinical Trials Hub, MATRIX-[*XXX*] Protocol Chair(s), and MATRIX-[*XXX*] Product Developer (PD)/sponsor and are to be implemented immediately upon issuance. IRB/IEC approval of this CM is not required by the PD/sponsor; however, investigators may submit the CM to the IRB/IEC overseeing the study at their site for information. This CM is official MATRIX-[*XXX*] documentation and is effective immediately. A copy of this CM must be retained in the PD/sponsor's and in each study site's Essential Documents file for MATRIX-[*XXX*]. No change in informed consent is necessitated by or included in this CM.

This document clarifies the language in the protocol regarding [*ADD primary driver for CM at this time*]; and clarifies that [*ADD brief listing of other protocol clarifications being made at this time*]. [*DELETE if not applicable:* This CM also updates the Protocol Team Roster.]

A detailed listing of clarifications is provided below.

## 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.

---

The following clarifications (*X-X*) were made to [*ADD primary driver for CM at this time; include number range if more than one clarification in protocol for primary reason*]:

1. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

   [*ADD exact protocol clarification made, using convention described in Instructions above*]

2. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

   [*ADD exact protocol clarification made, using convention described in Instructions above*]

The following clarifications (*X-X*) were made to [*ADD other protocol clarifications being made at this time; include number range if more than one clarification in protocol for a particular item*]:

3. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

   [*ADD exact protocol clarification made, using convention described in Instructions above*]

4. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

   [*ADD exact protocol clarification made, using convention described in Instructions above*]

[*ADD similar groupings for each additional protocol clarification being made at this time*]

5. [*DELETE if not applicable*] Protocol Team Roster – Removals:
6. [*DELETE if not applicable*] Protocol Team Roster – Additions:
7. [*DELETE if not applicable*] Protocol Team Roster – Updates:

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

# SUMMARY OF CHANGES
# INCLUDED IN THE [*REVISED/AMENDED*] PROTOCOL VERSION OF

**MATRIX-[*XXX*]**

**[*Insert Study Title*]**

**Cooperative Agreement #7200AA22CA00002**

**IND # [*Insert if applicable; If not, replace with "A non-IND study"*]**

**[*For protocol and/or sample consent form revisions prior to initial regulatory submission of USAID-approved protocol by Product Developer or study sites, ADD below*]**
**THE REVISED PROTOCOL IS IDENTIFIED AS: Version 1.0/ [*Month Day, Year*]**

**[*For protocol and/or sample consent form amendments after initial regulatory submission of USAID-approved protocol by Product Developer or study sites, ADD below*]**
**THE AMENDED PROTOCOL IS IDENTIFIED AS: Version 2.0/ [*Month Day, Year*]**

---

**Information/Instructions to Product Developer and Study Sites**

Please file this Summary of Changes Document with Version [*1.0/2.0/X.0*] of the protocol in your essential document files for MATRIX-[*XXX*].

Unless otherwise noted below, deleted text is noted by ~~strikethrough~~, added text is noted in **bold**, and text in ***bold italics*** was not added, but serves as a clarification of the implementation item in question.

**Summary of Revisions**

This [*revision/amendment*] [*impacts/does not impact*] the overall design or the study visit schedule for MATRIX-[*XXX*]. The purpose of this [*revision/amendment*] is to [*ADD primary driver for revision/amendment at this time*]. This [*revision/amendment*] also [*ADD brief listing of additional protocol modifications being made at this time*]. A detailed listing of revisions is provided below.

---

The following revisions (*X-X*) were made to [*ADD primary driver for revision/amendment at this time; include number range if more than one change in protocol for primary modification; may opt to describe protocol change instead of copying it exactly if change is extensive*]:

8. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

   [*ADD exact protocol revision made, using convention described in Instructions above*]

9. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

[*ADD exact protocol revision made, using convention described in Instructions above*]

The following revisions (*X-X*) were made to [*ADD other protocol modification being made at this time; include number range if more than one change in protocol for a particular modification; may opt to describe protocol change instead of copying it exactly if change is extensive*]:

10. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

    [*ADD exact protocol revision made, using convention described in Instructions above*]

11. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

    [*ADD exact protocol revision made, using convention described in Instructions above*]

[*ADD similar groupings for each additional protocol modification being made at this time*]

Additional minor modifications include [*ADD protocol team roster changes here if applicable*]:

12. [*ADD protocol section, sub-section, table, and/or figure number(s) and title(s)*]:

    [*ADD exact protocol revision made, using convention described in Instructions above*]

Additional minor edits were made throughout the document for clarity and consistency and/or to correct grammatical errors.