Scientific Advisory Group Charter

For

Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence (MATRIX)

USAID Cooperative Agreement # 7200AA22CA00002

Effective date: 11/14/2022

Abbreviations

AGYW: Adolescent girls and young women pregnant
API: Active Pharmaceutical Ingredient
ARV: Anti-retroviral
BC: Market strategy and Business Case
CMC: Chemistry, Manufacturing, and Control
CP: Critical Path
EST: Eastern Standard Time for the United States of America
FSW: Female Sex Workers
FIH: First in Human clinical trial
GLP: Good Laboratory Practices
GMP: Good Manufacturing Practices
HCD: Human Centered Design
HIV: Human Immunodeficiency virus 1
IDE: Investigational Device Exception
IND: Investigational Drug Application
ISP: Integrated Special Project
MATRIX: Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence
MBR: Milestone and Benchmark Report
MWRI: Magee-Womens Research Institute
MOP: Manual of Operations for MATRIX
MPT: Multipurpose Prevention Technologies
NDA: New Drug Application
NDE: New Device Application
PD: Product Developer
PDL- Product Development Leader
PI: Project Investigator
POC: Point of Contact
PRIME: Leadership of MATRIX, (Drs. Hillier and Palanee-Phillips)
R&D: Research and Development
SAG: Scientific Advisory Group for MATRIX
SBR: Socio-behavioral research
SRB: Sexual and reproductive health
SC: Steering Committee of MATRIX
SSA: Sub-Saharan Africa
TA-D1: Technology Accelerator Doman 1
TA-D2: Technology Accelerator Doman 2
USA: United States of America
USAID: United States Agency for International Development
PBFW Young women pregnant and breastfeeding women

Background

The Microbicide R&D to Advance HIV Prevention Technologies through Responsive Innovation and eXcellence (MATRIX) Collaborative is designed to expedite research and development (R&D) of products for prevention of HIV in women. MATRIX is funded by United States Agency for International Development (USAID, Awarded December 1, 2021) and is led by Dr. Sharon Hillier (Magee-Womens Research Institute (MWRI), Pittsburgh PA, USA) and Dr. Thesla Palanee-Phillips (University of the Witwatersrand Johannesburg, South Africa). Through a co-creation process with USAID and under their leadership the collaborative is composed of a wide range of inter-disciplinary partners with product Research and Development (R&D-related experience in women-initiated anti-human immunodeficiency virus-1 (HIV) -based prevention methods, including expertise in developing a range of antiretroviral (ARV)-based prevention modalities; drug formulation and delivery; long-acting, topical and systemic drug delivery; sexual and reproductive health (SRH), HIV prevention product development; socio-behavioral research (SBR) as well as market strategy and Business Case (BC) assessments and capacity strengthening. MATRIX is designed to be a dynamic and adaptable award with emphasis on actively managing projects through a "stage gating" process to remain time and resource efficient (e.g., timely discontinuation of activities that are no longer of the highest priority or projects which have met roadblocks threatening their feasibility). Stage-gating is defined as a time-based milestone-driven decision-making process that establishes Go/No-Go and achievement benchmarks for each product at defined development stages. MATRIX may also on-ramp new products judged to be of scientific priority to MATRIX to fill known gaps in biomedical HIV prevention. All R&D, SBR, clinical trial, and BC development within MATRIX are interconnected, with a priority focus on ensuring equitable leadership and representation by Sub-Saharan Africa (SSA) stakeholders, to advance products that meet the diverse HIV-prevention needs of adolescent girls and young women (AGYW), pregnant and breastfeeding women (PBFW), and female sex workers (FSW).

Scientific Advisory Group (SAG)

The SAG is critical to ensuring active curation of MATRIX's portfolio of products. The SAG is an external, neutral, cross-cutting, multidisciplinary committee that will provide expert data review and consultation services to inform the MATRIX stage-gating process. Biannually the SAG will provide an independent unbiased assessment of progress for MATRIX product development efforts. The SAG will be the primary evaluation body for assessing progress of Critical Path (CP) products and Technology Accelerator Domain 2 activities (TA-D2) using the stage-gating process (see Figure 1). The SAG will also evaluate mitigation plans used to report development problems and, in some cases, recommend off-ramping of CP products to TA-D2 for problem mitigation. The SAG will also make recommendations of futility determinations (stopping development) for Critical Path (CP) products and TA-D2 activities.

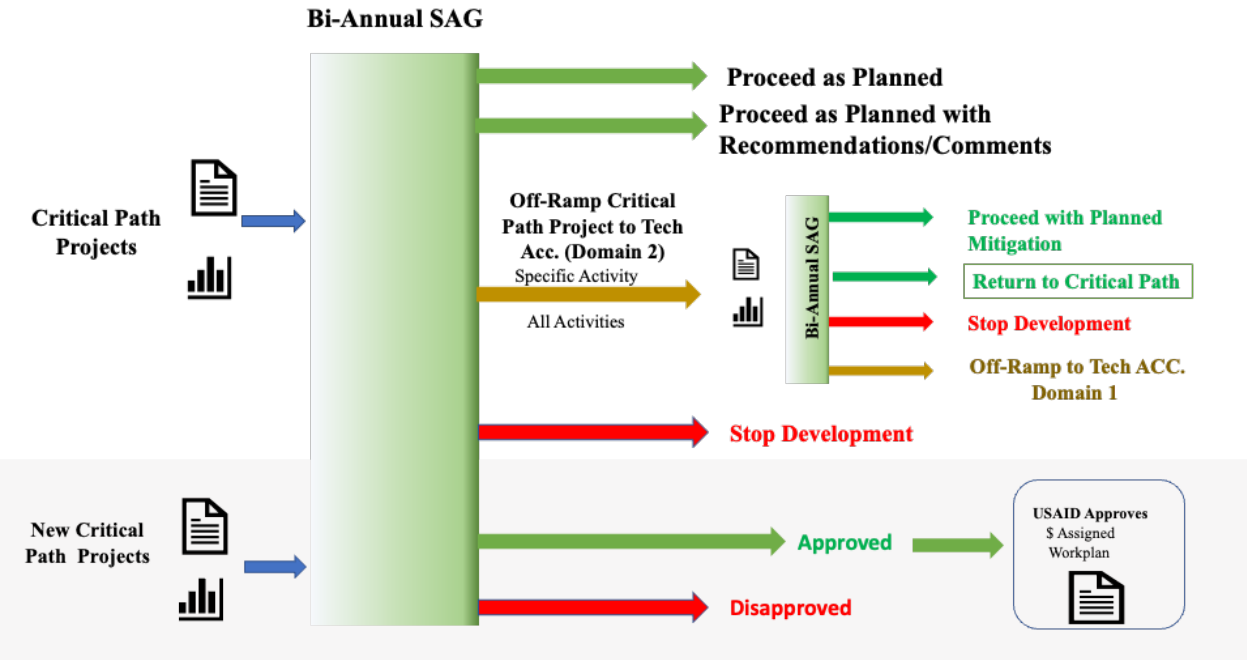
The SAG is solely an evaluation and recommendation committee for MATRIX supported activities. All final decisions impacting the CP products development program supported by MATRIX, are approved by USAID and implemented by MATRIX Prime.

Figure 1: Stage Gating Process

The SAG will be chaired by a USAID approved non-voting and non-conflicted representative of the PRIME. SAG membership (personnel and committee size) may vary as the portfolio of products advance and/or stage-gating eliminates or modifies the status of products within the MATRIX development environment. An alternative SAG chair will be appointed and approved by USAID and assume the SAG chairs duties when the primary SAG Chair is unavailable.

SAG outcomes will be used to measure the progress of HIV prevention and Multipurpose Prevention Technologies (MPT) products being developed by MATRIX. Measurement will be in the form of a considered evaluation of individual drug development efforts by evaluating progress on timelines, milestones, benchmarks, and Go/No-Go criteria at each meeting. Success is defined as achieving the proposed timelines, milestones, benchmarks, and Go/No-Go criteria (measures) for each CP product being developed. Although these measures vary from product to product and are based on their current state of development, all measure guided R&D efforts are ultimately focused on submitting a pre-IND, IND and/or enabling clinical testing of the products within the duration of the MATRIX award.

Figure 1: Stage Gating Process



Overview of the SAG Evaluation Process

Appendix 1 contains an overview of the 60-day SAG review evaluation cycle. The times given in the timeline are approximate and are provided as targets for deliverables, actual times maybe longer. The cycle starts with receipt of the Milestone Benchmark Report (MBR), Mitigation Plan, or New Project Request (NPR) (Appendices 4-6) 30 days prior to the SAG meeting from each project. During the interval between the receipt of plans and the SAG meeting, the completeness of the plans will be determined, and if complete, sent to USAID, SAG and PRIME for reading. Triage reviews (see below) are identified, approved by USAID and communicated to the appropriate product development leader(s) (PDL). Ten (10) days before the SAG meeting meets, the SAG Chair communicates with the PDLs to identify any essential MBR updates and develop PD specific questions to pose to the SAG. All supplemental information is then distributed to the SAG 3 days prior to the meeting. Ten days before the meeting it can also be determined if a pre-call with the SAG is required to facilitate the meeting. On day 0 the SAG meeting is conducted. The results (SAG final recommendations and comments) are communicated to the PRIME and USAID on day +1, and by day +7 the final recommendation document is submitted to USAID for approval or disapproval of the SAG recommendations. Once USAID concurrence is obtained, the PDLs will then be informed of the USAID final recommendations by day +10 to +15. Between the end of the meeting and day +30, the minutes will be drafted, approved by the PRIME and USAID and posted on the MATRIX website. All post SAG meeting due dates are subject to modification as required. This cycle will be repeated biannually.

SAG Composition

The SAG will be composed of nine (9) or more voting members, with a minimum of two (2) members with relevant expertise from SSA. A quorum will be defined as a minimum of five (5) committee members (with one (1) SSA representative). All efforts will be made to staff the SAG with a range of member expertise that can support and inform on all products and their potential to be successful. Efforts will be made to assure gender, race and geographical balance of the committee. Because of the need to ensure timely evaluations by MATRIX of CP, TA-D2 and new project requests MATRIX leadership may request on a case-by-case basis a waiver from USAID to allow a quorum of 5 without a SSA representative.

The SAG expertise profile may consist of the following expertise.

1. Pre-clinical HIV prevention product development. This may include expertise in animal pharmacokinetic/safety/efficacy models required for assessing anti-HIV and/or contraceptive activity.
2. Multipurpose Prevention Technologies: (MPT) Expertise in the development and testing of MPT products.
3. Regulatory. Required expertise should include experience in developing and evaluating pre-Investigational New Drug (IND), Investigational Device Evaluations (IDE) and development of regulatory submissions. Individuals from FDA and SSA regulatory bodies may be used.
4. IND-enabling safety and toxicology. Expertise in the conduct and interpretation of pre-clinical animal model safety, toxicology, and pharmacology studies, including familiarity with Good Laboratory Practices (GLP), International Organization for Standardization (ISO), and the

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

5. Chemistry, Manufacturing and Control (CMC). Expertise in a variety of formulations and analytical techniques, including familiarity with Good Manufacturing Practices (GMP).
6. Clinical trial operations and support. Expertise in the conduct of First in Human (FIH), Phase I, and Phase II clinical trial design and implementation of clinical studies in the USA and SSA.
7. Socio-behavioral sciences. Sociobehavioral research (SBR) expertise in end-user product perception, acceptability of products/protypes, preferred characteristics of prototypes/products, and SBR outcomes for products in stand-alone research and/or in early phase clinical trials.
8. Marketing and Business case development. Expertise in health product marketing and cost considerations particularly in SSA. This may also include specific expertise in Human Centered Design (HCD).

Selected SAG members may have experience and expertise in one of more of the identified expertise.

SAG Member Nomination

Initial development of the SAG committee:
The initial SAG will be constituted by nomination of the proposed members by the PRIME, MATRIX Steering Committee (SC) or USAID. The PRIME will develop a nomination slate minimally consisting of one main candidate and if available a back-up for that candidate. The two candidates do not have to have identical expertise profiles. The proposed nomination slate will be communicated to USAID for their comments and concurrence. USAID will respond with either approval or disapproval of proposed members within five (5) business days. For disapproved candidates USAID will provide a written justification (email) for disapproval. The PRIME has five (5) business days to contest the disapproval(s). If disapproval stands the PRIME will then work to identify a replacement nominee. Upon USAID concurrence with the nomination slate the potential nominees will be contacted by MATRIX leadership or its designees to determine if the candidate is interested in participating. If the nominee agrees to serve an information packet will be sent to the nominee. The information packet may contain a summary of MATRIX products and partners, redacted MATRIX application, information on renumeration and engagement, and any additional information that maybe relevant.

SAG committee membership is envisioned to be dynamic and nimble, adjusting through management of expertise mirroring the development of the MATRIX products as progress is made and/or problems are encountered. Therefore, SAG members will only be engaged for a single meeting (except for the first year where members will be engaged for both meetings). Individual SAG members may participate in serial meetings, but there will be no anticipation of long-term SAG membership by its members, the PRIME or USAID.

SAG members must be able to provide unbiased assessments of individual CP and TA-D2 projects to support the stage-gating process. All SAG candidates will undergo an assessment of real and

potential CoI (see below). Every effort will be made to ensure SAG members are free of CoI and follow MATRIX's CoI policies (see MATRIX MOP).

Special Case SAG Membership
USAID may require that a specific individual(s) be included in the SAG. These members will undergo and be subject to the same nomination process above. USAID will communicate their nomination to the PRIME and provide a picture, contacts, short biosketch and brief justification for inclusion in the committee. The PRIME will follow the contact and vetting schema above and determine the willingness of the nominee to participate. If the nominee is willing to participate MATRIX administrative personnel will proceed with onboarding for that specific meeting. If the PRIME identifies a potential conflict or has a significant issue with the USAID nomination the MATRIX PRIME will submit in writing a rebuttal to the nomination within five (5) working days of receiving the nomination.

Inactive and Retired SAG Members
Given the proposed dynamic nature of the MATRIX research agenda and the desire to have a nimble, neutral, cross-cutting, multidisciplinary committee that has the appropriate expertise for each biannual evaluation, the PRIME may retain a list of approved but inactive SAG members. Inactive SAG members will be individuals who have been approved by the nomination process and remain free of CoI.

Members may also be retired from the SAG. SAG members identified for retirement may no longer have relevant expertise to MATRIX projects. MATRIX will retire SAG members following consultation with USAID. A SAG member may also be retired due to unmitigable CoI and/or conduct or actions that are deemed inappropriate for a SAG member. Conduct/actions may include failure to attend meetings and lack of participation in meeting discussions.

Replacement of SAG members who voluntarily withdraw:
SAG committee members may voluntarily withdraw from the SAG if they develop issues which they believe compromise their ability to participate in the SAG, e.g., CoI due to a new position, time commitment, personal reasons, etc. To facilitate rapid replacement of the member and if replacement is warranted, the PRIME will search and/or solicit from MATRIX membership potential nominees. The nominees may have expertise similar to the departing member or a new expertise profile maybe defined based on the current scientific needs of MATRIX. The nominee will be contacted by the PRIME and willingness to serve determined. If the nominee is willing to join the SAG, the PRIME will present the nominee to USAID. USAID will be asked if they concur, and they do, the new SAG member will be onboarded.

Conflict of Interest (CoI)

The complexity of the MATRIX award and the interconnectedness of the HIV and prevention field may result in real and/ or perceived CoI with specific research project(s) and/or individual researchers involved in MATRIX. The SAG will follow the CoI policies laid out in the MATRIX MOP. MATRIX will work to manage both real and perceived CoI. SAG specific CoI policies follow.

SAG members must be free of competing CoI, i.e., significant involvement with a MATRIX research project and/or be employed by a pharmaceutical company supporting MATRIX developers. This prohibition applies to for-profit and not-for-profit individuals/companies supplying in-kind research material(s) such as drug product(s), drug substance (s), active pharmaceutical ingredients (API), and/or delivery devices/ device components for use by MATRIX researchers. Prior to installation on the SAG, committee nominees will sign a CoI and identify any potential real or perceived CoI. Prior to each SAG meeting a CoI declaration will be signed to ensure that any emergent conflicts among SAG members are captured and addressed. The signed CoI will be placed with that meeting's SAG documentation on the Matrix4prevention .org website. At the close of the meeting or after the meeting in a follow-on email the SAG members will be reminded of CoI policies and asked if any new CoI was identified.

It is acknowledged that there may be cases where a SAG committee members CoI cannot be avoided, and the expertise of the conflicted individual(s) is required to adequately advise the stage-gating process. In this case the conflicted individual(s) will act as an informational resource to the SAG. The conflicted SAG member(s) will be excused from voting on the product(s) or providing directive comments or suggestions to the PD for which they have a conflict. If the PRIME judges that the conflict will remain an issue in future SAG meetings the member maybe retired from active participation on the committee. The PRIME will inform USAID of this decision. A SAG member with CoI may also be retained as a consultant (active or ad hoc) to the SAG.

SAG Chair and Alternate Responsibilities

The SAG Chair and Alternate will be appointed by the PRIME. USAID will provide concurrence for the nomination. The SAG Chair and Alternate unlike the SAG members, will be a member of the MATRIX team, and will not be directly involved in MATRIX supported research or activities. The SAG Chair and Alternate will be non-voting members of the committee. In the case that the SAG Chair is not available the Alternate chair will conduct the meeting. The SAG Chair and Alternate Chair will be appointed for the duration of the award, unless otherwise determined (see below, Removal).

During the meeting the SAG Chair will be responsible for coordination of the meeting and supporting activities (see below and Appendix 1 and 2). The Chair will be assisted by the appropriate MATRIX administrative personnel. The SAG Chair's primary responsibility will be to manage the flow of the biannual SAG meeting to assure the meeting adequately evaluates the CP and new CP project requests under review. The SAG Chair is also responsible for assuring a clear outcome of SAG deliberations. To accomplish this the SAG Chair will be involved in pre-, during, and post-meeting activities (described below).

The SAG Chair will act as a liaison between the PRIME, SC, USAID, MATRIX PDL, and be responsible for assuring the SAG meeting achieves its objectives, adheres to charter policies, and accomplishes its agenda. Prior to each biannual meeting the SAG Chair will review the MBR, Mitigation Plans and NPR (submitted one month prior to the meeting) and clarify with the PDL any issues that might have been identified. One (1) week before the meeting the chair will communicate with the PDL to determine if there are any critical updates to the submitted report/plan. If there are updates the PDL (with support of the SAG Chair) will develop a brief

(maximum one (1) page) addendum to the MBR. The SAG Chair can provide an "on the spot' waiver to the one-page limit if it is deemed necessary to communicate the update. At this time SAG Chair and PDL will also identify any specific questions the PDL wishes to pose to the SAG during the open/closed sessions and prepare these for discussion. During the meeting the SAG Chair will facilitate the discussion in the open session and when appropriate bring the open session to a close and initiate the closed meeting. In the closed session the SAG Chair will lead the SAG and facilitate discussion and consensus on recommendations and voting on one of the defined SAG outcomes (see below). The chair will also assist the SAG in formulating any additional comments from the SAG to the PDLs. Post-meeting, the SAG Chair will provide, following approval of the PRIME and USAID, the final recommendation of the SAG and any comments to the PDLs. The SAG Chair will distribute the final recommendations to USAID, MATRIX PRIME, designated PDL, and request uploading of the recommendation to the secure Matrix4precention .org website. The SAG Chair will review the draft minutes of the meeting and assure they are posted to the internal MATRIX website within 1 month of the meeting. The SAG Chair will ensure the minutes are uploaded to the secure Matrix4precention.org website.

The SAG chair may also be responsible for communicating the evaluation by USAID of the USAID Microbicide R&D Assessment. This evaluation is performed by USAID and is independent of the SAG review but is linked to the SAG outcomes because of the inclusion of the USAID Microbicide R&D Assessment document in MBR and NPRs. The SAG Chair in this case can transmit USAID recommendations and comments to the PDL and direct them to be uploaded into the matrix4prevention.org website.

SAG Final Opinion, Recommendations and Comments Reporting
The SAG Chair and assigned MATRIX administrative personnel will capture the final opinion and any additional comments and/or recommendations made by the SAG for each project during the closed sessions. The results will be collated for each project and assembled for distribution to the PRIME and USAID. PDLs will only receive the recommendations and specific comments for the projects they represent. The complete (all recommendations and comments) final opinion, will be placed in a password protected section of the MATRIX website, available only to the PRIME, SAG Chair, USAID and individuals identified by the PRIME who need access to the document for administrative purposes.

SAG Chair or Alternate Removal
The SAG Chair or alternate may be removed as chair in the case of malfeasance, and/or development of a CoI with MATRIX product developer(s). Removal may be initiated by either the PRIME or USAID. Removal initiated by the PRIME requires concurrence by USAID.

The SAG Chair or Alternate Chair may for personal reasons request to either 1) not participate in on or more meetings or 2) be permanently removed as chair for personal or other reasons. If replacement is needed MATRIX PRIME will initiate a process whereby the Chair is either temporarily or permanently replaced.

Responsibilities of the PRIME

The PRIME, if required, may nominate a temporary replacement for the SAG Chair or Alternate Chair and determine if the SAG Chair and/or Alternate should be permanently replaced.

The PRIME will provide administrative support for all SAG operations including collating progress reports and communicating them to the SAG members, supporting meeting conduct (virtually or in person) and initial drafting of the official minutes for the SAG open meeting sessions.

The PRIME will be responsible for communicating all SAG nominations and SAG personnel actions to USAID. The PRIME will identify a SAG Chair and alternate and present them to USAID for concurrence.

The PRIME will be responsible for liaising with USAID to obtain concurrence with SAG recommendations and approval for release of the recommendations to the PDLs. The PRIME will also be responsible for directing the SAG Chair or Alternate to distribute the USAID Microbicide R&D Assessment to the PDL.

USAID Responsibilities

USAID personnel will be responsible for appointing and providing USAID employees to monitor the SAG meetings, and for providing approvals of SAG recommendations in a timely manner. USAID will provide approvals for SAG member nomination and provide appropriate input for disapproved nomination slate members. USAID personnel will work with the SAG Chair to develop any specific questions they wished posed to the SAG during the open and/or closed sessions. If questions arise during the SAG meeting USAID will pose them through the SAG Chair using an agreed upon communication strategy.

USAID personnel will be responsible for evaluating the USAID Microbicide R&D Assessment and developing specific recommendations and communicating its readiness for distribution to the PDLs.

SC Member Responsibilities.

The SC members of MATRIX are the leaders of each product development efforts and the MATRIX supporting Hubs. The PRIME will engage SC members as needed to provide potential SAG nominees and other support as required by the PRIME. The SC member may also be the PDL designated to represent the project (s) to the open session of the SAG meeting. If the SC member is not the representing PDL, the SC member is responsible for appointing and preparing a substitute PDL for the SAG meeting.

SC members will follow MATRIX MOP CoI policies and the specific CoI policies that apply to SAG operations. When conflicts are identified, SC members may be excused completely from discussion of CoI-involved issues or may be allowed to participate in a limited manner as an informational resource to the MATRIX PRIME, remainder SC and USAID.

MATRIX Product Development Leader (PDL) Responsibilities

The MATRIX PDL is anyone responsible for overseeing the conduct of research for MATRIX product development activities. The PDL maybe a member of the SC or an individual guiding or leading a project/subproject under a SC member. The PDL will liaise with the SAG Chair, and PRIME to facilitate the stage-gating process.

The PDL are responsible for providing the MBR report cataloguing the progress made during the reporting period on the specific programs funded milestone(s), benchmark(s) and Go/No-Go criteria governing or other relevant to enabling the stage-gating process. PDLs are also responsible for identifying the need for mitigations and developing a Mitigation Report for any Class 2 or 3 mitigation event (see below). PDLs are also the primary point of contact (POC) for the SAG Chair/Alternate Chair, in preparation for or following biannual SAG meetings. PDLs are also responsible for completing the MBR and NPR appendices with the required project information.

One (1) week prior to SAG meetings the PDL and the SAG Chair will determine if there are any specific questions the PDL wants posed to the SAG or if there are any updates to the MBR that could impact SAG recommendations. These could include solution of a Class 1 mitigation finding and/or updating information on a milestone, benchmark, or Go/No-Go that could influence the SAG recommendation. If there are updates or questions the PDL will develop a brief (one page) addendum to the MBR to be submitted to the PRIME, SAG Chair and USAID. As noted above, the SAG Chair can grant a one time "on the spot" allowance for use of more than one page in the update, if a one-page limitation is insufficient to communicate the update.

The PDL or a representative must attend the open session of the SAG meetings for their specific product(s). For ongoing CP projects, the PDL will not be required or expected to provide any formal presentations to the SAG and is present during the open session only to answer any questions the SAG may have for them. At the discretion of the SAG Chair and SAG Committee PDLs. may be allowed an "on the spot" exemption to present data not captured in the MBR update and deemed critical to the SAG deliberations. For onboarding new CP projects, the PDL will be required to present a brief introductory presentation outlining the prevention strategy and its value to MATRIX/USAID. During special request evaluations (see below) the PDL maybe required to prepare and share a topic specific presentation with the SAG.

The PDL will not participate in the closed session of the SAG.

Responsibilities of the SAG Members

It is the responsibility of the SAG members to assure that their participation in the SAG meeting does not violate CoI policies of MATRIX and to be familiar with the MBR, Mitigation plans, NPR and pre-meeting updates submitted by the PDLs. The SAG members are also responsible for keeping any written or printed documents (e.g., MBR reports) and closed session discussion confidential. Each SAG member is encouraged to actively participate in the discussions. This participation is critical to achieving the end-to-end evaluation of the products and progress that the stage-gating process requires.

SAG members who routinely fail to actively participate in SAG discussions may be removed from the SAG, after communication issues are identified by the PRIME and concurrence is obtained by USAID.

Requirements to Conduct a SAG Meeting

The SAG committee consists of a minimum of nine (9) members with a quorum defined as five (5) members either present in person, virtually or a combination of both modalities. A quorum requires the participation of at least one (1) SSA attendee. If delay of the meeting due to availability of a SSA member would adversely impact USAID/MATRIX work planning activities a USAID waiver specific to the proposed meeting for a five (5) member quorum without a SSA representative maybe requested by the PRIME. For each meeting the SAG members must commit to the equivalent of a full day of participation. A day's worth of participation maybe conducted as one contiguous day, or 2 half days as needed. A full day is defined as 9 hours, starting no later than 9:00 AM EST and ending no later the 6:00 PM EST.

SAG Meeting Overview

The biannual SAG meeting will be composed of 2 sessions: an open and closed session for each product development activity under review (CP, TA-D2 (mitigation progress), and new CP Project). It is envisioned that each session (open or closed for each product) will take no more than 30 minutes and be facilitated by the SAG Chair or Alternate Chair. Appendix 2 contains a flow chart of the SAG meeting.

The official meeting will start with the SAG Chair calling the meeting to order.

The SAG Chair will welcome the SAG members and conduct introductions of SAG members, MATRIX and USAID personnel, as appropriate and relevant to meeting conduct. PDL representatives will not be present, during this portion of the meeting. Open session representatives of the PRIME, USAID and administrative personnel responsible for minutes and meeting conduct will be present as observers only and will not actively contribute to the meeting unless specific questions are addressed to them by the SAG, thru the SAG Chair.

The SAG Chair will communicatee the CoI policy to the SAG. If the meeting is in person, MATRIX administrative personnel will collect signed CoI forms. If the meeting is virtual or a SAG member is virtual MATRIX administrative personnel will facilitate obtaining a signed COI prior to the start of the meeting. If new CoI is identified by a member, it will be determined by the PRIME and SAG Chair if the SAG member should be excused from a specific product stage-gating discussion and/or participation be limited to a non-voting presence. Concurrence will be requested from USAID.

The SAG Chair will ask for approval of the minutes of the last meeting by a nomination and second. If the SAG members pose an objection or request modifications, after

resolution of the issue(s) the SAG Chair will ask for a motion to approve and second. The minutes will stand as approved. The SAG members will have received the minutes within 30 days of the last SAG meeting and will have had a chance to propose corrections prior to the next meeting.

The meeting will proceed to the order of business. Prior to the start of the first open session the SAG Chair will review the agenda of projects to be discussed.

> The SAG Chair at this time will identify any projects that may not require extensive discussion and maybe triaged (see below). If there are no PDL questions or other issues the SAG Chair may recommend that the project be assigned a "Continue as Planned" outcome with a majority vote of the SAG. If continued as planned vote is not unanimous the minority opinion will be captured and placed in the minutes and an open and/or closed session be conducted, as required. For projects with specific enquiries to the SAG that are proposed and approved for triage an open session will be used to provide the PDL feedback on their questions.

The first open session will be initiated. The PDL will be invited into the meeting and introduced. The PDL will be asked to provide a brief, verbal summary of their progress and issues encountered. The question and answer period will begin. Discussion will be facilitated by the SAG Chair. During the open session the SAG members will discuss the MBR/Mitigation Plan, New Project Request and may ask clarifying questions of the PDL. The SAG, thru the SAG Chair, may ask procedural questions of USAID and/or the PRIME. No specific recommendations will be made during the open session (see below). At the end of the open session the SAG Chair will summarize the discussion and the PDL will be excused, and the session closed. The open session will be recorded to facilitate minute development.

The closed session will be started by the Chair. During the closed session the SAG may openly discuss the reports and provide their final evaluation, making 1 of 6 possible evaluative recommendations of the project under discussion (Table 1). USAID may pose specific questions to the SAG via the SAG Chair. After the SAG meeting is closed the SAG recommendations will be collated and presented to USAID for concurrence or disapproval. Specific minutes or recordings of the closed session will not be taken and only the final evaluations and any additional specific recommendation(s)/comment(s) of the SAG will be captured.

Table 1 Summary of SAG Recommendations

Recommendation	Comment	CP	TA-D2
Continue as Planned (with or without comments/ recommendations)	All activities	X	X

Discontinue Activity	CP all or Selected Parts	X	X
Off-Ramp to TA-D2	All or Selected Parts of CP	X	
On-Ramp To CP	Return To CP		X
New CP Project	CP	X	
Disapprove New CP Project	CP	X	

SAG Recommendations

The SAG may make the following recommendations for each project reviewed.

1. Continue as planned (with or without comments/recommendations) for CP or TA-D2. The SAG does not recommend any changes to the proposed development activities based on the MBR but may provide additional recommendations/comments for the PDL and team to consider.
2. Discontinue the Activity.
    - CP projects. The recommendations will include either a direction to stop and close out all activities or to continue specific activities within the project that the SAG deems of high value. USAID must concur with this recommendation.
3. Off-ramping from CP to TA-D2. If a CP project has a significant mitigation finding (class 2 or 3), the SAG may recommend off-ramping to TA-D2. If a Mitigation Plan was not attached to the MBR (see below) the PDL in collaboration with the PRIME will create a Mitigation Plan specific to the planned TA-D2activities.
4. On-ramp/return to CP a previously off-ramped (TA-D2) CP project following resolution of the mitigated problems. This recommendation applies only to Off-ramped CP projects.
5. New CP Projects. Following the procedure for evaluation of new projects, the SAG will review the new project and provide a recommendation to either onboard as a new CP or not (See New Projects section below and the NPR form Appendix 5).
6. Disapprove on-boarding of new CP project. The new CP project will not be on-boarded by MATRIX, following USAID concurrence.

Disagreement of USAID with Final SAG Determination
USAID has the right to overturn all SAG final determinations as the funder of the MATRIX consortium. It is expected that these disagreements will reflect broader USAID operational issues beyond the drug development progress the CP has made and may be independent of the achievement of milestones, benchmarks, and Go/ No-Go criteria. In these cases, USAID will provide a justification for overturning the SAG recommendation that will be placed in the record of the SAG meeting. The revised recommendation will be placed in the final outcome section of the MBR. It will be at the discretion of USAID to provide further information to the PDL on the decision and how to communicate the change to the SAG.

Project Triage at the Start of SAG Meetings

Because of the number of projects in the MATRIX portfolio and to facilitate a one-day meeting a triage process may be used at the start of the meeting. This triage process will only be for projects that indicate in the MBR that they are proceeding as planned. Projects with an active Mitigation Plan are not eligible for triage. Projects eligible for triage as determined by the PRIME and USAID will be introduced at the beginning of the meeting by the SAG Chair and if there are no SAG objections or concerns the project(s) will be assigned "Continue as Planned" and no open/closed session conducted.

If the SAG expresses concern regarding the triage, the SAG will be asked if they require the PDL for consultation in an open session or want to proceed into the closed session for discussions with the PRIME and USAID regarding their rationale for triage. The SAG will decide this by majority voting. If the SAG requires PDL input, an open session will be started and the PDL will be invited into the meeting where the SAG may propose specific questions to the PDL. Once the SAG is satisfied the PDL will be excused, and the meeting proceed into a closed session. If the PDL is not needed the meeting will proceed directly to the closed session. In a closed triage discussion session, the SAG may directly question the PRIME and USAID regarding the decision to triage. For cases where there is disagreement within the SAG about tirage or the meeting proceeds to a closed triage session any minority opinion(s) will be captured in the open meeting minutes.

Futility Determinations
Futility is defined as a project that no longer demonstrates a reasonable chance of completion during the award, a major experimental failure/finding that raises significant concerns regarding the ability to meet long-term milestones, benchmarks, and/or Go/ No-Go criteria, or advances in HIV virology, and/or the prevention field render the proposed innovation no longer of significant value to USAID. A SAG majority is required to recommend futility.

There are 2 scenarios under which the SAG might recommend futility.

- The first is concurrence with a request by the PRIME and USAID to assign futility to a CP, or TA-D2 project. A determination of futility maybe requested based on MBR reports, PDL use of serial mitigations of any class within a project, failure of a Mitigation Plan and/or a USAID research or fiscal priority. Because the action is requested by MATRIX leadership and USAID, a simple majority will be used for approval. Any dissenting opinion(s) will be captured.
- The second is a recommendation made by the SAG during a closed session based on the contents of a MBR report and/or past performance (MBR content, serial mitigations, etc.). In this case, a majority of the SAG must recommend futility. The dissenting opinion will be captured.

In all cases, action upon a futility recommendation must be ratified by USAID before any action is taken to end the project.

Mitigation
Because research is under the influence of both inside (experimental design failure) and outside (availability of reagents, administrative approval delays, etc.) factors that can impact the accomplishment of R&D objectives for the overall or specific parts of an R&D plan, proactively addressing these issues by planning their resolution can reduce the impact of these events on

achievement of milestones, benchmarks, Go/ No-Go criteria. Therefore, MATRIX has instituted the use of Mitigation Plans with SAG evaluation as a tool to proactively address and manage R&D delays. The template for the Mitigation Plan can be found in Appendix 4. A Mitigation Plan is defined as a PDL proposed, proactive plan designed to address unexpected experimental delays and minimize their impact on the overall R&D effort by proposing a specific set of experiments to address the mitigatable issue. A Mitigation Plan is developed by the PDL with or without input of the PRIME and USAID and evaluated by the SAG for the purposes of monitoring progress and making additional recommendations to the PDL, PRIME and USAID. The SAG may also recommend creating a Mitigation Plan based on the MBR report.

There are two types of mitigations.

- The first is a request by the PDL based on findings reported in the MBR. In this case, the Mitigation Plan will be attached to the MBR and evaluated by the SAG.
- The second case is when the SAG determines there is a need for mitigation, based on the contents of the MBR and open session responses of the PDL.

The SAG will be asked to provide input on Mitigation Plans for Class 2 and 3 mitigations (see below) when they are provided with the MBR. If a class 2 Mitigation Plan extends beyond 6 months (1 reporting interval) or a class 3 Mitigation Plan extends beyond 12 months, the SAG will be asked to consider if or when a recommendation of futility is appropriate. If the SAG provides a futility recommendation it will be passed to the PRIME and USAID for action. All futility recommendations will be done by majority voting. If the voting is not unanimous the minority opinion will be captured and communicated only to USAID by the PRIME.

In the second case, The SAB identifies concerns that they believe are either mis-labeled or based on the MBR identify a critical issue(s) that is not being addressed and must be mitigated prior to achieving the projects timelines milestones, benchmarks, Go/No-Go criteria and TPP specifications. In this case, the PRIME and USAID will instruct the PDL to create a Mitigation Plan. To reduce the delay between mitigation report, approval, and implementation, USAID and the PRIME will evaluate and approve the plan outside of the SAG review process. The need for a Mitigation Plan will be communicated to the PDL immediately after the meeting and with the plan due in two (2) weeks to the PRIME, and USAID. The plan will be approved or disapproved in one (1) week. At the next SAG meeting the new Mitigation Plan will be attached to the MBR and discussed by the SAG during the open and closed sessions.

New Projects

The HIV prevention field is dynamic in nature and requires a nimble approach to addressing and creating the optimal prevention strategies for AGYW, PBFW and FSW in SSA. Additionally, there can be specific barriers to implementation of a HIV prevention strategy, such as the need to monitor point-of-care drug concentrations, engineer health care professional friendlier device application and removal processes, etc. Thus, the potential for identifying and implementing new CP projects has been incorporated into MATRIX. A new project is defined as a scientific opportunity that has a defined scientific/experimental approach that if successful could add significantly to the USAID prevention portfolio or their efforts to implement the portfolio. The template for the NPR is in Appendix 5. Final approval to implementation new projects is under the control of USAID.

Through a separate process that does not involve SAG approval to onboard a research activity, new projects may be added to the MATRIX research portfolio under the Technology Accelerator Doman 1 (TA-D1) umbrella. These new projects are of short duration (~18 Months) have a constrained budget ($150,000 US) and are considered high-risk/high innovation "game-changer" projects with a focus on supporting capacity strengthening research in SSA. Given their substantial difference in resources, duration and research focus TA-D1 projects are overseen and monitored via the separate TA-D1 charter process, involving interfacing with technical experts provided by MATRIX. Since the TA-D1 projects could have a significant impact on HIV prevention in SSA and/or could inform on CP product development the SAG will be informed of their existence, but not required to provide oversight.

NPR requests for on-ramping a new CP project will proceed via open and closed session discussions. If multiple projects are proposed for on-ramping that are similar, e.g., all MPTs, the SAG Chair and Prime may propose a combined open-session followed by a single closed session for onboarding recommendations. The SAG will be asked to consider whether to recommend on-ramping of any new CP. SAG members will be asked to provide a majority opinion for either approval or disapproval for the on-ramping request. The SAG will identify the potential and specific advantages of addition of the proposed CP activity to MATRIX. The recommendation will be forwarded to USAID for final ratification or rejection.

Meeting Format

The SAG meeting with a quorum of SAG members will be conducted in one of 3 formats.

1. Virtual,
2. In-person,
3. Hybrid: mixture of virtual and in-person attendance.

A quorum is defined as a minimum of five (5) SAG voting members, whether in person, virtual or hybrid. When scheduling meetings every effort will be made to assure participation of one (1) or more SSA SAG members. In special cases a waiver for the meeting to be conducted may be obtained from USAID to complete a quorum if availability of the SSA SAG member negatively impacts the ability to conduct a SAG or impacts negatively on USAID workplan development.

For meetings with an in-person component written minutes will be taken, If the meeting is fully virtual the meeting will be recorded, and a written transcript developed. During virtual or hybrid meetings, virtual members must be present and vote for a minimum of 2/3 of the projects on the agenda for which they have no CoI.

Voting

Voting will occur during the closed session.

Based on the open meeting and closed meeting discussions, the chair will summarize the discussion and identify potentially relevant voting outcomes (discontinue/stop, continue as planned, create a Mitigation Plan, etc.) for the report/project under discussion. The SAG Chair

will then call upon the SAG members to propose a motion and second. If the vote is not unanimous, the chair will facilitate a discussion to determine if a unanimous opinion can be reached. If a unanimous opinion cannot be reached; the majority opinion will be provided to the PDL and published on the internal MATRIX team web page (see Communication below).

If a consensus cannot be reached the SAG Chair will ask for the minority to provide a brief summary of the issue driving their opinion. The minority opinion will be provided to the PRIME and USAID and they will decide if the minority opinion is provided along with the majority opinion to the PDL and/or placed on the internal MATRIX team web page.

If the SAG or any of its members want to provide specific recommendation(s) or comments(s) to the PDL during the closed session, they may do so. If additional recommendations/comments are made that could substantially change the category of recommendation or scope of the CP, the SAG Chair may ask for a vote in support of the recommendation. Recommendations must be approved by a majority of the SAG members present. If a majority in favor of the recommendation cannot be obtained an official recommendation will not be sent to the PDL.

An e*n bloc* approval of SAG recommendations and comments at the discretion of the SAG Chair may be used at the end of the closed session by a simple motion and second.

Mitigation: Plans and Classification

It is recognized that unexpected problems may arise that have minor to catastrophic impacts on product development activities. To facilitate SAG review, the following mitigation classifications (below) will be used to describe these problems. The classification system is in place solely to facilitate SAG, PRIME and USAID actions, and thus uses a broad classification system for its assignments. The Mitigation Plan and the classification system have been developed to assist CP and TA-D2 PDL in resolving, in a timely manner, technical issues that impact milestone, benchmark, Go/No-Go criteria and TPP specification achievement. If the mitigation is reported in the MBR without pre-classification by the PDL the PRIME and PDL prior the SAG meeting will assign a classification. If a recommendation for mitigation is the outcome of SAG discussions, the Prime and USAID will designate a classification based on communication with the PDL and approve the PDLs Mitigation Plan.

Mitigation Classes
Class 1: Minor or transitory delays in research. The resolution of class 1 mitigation issues is in general out of the hands of the PDL. The resolution of the mitigation issue is reasonably expected to take no more than 6 months or 1 SAG reporting interval. Examples of this type of mitigation are timing of animal studies by CROs, delays in IACUC or IRB approvals, natural disaster delays, PDL institutional administrative delays, regulatory delays, etc. In this case, the PDL will place an explanation of the delay in the MBR report and provide a projected best- and worse-case resolution scenario, timeline, as well as alternatives, if any (e.g., alternative source or CRO) to resolve the issue if it cannot be resolved in the SAG reporting interval. Due to the nature of class 1 mitigations, there is no plan for upgrading the mitigation classification to a 2 or 3, however, futility maybe called if the delays become extensive >6-12 months and/or negatively impacts the achievement of

other project milestone(s). An example of such a delay is extensive delay in SSA regulatory approvals for starting a single site in a multi-site clinical trial that jeopardizes progress, where the sites in question participation maybe compensated by other sites where regulatory approval has been obtained. In this case a futility designation (as described above) may be requested by the PDL for the class 1 mitigation or independently made by the PRIME, and USAID. The SAG will be informed that activity has been removed from consideration at the next meeting.

Class 2: Moderate Delays in Research. These are cases where a resolution of the issues encountered are possible within a limited time frame which will not significantly impact overarching milestones (i.e., clinical testing in 4 years) benchmarks, and Go/ No-Go criteria but require a focused research effort to keep the R&D process on track. Class 2 mitigations should be resolved as quickly as possible. It is expected that resolution of a Class 2 mitigation could take more than 6 months but are likely to be resolved in less than 12 months. Examples are minor modifications of formulations to meet stability requirements, need for a minor modification of a synthetic or manufacturing process, minor adjustments to formulations or delivery devices to meet desired/pre-defined rheological properties, etc. In the case where the Class 2 mitigatable finding is discovered in the interval between SAG meetings, the PDL with the PRIME and USAID will agree mitigation is appropriate and they will work with the PDL to create a Mitigation Plan (Appendix 4). The Mitigation Plan will be attached to the MBR and communicated to the SAG at the next biannual meeting.

Because of the anticipated quick resolution of class 2 mitigations, it is not expected that these mitigations will initiate off-ramping to TA-D2. However, if mitigation efforts extend beyond 12 months, with the consent of the PRIME and USAID, the mitigation can be reclassified as a Class 3 and the project moved to TA-D2. Off-ramped projects of this type are subject to Class 3 mitigation and serial mitigation rules (see below).

Class 3: A severe to catastrophic problem/delay in product development that could either completely halt development (fatal flaw in drug substance or product) or delay development for an extended period (>12 months) is identified. Examples are failure of a stability program that indicates major changes are needed in the formulation or API, a serious safety finding or adverse event in preclinical or clinical studies, respectively, failure of GMP manufacturing or meeting GMP quality requirements or product release specifications. Like Class 2 mitigations a Class 3 mitigation can be discovered and reported between reporting intervals or at the SAG meeting, in both cases the procedure to initiate, approve and SAG review the plan will be used.

A critical part of any Class 3 mitigation will be a determination if all or part of the parent CP project requiring mitigation needs to be off-ramped to TA-D2 and whether other activities within the CP should continue while the component is off ramped, with or without modification. The SAG will evaluate the impact of the Class 3 mitigation on the overall CP objectives and make recommendations concerning the scope of off-ramping and whether other activities in the CP should be continued. USAID will determine if these recommendations are followed.

Class 3 Mitigation Plans will be submitted to the SAG for review at a regular scheduled meeting. Because it is expected that Class 3 mitigations are of sufficient severity to trigger off ramping to TA-D2 and that success of off-ramped projects are directly tied to the potential success of the CP

project it is expected that the majority of Class 3 mitigations will automatically be off-ramped to TA-D2.

SAG review of ongoing projects with a Mitigation Plan (Class 2 or 3) may result in the following recommendations by the SAG.

1) Mitigation efforts should continue as planned. The SAG will estimate the likelihood that resolution of the mitigation within the CP or off-ramped TA-D2 project will be completed in the projected time; however, if the problem is not resolved within a reasonable timeframe (see above Class 3 definition) the SAG will be asked to consider recommending futility. Additionally, if the SAG believes the likelihood of resolution is low the SAG may recommend futility and stopping of activities. Policies for futility (above) will be followed and USAID approval obtained.

2) Development is terminated with or without continuation of other specific CP activities. If other activities in the CP are identified as providing significant advantage to MATRIX and USAID, then the SAG may recommend they be continued. TA-D2 off-ramped projects with this recommendation, since they are focused on a specific mitigation effort, will not be considered for partial restoration or preservation of research activities (will not be automatically retained in TA-D1 beyond the futility/stop recommendation). USAID will approve the final determination. If there are other CP activities to be continued, they will continue to be reviewed by the SAG and held to their milestones, benchmarks, and Go/ No-Go criteria. An example is although product development cannot continue without a major reengineering of the drug product, ongoing behavioral social research, users' preferences, business case determinations, and/or marketing assessments could provide substantiative information of benefit to MATRIX and the USAID research agenda.

3) Return to CP of a TA-D2 activity. The PDL with consent of the PRIME and USAID, may request that the off-ramped project be returned to the CP following resolution of the mitigation issues. The SAG will review the request and with appropriate evidence in the MBR recommend return of the off-ramped activity to the CP. The PRIME and USAID will review the recommendation and approve or disapprove re-ramping and continuation of the restored CP project.

SAG Identified Mitigations

The SAG may identify a mitigatable issue during a scheduled meeting and recommend it be addressed with a Class 2 or 3 mitigation. The SAG will describe the proposed mitigation, classify the mitigation, identify what a potential resolution looks like and recommend that the PDL creates a formal Mitigation Plan based on their recommendations. The PRIME and USAID will confer and if appropriate direct the PDL to create and implement a Mitigation Plan. The Mitigation Plan will then be evaluated along with its associated MBR at the next SAB meeting.

Serial Mitigations

Serial mitigations are defined as multiple mitigations (Class 2 or 3) for one project (CP) or requesting additional mitigations (CP or within a TA-D2 off-ramped activity) while a current

mitigation is ongoing. Mitigations are meant to be used to provide a safe space where a defined problem can be resolved, while minimizing its impact on milestones, benchmarks and Go/ No-Go criteria being used to measure overall CP progress. Multiple mitigations may be considered as evidence of a problematic R&D effort, drug and/or delivery system. PDLs that request multiple Class 2 and 3 or concurrent mitigations may undergo a special evaluation (see below) at the request of USAID and/or the PRIME.

Special Case: TA-D1 On-Ramping to CP
There is the potential for TA-D1 game changer/capacity strengthening projects that are highly successful and have a significant impact to warrant expansion and on-ramping to create a new CP project. Consideration for this type of on-ramping will be initiated by USAID in collaboration with the PRIME using the NPR forms and process. Central to this on-ramping process will be the provision of budgets, Gantt chart with milestones, benchmarks, and Go/No-Go criteria, timeline, project descriptor, and TPP that supports the projects as having significant value to USAID and MATRIX. These projects once identified for on-ramping will be introduced to the SAG and undergo a full SAG evaluation as an NPR request.

Confidentiality of the SAG Meeting

Because the SAG meeting will generate outcomes that may be critical of a product development path (CP or TA-D2) effort and result in negative outcomes for the developer (i.e., reduction of or loss of funding), it is critical that the closed deliberations of the SAG committee remain confidential. SAG members will be reminded at the close of the meeting that all closed session discussions are confidential and that only the final recommendation and a minority opinion, (if applicable) will be communicated to the PDLs. The SAG members will also be instructed that if they are contacted by a PDL for specifics about the closed meeting that they are not to divulge any information and contact either the SAG Chair and/or PRIME.

Deliverables to the SAG Milestone Benchmark Report (MBR), Mitigation Plan and New Project Reports (NPR)

Milestone Benchmark Report (MBR)
One (1) month prior to the scheduled SAG meeting the PDLs will submit a MBR for each project identified for stage-gating by the PRIME. The template for the MBR can be found in Appendix 3. The PDL will complete the MBR and submit it to the SAG Chair for communications to the PRIME, USAID and SAG.

Mitigation Plan
If Class 2 or 3 mitigation issue(s) is/are identified by the PRIME, USAID or PDL a Mitigation Plan (Appendix 4: template attached) is required. This report should be included with the MBR if the mitigation is identified prior to the SAG meeting or generated after the SAG meeting if mitigation is identified by the SAG or USAID. In general, the Mitigation Plan contains a brief description of the issue to be mitigated, an assessment of how it impacts the existing development plan and a description of the activities to be performed to mitigate the issue. Appropriate

milestones with specific benchmarks and Go/No-Go criteria are identified. Objective, observable milestones benchmarks, Go/ No-Go criteria, and timelines are created to support that the mitigation has been successful. Any budget implications are also included. If it the mitigation is for a CP project, a rational for continuation or pausing other project activities while the mitigation is in process is included. The PDL can request that his/her project be directly off-ramped into the TA-D2 for a Class 3 mitigation effort. The SAG will be asked for their concurrence if the PDL asks for off-ramping. USAID will make the final decision for whether the project can be off-ramped and appropriateness of the proposed milestones, benchmarks, and Go/ No-Go criteria.

New Project Requests (NPR).
The SAG will review NPR for CP and by investigators inside and outside of MATRIX for inclusion into the MATRIX program.

Note: TA-D1 projects will be selected, monitored and administered per the TA-D1 charter process. A summary of the approved (or updated) TA-D1 project will be included in the SAG package (for information only).

The SAG will perform a full evaluation for new CP project requests and make recommendations to PRIME and USAID to either on board or not to onboard the new CP project. Following the meeting USAID will determine if the project will be onboarded. These projects will require the establishment of a project descriptor, TPP, Gantt chart, and USAID Microbicides R&D Assessment, in addition to establishing milestones, benchmarks, and Go/No-Go criteria for the research and provide a 1-year detailed budget.

Special Case: New Projects Derived from Terminated TA-D2 or CP Projects.
In rare, select cases terminated project elements may be eligible for new project consideration. The new project element for consideration must contain highly innovative game changing research which the PRIME and USAID identify as high-value that may provide proof-of-concept or preliminary feasibility data for future development activities (inside or outside MATRIX). The PRIME with USAID concurrence will decide the scope of the new project and invite the PDL of the terminated activity to make a topic focused NPR submission. These projects will be given a full review by the SAG and either approved or disapproved for onboarding. The new project request will require identifying milestones, benchmarks, and Go/No-Go criterion to measure research progress and achievement of the new project objectives. An impact statement will also be required identifying the specific value of the "rescued" project to USAID. Depending upon the scope of the project the TA-D2/CP component may also be onboarded as a new TA-D1 (and managed by the TA-D1 process) or Integrated Special Project (ISP, and managed under the ISP SOP).

Special evaluations
At the request of the PRIME or USAID the SAG may be asked to evaluate a "special" project (CP or TA-D2) even if it is currently on schedule and meeting milestones, benchmarks, and Go/No-Go criteria. Special evaluations are triggered by the emergence of evidence and/or new data from within MATRIX or the HIV prevention field that could make an existing MATRIX project activity no longer relevant to MATRIX and/or USAID priorities or require significant adjustment of project priorities. Examples of the types of data that could trigger a special evaluation are business

case evaluations demonstrating significant impediments to post approval marketing or use, SBR data that reduces the confidence that target populations will use the prevention innovation, safety/implementation issues from other products developed outside MATRIX that suggest lack of efficacy, effectiveness or harm to users by the MATRIX product and/or opinions/interactions with regulatory bodies that suggest that current data portfolios or portfolios under development by PDLs will not support regulatory approvals (pre-IND, IND, New Device Exemption (NDE), New Drug Application (NDA), etc.). The goal of the special evaluation will be to assess the viability of the overall activity with a final determination by the SAG of continue as planned, modify plans or halt activity. The SAG will not be asked to make additional comments/recommendations as they would for a regular MBR evaluation. For these evaluations *ad hoc* SAG members with expertise in marketing, cost analysis, business case development and post-licensure manufacturing, distribution and marketing may be added to the SAG. For these meetings, the PDL maybe requested to provide a specific update at the meeting. In this case the PDL may be requested to present relevant information in a brief PowerPoint format.

Communication and Documentation

SAG communication and documentation practices will follow all MATRIX MOP procedures for internal/external communication, documentation, and computer security. Every effort will be made to maintain confidentiality of the records generated during support and conduct of SAG meetings. Below are communication, documentation and security practices specific for SAG operations.

The open and closed segments of the SAG meeting will be documented as follows. The open session will be documented using either administrative minutes (in-person sessions) or by unedited recordings and their transcription (virtual). For hybrid sessions administrative minutes will be captured and a transcribed recording provided of virtual portions of the meeting. Minority opinions for specific activities (identified above) will be captured as indicted. Minutes after approval will be placed in a password protected section of the MATRIX4prevention.org website. PRIME, PRIME designees and the SAG Chair/Alternate Chair will have password protected access to these documents.

PRIME designees may include MATRIX administrative personnel responsible for minute taking, drafting, and posting and the SAG Chair and alternate. PRIME designees will only be individuals without or managed CoI with CP, and TA-D2 Projects.

Communication and documentation of SAG outcomes to PRIME, SC and USAID will be a 2-stage process. Stage 1 will be approval by the PRIME and USAID of the SAG outcomes. Following the meeting the SAG Chair will submit the results of the closed session to the PRIME and USAID for concurrence with the SAG. Once USAID input is received the outcomes will be posted in a secured section (access by PRIME, PRIME designees, SAG Chair, and USAID) on the MATRIX4prevention.org website. If USAID does not concur with the SAG an explanation for the lack of concurrence will be documented by USAID and placed with the SAG recommendation on the secure team website. Stage 2 will be approval of the SAG meeting open session minutes. Post meeting the SAG Chair will work with the MATRIX administrative group to assemble a draft

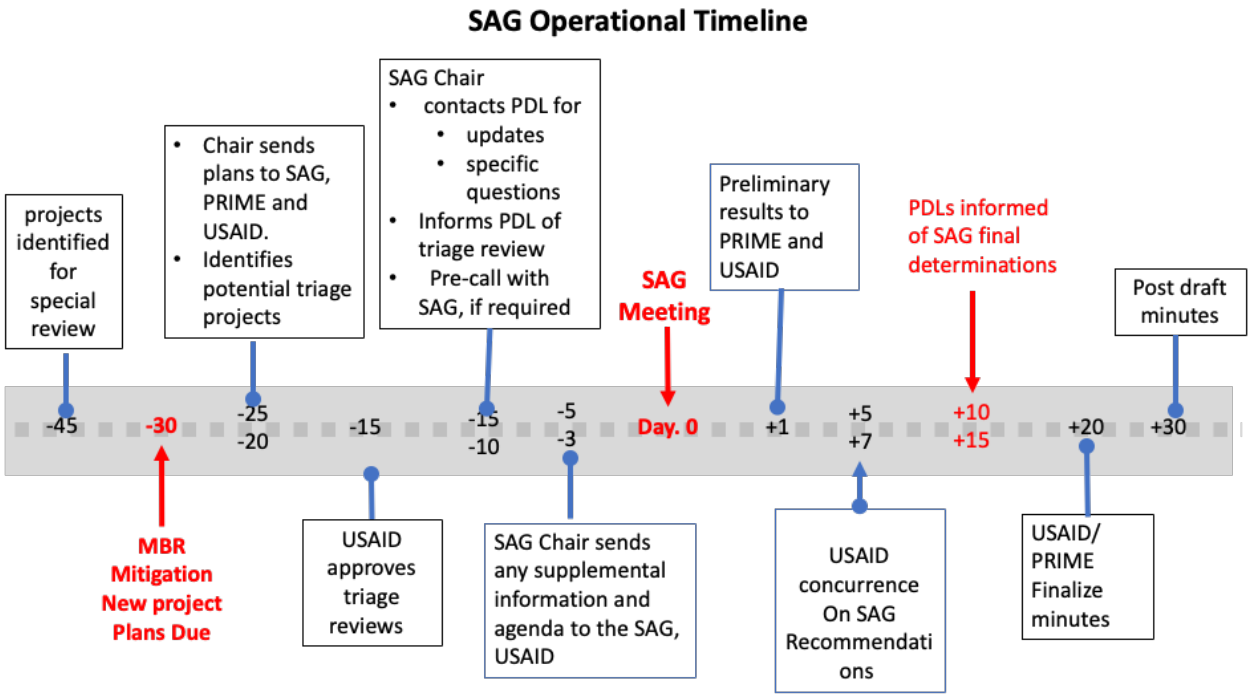
minute's document. The draft minutes will be submitted to the PRIME and USAID for concurrence. The minutes will then be submitted for approval by the SAG at the next meeting using the process described above, the minutes after SAG approval will be posted in a secure section of the MATRIX4prevention.org website. Virtual recordings will be transcribed and follow the same posting and approval process. The actual recording will be destroyed.

Final SAG recommendations will be placed in a non-public password protected portion of the MATRIX4prevention.org website. PDL will have password protected access to only the final recommendations for their project(s).

MBR, Mitigation Plans and NPR will be placed in a non-public password protected subsite in the MATRIX4prevention.org website. Only the PRIME, PRIME designees, SAG committee members and USAID will have access to these documents. PDL, and PDL designees will only have access to the documents supporting their CP or TA-D2 project. PRIME designees will include the SAG Chair, alternate chair, and administrative personnel responsible for report curation.

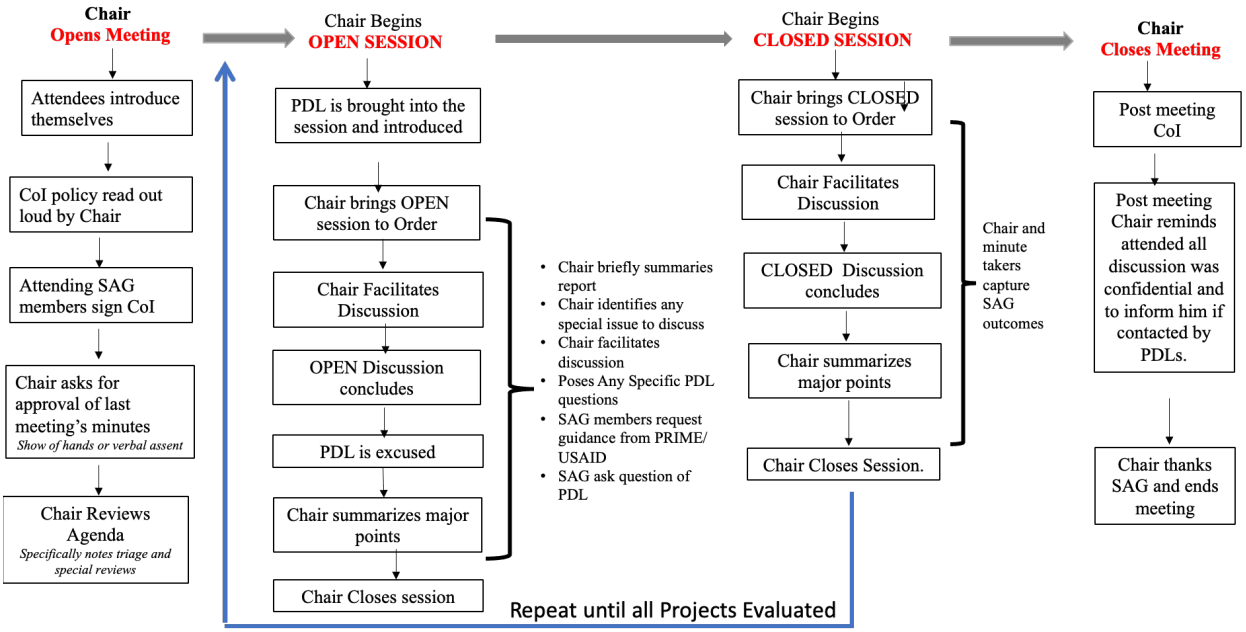
Summaries of MATRIX SAG activities may be placed on the external public website and may include an overview of SAG evaluations and their recommendations. These postings will be redacted for confidential, sensitive, and intellectual property information and the content approved by the PRIME, SAG Chair and PDL.

Appendix 1: SAG Operation Timeline



Appendix 2: Flow Chart for SAG Meeting

Flow Chart for SAG Meeting



Appendix 3: MBR Report Template

MBR Contents

Checklist provided to facilitate report generation.

List of abbreviations

Appendix 1: Mitigation Definitions

Appendix 2: TPP

Appendix 3: Project Descriptor

Appendix 4: Gantt Chart

Appendix 5: Product Specifications

Appendix 6: Decision Tree(s)/Selection Algorithm(s)

Appendix 7: Hub Involvement

Appendix 8: Clinical Trials

Appendix 9: Milestones

Appendix 10: Supplemental information

Appendix 11: Mitigation Plan

Appendix 12: Budget Modifications

Appendix 13: USAID R&D Microbicide Assessment

MBR Report Template

MDR reports must be in Microsoft Word with 12-point Times new Roman Font. All margins should be set at no less than 1 inch and must include the document headers and footers. Headers should identify the product and group/organization and footers have "Page X of X" page numbering format. Figures should be legible without magnification in MS Word. Reports that do not conform with formatting requirements and/or page and word limits will be returned as non-compliant

Date: Date of SAG meeting
Group/Organization:
Product: Drug/delivery system, duration
Are Mitigations Identified in Report: ____YES ___ NO **What is the proposed Mitigation Class**: Provide a suggested mitigation class. The f mitigation class maybe modified by the SAG with concurrence of PRIME and USAID. Attach the Mitigation Plan using the mitigation plan for class 2 and 3 mitigations (Mitigation definitions Appendix 1 Mitigation plans are inserted in Appendix 11 of the MBR report.

List of abbreviations used in this report: Please provide a list of all abbreviations used in your report. Please add your abbreviations to the list below.

CP: Critical Path
LNG: levonorgestrel
MBR: Milestone Benchmark Report
PD: Product Developer
SAG: Scientific Advisory Group
TA-D1 Technology Accelerator Domain 1
TA-D2 Technology Accelerator Domain 2
TPP: Targeted Product Profile

SECTION I: Project Description

1. **General Project Description:** Provide a brief description (200 words or less) of the project. This should be a brief high-level description of the project and its goals. This description is intended to inform/familiarize the SAG with the project they are about to evaluate. From report to report this section may only receive minor modifications as development progress*es*.

2. **Project descriptors**

   This section of the MBR is designed to describe the CP project for the SAG, through the use of in section checklists and associated appendices.

   Appendix 2: TPP insert link to appendix 2
   Appendix 3: Project Descriptor. inset link to appendix 23
   Appendix 4: Gantt Chart: insert link to appendix 4

3. **Product Specifications:**

The specification of the final target product and current protype in development (if appropriate) are in **Appendix 5**

Product specifications differ from the TPP in that these are the precise characteristics of the prototype or final product being developed. if you are currently optimizing the product provide both the current protype and proposed target product specifications. Specifications must be in a tabular format as identified in Appendix 5.

Specification are provided for: Identify what specifications are included in the table in Appendix 5. Mark all that apply.

___ Current protype insert link to appropriate specification in Appendix 5

___ Targeted GMP product insert link to appropriate specification in Appendix 5

___ Final GMP Product insert link to appropriate specification in Appendix 5

___ Other:_____ insert link to appropriate specification in Appendix 5

4. **Product Decision Tree(s)/ Selection Algorithm(s)**

Attach decision tree(s) and/or selection algorithm(s) guiding the development of your product in Appendix 6. The overarching decision tree/selection algorithm should reflect your CP product development plan. If the development plan includes iterative optimization of a drug/device through a prototype testing process an additional decision tree/algorithm that describes the critical decisions may be used to describe the prototyping effort, if those decisions are not captured in the overarching decision tree/selection algorithm.

Types of decision tree(s)/selection algorithm(s) included in Appendix 6

Overarching: ____ insert link to appropriate decision tree(s)/selection algorithm(s) Appendix 6

Prototype optimization: ___ insert link to appropriate decision tree(s)/selection algorithm(s) Appendix 6

Other: ___ insert link to appropriate decision tree(s)/selection algorithm(s) Appendix 6

5. Hub Involvement

Hub(s) involved:

____ D2D ____ Number of activities insert text ink to Appendix 7.

____ BACH ____ Number of activities insert text ink to Appendix 7

In Appendix 7 you will describe the HUB activities you are engaging in to support your product development. Reportable Hub activities are those that will have an impact on the operations and/or product development activities of the CP, e.g., business case development, end user studies, etc. Reported Hub activities should have the potential for substantial impact on CP product development and/or progress toward major objectives. Do not report routine Hub interactions that do not have a potential impact on your proposed product. For each reportable Hub activity provide a description of the activity using the format provided in the Appendix.

Status/Type of HUB Involvement activity described in Appendix 7 multiple choices maybe selected below to address multiple ongoing activities with hubs.

Please insert text links to appropriate pages in Appendix 7

___ Proposed. Currently in discussion with the Hub to define a project or activity.

___ In development. The Hub and PD have identified a project and are now identifying resources and outlining the proposed activity.,

___ Ongoing. The Hub and CP are actively conducting the proposed activity.

___ Completed. Date Completed:

Will only be checked for Hub activities that have been completed and are reporting the outcomes to the SAG for the first time.

6. Clinical Trials:

Clinical trials are described in Appendix 8

Type(s) of trial: there may be multiple types of trials and statuses checked below.

___ Placebo controlled End User research

___ Phase 1 safety testing

___ Other(s)

Description of Trial(s): This section maybe duplicated ofr each trial being conducted.

___ proposed. Start date

___ In development

___ Protocol in development

___ Protocol submitted to local IRB and/or Ethics committee Date Submitted __

___ Protocol awaiting Regulatory authority approval Date Submitted _.

___ Protocol Started. Start Date _____

___ Protocol completed in Data analysis
Completion Date: _____

Provide a brief description of each trial (100 words). The trial schema and endpoints will be listed in Appendix 8. Use text hyperlinks in the description to refer to this information. It is recognized that the information given for clinical trials maybe forward looking. However, this "predictive" information can be important in establishing that other planned activities are supporative of achieving the clinical trial. The trial description may not change substantially from MBR to MBR, until there is a protocol for the trial, and after protocol finalization the description will again be fairly static until completed.

SECTION II: Progress Description

1. Summary of Milestones for the Reporting Period (from XX to YY)

The milestone table is located in Appendix 9.text hyperlink to Appendix 9

The milestone table summarizes the milestones, timeline and Go/ No-Go for each activity described in the formal USAID/MATRIX work plan.

Milestones completed in this reporting period: Provide a brief summary of any completed milestones and Go/No-Go achieved snce the last SAG meeting, Example: RAT PK study completed, no safety issues and drug release target of XX achieved, etc.

Problems Encountered: Provide a brief description of problems encountered in achieving specific milestones and action to correct. Example: Delay in starting study due to failure of GMP batch release, study rescheduled for XXX, etc.

2. Progress Narrative (1 Page)

Provide a brief specific narrative of progress since the last SAG meeting. This is a concise narrative of the work done in the reporting period and its relationship to the goals of the CP. Data may be included. Tables and legends may not be smaller than 10-point font. Figures must be readable as a paper copy to accommodate all possible modes of SAG member evaluation, electronic or paper. Margins must be 1 inch.

___ Supplemental information

Mark if supplemental information is included in Appendix 10.

Appendix 10 may be used to provide additional information to support statements in the progress narrative. Appendix 10 may be no longer than five (5) pages. If the Appendix is used to provide supporting data for the progress narrative, the data in the Appendix must be hyperlinked to the statements in the narrative.

The SAG is under no obligation to read Appendix 10.

3. Problems and Unanticipated Outcomes: (500 words)

The objective of this section is to inform the SAG of any issues that may be impacting your CPs progress. This section may also be used to tell the SAG how you addressed their recommendations from the last SAG meeting.

Summarize experimental and operational problems encountered during the reporting period, The problems and unanticipated outcomes should reflect your efforts to achieve your work plan milestones. They may deal directly or indirectly with the ability to meet a proposed Go in the time specified. Problems may be identified that are outside the control of the PD and CP project, such as extended delays in research/regulatory approvals, and out of stock issues. The objective of this section is to inform the SAG on issues that may be impacting your CPs progress and demonstrate you are actively addressing these issues.

4. For Critical Path (CP) Projects Only

Is off ramping to Domain 2 of the Technology Accelerator requested?

___ No ___ Yes Mitigation plan required

If Yes, briefly describe (250 words or less) the component proposed for off-ramping**?**

Briefly describe the reason for off-ramping. Identify if all or a portion of the CP is requested to be off-ramped. Provide a justification for the off-ramping and whether return to the CP is anticipated and when.

Attach Mitigation Plan in Appendix 11. Insert hyper link to Appendix 11

5. Budget Status

On budget ____ Underspending ____ Overspending _____

If there are modifications to the budget, please provide a revised budget in Appendix 12.

Budget narrative (100 words) (only for overspending and underspending)

Provide a brief narrative of the issues resulting in overspending or underspending. Include in the narrative a brief description for how you will correct the budget issue, e.g., Underspending: hire more people, increase activity, etc.; Overspending: request increased dollars, reprioritize activities, etc. If you are requesting additional funds in the Appendix, provide a brief summary here of the request.

Section 3: SAG Recommendation

To be filled out by the PRIME after concurrence of USAID with the SAG recommendations. The recommendation will include the evaluation of the Mitigation Plan, if appropriate.

In lieu of completing the checklist below Recommendations maybe complied by the SAG Chair and placed in a password protected section of the matrix4prevention.org website.

In all cases only the projects PD, PRIME, PRIME administrative desginees, and USAID will have access to the recommendations.

Primary Recommendation:

___ Proceed as proposed

___ Proceed with the provided recommendations and comments

___ Off-Ramp identified activities to Technology Accelerator Domain 2

___ Return off-ramped activity to Critical path

___ Stop development

___ Create a mitigation plan

Description of Activity requiring mitigation:

Additional SAG Comments: Optional

Recommendations may be placed in a separate file stored with the MBR submission.

End of page

Appendix 1: Mitigation Class Definitions

See full description of the mitigation classes and process in the SAG charter

Class 1: Minor or transitory delays in research.

- The resolution of Class 1 mitigation issues is in general out of the hands of the PD.
- No separate mitigation report required.
- The resolution of the mitigation issue is reasonably expected to take no more than 6 months or 1 SAG reporting interval.

  Examples of this type of mitigation are timing of animal studies by CROs, delays in IACUC or IRB approvals, natural disaster delays, PD institutional administrative delays, regulatory delays, etc. In this case, the PD will place an explanation of the delay in the MBR report and provide a projected best- and worse-case resolution scenario, timeline, as well as alternatives, if any (e.g., alternative source or CRO) to resolve the issue if it cannot be resolved in the SAG reporting interval.

Class 2 : Moderate Delays in Research.

- Adverse finding where a resolution of the issues encountered are possible within a limited time frame that will not impact overarching milestones (i.e., clinical testing in 4 years) benchmarks and Go/ No-Go criteria but require a focused research effort to keep the R&D process on track.
- A mitigation report is prepared
- Class 2 Mitigations should be resolved as quickly as possible. It is expected that resolution of a Class 2 mitigation could take more than 6 months but are likely to be resolved in less than 12 months.

  Examples are minor modifications of formulations to meet stability requirements, need for a significant modification of a synthetic or manufacturing process, adjustments to formulations or delivery devices to meet desired/pre-defined rheological properties, etc.

- Because of the expected quick resolution of Class 2 mitigations, it is not expected that these mitigations will initiate immediate off-ramping to Technology Accelerator Domain 2. However, if mitigation efforts extend beyond 12 months, with the consent

of the PRIME and USAID, the mitigation can be reclassified to a Class 3 and the project moved to Domain 2 of the Technology Accelerator.

Class 3: A severe to catastrophic problem/delay in product development

- Could potentially halt development (fatal flaw in drug substance or drug product) or delay development for an extended period of time (>12 months), resulting missed milestones, benchmarks and Go/No-Go criteria.

- A mitigation report is prepared

  Examples are failure of a stability program that indicates major changes are needed in the formulation or API, a serious safety finding or adverse event in preclinical or clinical studies, respectively, failure of GMP manufacturing or meeting GMP quality requirements.

- A critical part of any Class 3 mitigation will be a determination if all or part of the CP project requiring mitigation needs to be off ramped to TA-D2 and whether other activities within the CP should continue, with or without modification. The PD should identify parts of the CP that should continue as planned The SAG will recommend off-ramping and whether other activities in the CP should be continued. USAID will determine if these recommendations are followed.

Appendix 2: TTP

Paste the 2-page TPP submitted for the MATRIX application in this section.

If the TPP requires updating mark changes in Red

SAG requirement:
Efficacy Estimates should not be made versus placebo.

TPP efficacy estimates used must be directly linked to known clinical efficacy of licensed HIV drugs i.e., cabotegravir CP projects to CAB LA and vaginal film to dapivirine IVR. For products without an established clinical efficacy an appropriate standard that reflects the current landscape for prevention and MPTs should be used. All TPP contraceptive efficacy estimates for MPTs, should include a comparison to a relevant licensed contraceptive., e.g., MPT LNG to LNG use to prevent pregnancy.

For the March/April 2023 SAG you will indicate this change in **green**.

Leave the red changes from previous MBR reports, unless directed to remove them by the PRIME or USAID.

Appendix 3: Project Descriptor

Paste the 2-page project descriptor submitted for the MATRIX application or New Project Request into this section.

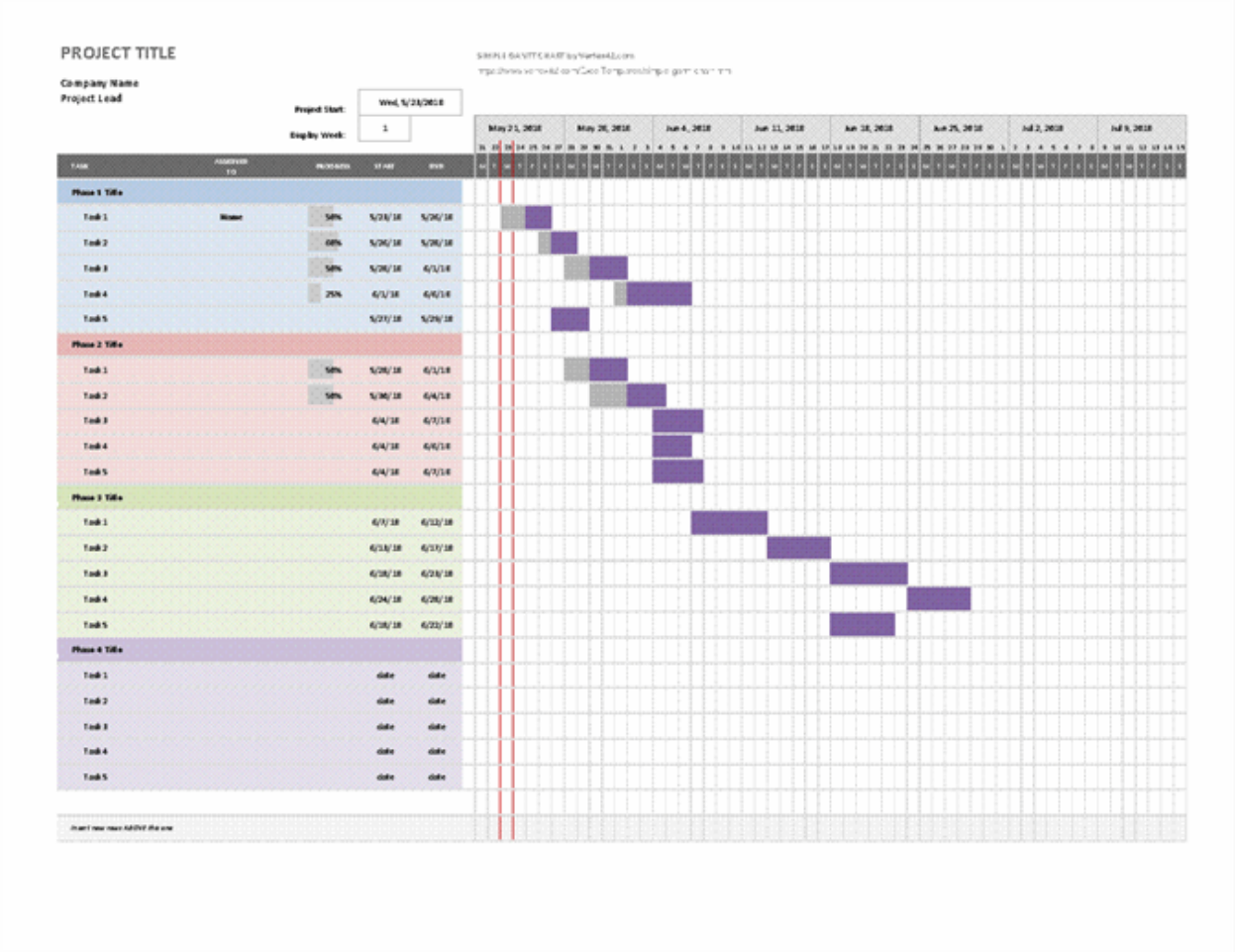
If the project descriptor requires updating mark changes in Red

Leave the red changes from previous MBR reports, unless directed to remove by the PRIME or USAID

Appendix 4: Gantt Chart

NOTE: per August 23/24, 2022, SAG: Gantt chart should be an industry standard Gantt chart—see example below

This is a Microsoft Office Simple Gantt chart https://binaries.templates.cdn.office.net/support/templates/en-us/tf16400962_win32.xltx This is provided as an example –It is NOT a requirement to use this template



Provide a Gantt chart for the Project activity.

If the Gantt Chart requires updating mark changes in Red

Leave the red changes from previous MBR reports, unless directed to remove by the PRIME or USAID

Appendix 5: Product Specifications

If the CP or TA-D2 is currently working to optimize the product toward the final specifications, please put the current protype specifications in column 2. If the development is finalized leave column 2 blank

Product specification should be in a table format.

Parameter	Targeted Product Specifications	Current Prototype Specifications
Duration		
Release Rate		
Storage condition		
Include other parameters as appropriate		

TBD: To Be Determined

Use TBD for specifications that have yest to be determined

Example

Please provide the parameters you are targeting for your final product. This may include physical, rheological and other targeted properties.

Product specifications must include targets for duration and release rate.

Parameter	Targeted Product Specifications	Current Prototype Specifications
Water content	0%	25%
Stability	100% 37C 1 yr.	100% 37 C 6 mo
Physical description	White powder	Off-white powder
Storage conditions	TBD	4C
Duration	6 months	TBD
Release rate	2mg/day	TBD, experiment ongoing
Purity	99%	80%
Duration of PK tail	6 weeks	TBD
Other parameters, e.g. oxidation, contaminates, depredated products. Etc.		

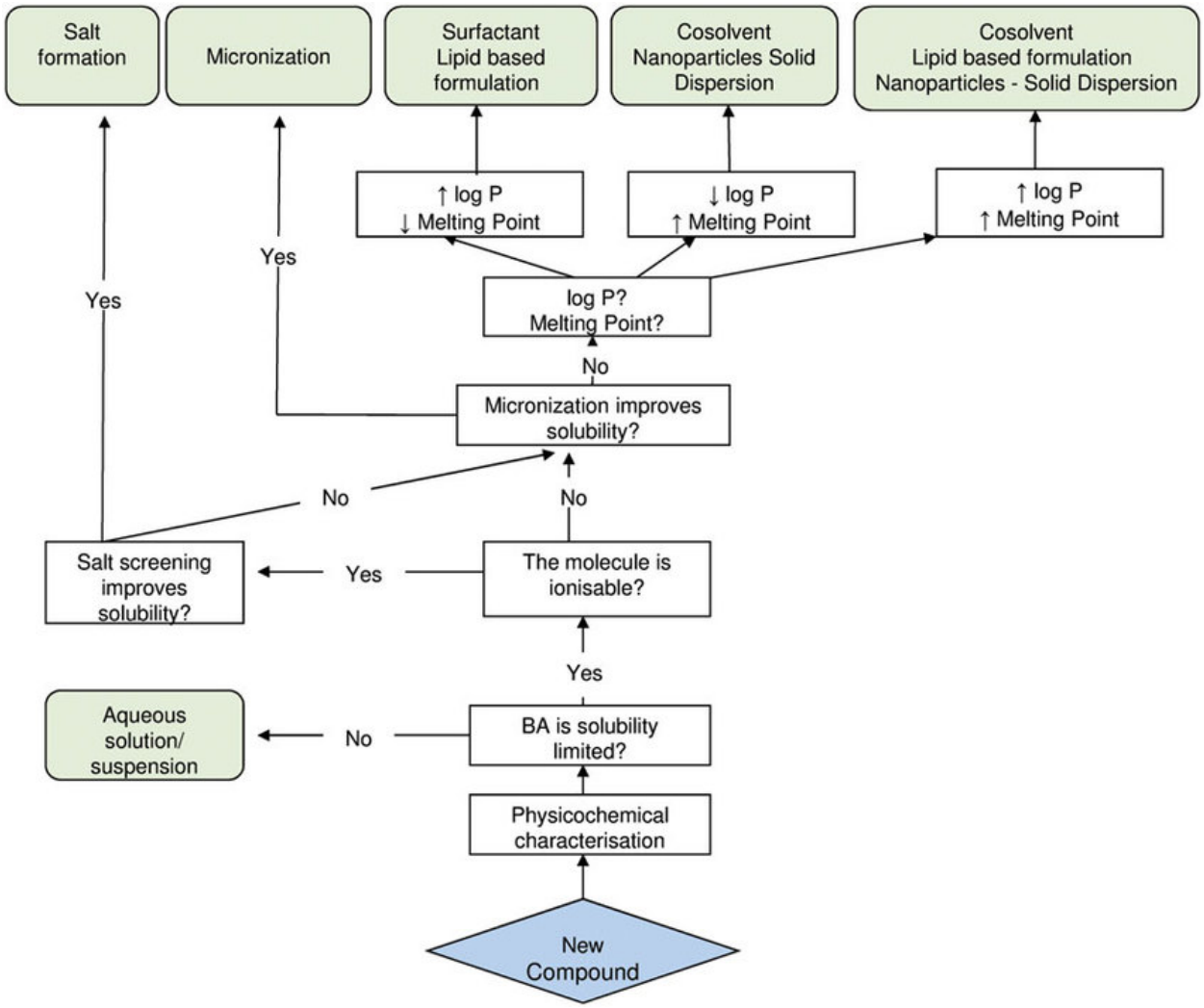
Appendix 6: Decision Tree/Selection Algorithms

Please provide decision trees for both your CP project target product and any decision trees being used to optimize products for the overarching decision trees, i.e., prototype selection. You can use a separate page for each decision tree/selection algorithm being used. Please label decision trees clearly, i.e., prototype depot injection, prototype vaginal film, final insert, etc..

Overall CP Project Decision Tree--Insert

Prototype Optimization Decision Tree(s) --Insert

Example



Appendix 7: Hub Involvement

Provide a description for each Hub activity reported in section 1.5 of the main report. Hub activity descriptions should not be more than 1 page in length.

You should only report Hub activities that result in an activity, protocol, study, etc., that is directly related to or designed to guide product development or inform on final product characteristics.

Note if the activity was reported as completed for the last SAG review, it does not need to be reported again.

The following section and information should be duplicated for each Hub activity identified in Section I of the MBR.

Hub:

Title of activity e.g., end user studies of X to support final protype development, business case development, etc.

Description of Activity (250 words): Briefly describe the activity and its objective(s).

Impact of Activity on MATRIX award (250 words):
Provide a brief statement for how the Hub activity will support the CP product development. The statement may address impact on the CP project and/or impact on the operations of the Hub. Please identify what overarching objective this activity supports.

Outcome: Describe the projected outcome of the activity or describe the results of the activity is completed in this SAG reporting period

Appendix 8: Clinical Trials

Use a separate page for each clinical trial reported in Section 1.6

The provided clinical trial information may be a draft, a proposed or a final used in a protocol. Please in the title of the schema and objectives indicate its current development phase. It is recognized that the schema and objectives may not be final. The goal of this requirement is to provide the SAG with an understanding of proposed or ongoing clinical activities and it is acknowledged that early schemas may change dramatically as the proposed clinical trial is developed.

Proposed or actual start date:

Projected completion date:

Completion date: Use only if trial is completed during the reporting period

Section A

Insert clinical trial schema:

Section B

Primary objectives:

Secondary objectives:

Exploratory objectives:

Summary of trial results (1 page), only if trial completed).

If a trial of end-user preferences, indicate how the identified preferences and/or feedback/recommendations informed modification(s) to the product specifications, design, use and/or performance.

Appendix 9: Milestones

Insert milestone table from your USAID Work plan. If milestones were modified during the reporting period indicate the changes in red.

Note the format of the milestone report is landscape view: Section breaks have been used to allow use of landscape format in this section.

Indicate in the table which milestones are complete, in progress or will be initiated in the next reporting period.
Highlight the Go or No-

Workplan Milestone Table

Project Specific Activity (As described in the workplan)	**Milestone**	**Type***	**Projected completion (Date: month/year)**	**Go Criteria**	**No-Go Criteria**	**Action**
						Indicate the action to result from meeting (G) or not meeting (NG) the milestone

* Milestone type

O= overarching
S= Supporative

G= Go
NG= No-Go

Appendix 10: Supplemental Information

Page limit 5 pages.

The SAG is under no obligation to read this Appendix and it is provided to allow the product developer to expand on statements made in the 1-page project narrative Section II.2.

All data provided in the Appendix must be hyperlinked to the appropriate part of the Project Narrative for the convenience of the SAG.

All text must be in 12 pt times new Roman and Figures cannot use fonts smaller than 10 pt. Figures must be readable as a paper copy to accommodate all possible modes of SAG member evaluation, electronic or paper.

Appendix 11: Mitigation Plan

Fill out the mitigation plan template and insert the plan here

Appendix 12: Budget Modifications

If changes are required to the budget prepare a dual column budget that indicates the original budget and the modified budget.

Item	Original Budget	Revised Budget	Justification

Indicate any additional funding that maybe needed for the current work plan. This maybe funding needed to address increased activities due to faster achievement of milestones, opportunities identified during the reporting period that can enhance CP product development and/or unexpected costs of doing business.

Anticipated additional funding

Item	Requested Budget	Justification

Appendix: 13: USAID Microbicides R&D Assessment *(required by USAID)*

Because of the size of the R&D assessment it may need to be submitted separately from the MBR report.

The USAID Microbicides R&D Assessment must be reviewed and updated by the development team prior to each biannual SAG meeting.

Summary of new information added to the assessment

The Assessment is a dynamic living document that USAID uses to determine funding priorities and impact of funded projects in their portfolio. To assist USAID In evaluating the assessment please catalogue the changes made in the assessment in the table below.

Briefly describe change:

Scientific Priority/Indicator	Modifications /Additions to Assessment	
	Rationale	Supporting Reference Materials

Appendix 4: Mitigation Plan Template Mitigation Report for Class 2 and 3 Mitigations

Mitigation Plan Template Mitigation Report for Class 2 and 3 Mitigations

MBR reports must be in Microsoft Word with 12-point Times new Roman Font. All margins should be set a no less than 1 in. and must include the document headers and footers. Figures should be legible with no more than 150% magnification in MS Word. Reports that do not conform with formatting requirements and/or page and word limits will be returned as non-compliant

Date: *Date of SAG meeting*
Group/organization:
Product: *Drug/delivery system, duration*
Proposed Mitigation Class *(Class definitions MBR Appendix 1), Final mitigation class will be determined by SAG with concurrence of PRIME and USAID.*

Briefly list and describe (250 words or less) any other ongoing Mitigation activities for this CP or TA-Domain 2 project.

Briefly list and describe any ongoing class 2 and/or 3 mitigations and how this mitigation request relates to the previously approved mitigation plan(s). Specifically address the impact of the multiple mitigation plans on each other. Is resolution of one plan continent on the success of the other? Briefly quantify the impact of this plan on project timelines, identify whether this plan will result in significant changes to the project plan s Gantt chart, TPP, Milestones, benchmarks and Go/ No-Go criteria.

Indicate the projected time required to complete the mitigation activities.

Provide a projected project duration for the mitigation plan. Provide both best case and worse case estimations. Identify whether the time to resolution is dependent upon factors out of control of the product developer, i.e., requires IRB, IACUC or other administrative/regulatory approvals to implement.

For Class 3 mitigations only, are you requesting approval to off-ramp all or part of the Critical Path Project (CP) to Domain 2 of the Technology Accelerator?

If the answer is no, move to the next question. If the answer is yes, identify whether all or a part of the critical path project will be off-ramped. If only a part, in the table below list the activities and associated milestone, benchmark or Go/ No-Go criteria associated with the components to be and not to be off ramped.

CP Activity	Milestone, Benchmark, Go/No-Go criteria*	Off-Ramping Yes/No	Comments

**Milestone, benchmark, Go/ No-Go associated with the CP activity.*

Describe the Mitigation Plan (500 words or less).

Describe the issue(s) to be mitigated and how it will be mitigated. Indicate how the mitigation plan will resolve the issues encountered. Describe the experimental design to be used and the expected outcomes, where appropriate.

Multiple mitigations that are interrelated (e.g., redesign a formulation and perform stability testing) can be described in the same description. If they are multiple mitigations describe provide a mitigation classification for each.

In Appendix 1 Provide a Gantt chart, and Timeline for the Mitigation Plan (2 pages).
Identify any relevant dependencies in the Gantt Chart and indicate critical milestones, benchmarks, and Go/ No-Go criteria in the timeline

Describe a Successful Mitigation and the Decision Points for Determining a Successful Mitigation (200 words or less)
What needs to be accomplished to return to the CP? What Milestones, Benchmarks, Go/ No-Go criteria must be met to signal a successful mitigation. If you are requesting off-ramping to Domain 2, what criteria need to be met to return to the CP.

Does the need for or the outcomes of the mitigation plan result in changes in the CP project descriptor, Gantt Chart, TPP or USAID Microbicide R&D Assessment?

If yes which appendices were modified.

Modify the appropriate documents in the appendices of the MBR, following the instruction in the Appendices for each component
Appendix 5: Project Description
Appendix 6: Gantt Chart
Appendix 7: TPP
Appendix 8: USAID Microbicide R&D Assessment

Describe Futility (150 words or less)
Provide a 150 word or less discussion of what futility would look like. Futility is defined as the inability to mitigate the identified problem sufficiently to continue with the planned CP project.

Projected time to complete the mitigation.
Best Case Scenario: *Days or date*
Worst Case Scenario: *Days or date*
Provide a best- and worst-case scenario for completion of the proposed mitigation plan. These times should be reflective of the Gantt Chart and Timeline provided in Appendix 6.

Mitigation Plan Budget
Provide a brief (200 words or less) narrative of the budget required for the mitigation, its impact on the CP, and how it will be obtained. A more detailed budget will be provided in Appendix 2.

Indicate whether rebudgeting will be sufficient to complete the mitigation plan or if new funding is anticipated to be needed. Indicate the amounts of to be rebudgeted or new funds to be requested.

Indicate whether budgeting will create a shortfall in future activities and whether that shortfall can be met by rebudgeting other CP activities in out-years.

If other CP activities will be ongoing during the Mitigation plan implementation describe any potential impact on these studies.

SAG Recommendation
To be filled out by the PRIME after concurrence of USAID with the SAG recommendations. The SAG may recommend a variety of outcomes for the Mitigation plan. They may recommend proceed as planned, recommend off-ramping to Domain 2 of the Technology Accelerator (not requested in the plan) or may recommend futility for the CP project based on the severity of the mitigatable issue. In all cases, the mitigation plan will not be officially implemented until concurrence is received from USAID.

Additional SAG Recommendations

Appendix 1: Gantt chart and timeline for the Mitigation Plan

Two (2) pages.

Gantt chart and timeline formatting should follow original document fonts and sizing submitted with the MATRIX application

Identify any relevant dependencies in the Gantt Chart and indicate critical milestones, benchmarks, and Go/ No-Go criteria in the timeline.

Appendix 2: Mitigation Plan Budget

Provide a detailed budget for the mitigation. Indicate where the funds for the mitigation are coming from and any shortfalls or reduction in scope the new budget will create for the CP.

Appendix 5: New Project Requests

NPR Contents

Check boxes provided to facilitate report generation, please use boxes to ensure all sections are present.

__ **List of abbreviations**
____ **Appendix 1: Mitigation Definitions:**
___ **Appendix 2: TPP**
___ **Appendix 3: Project Descriptor**
___ **Appendix4: Gantt Chart**
___ **Appendix 5: Product Specification**
___ **Appendix 6: Decision Tree(s)/Selection Algorithms**
___ **Appendix 7: Proposed Hub Involvement**

___ **Appendix 8: Proposed Clinical Trials**
___ **Appendix 9: Milestones**
___ **Appendix 10: Budget**

___ **Appendix 11: USAID R&D Microbicide Assessment**

List of Abbreviations

Please provide a list of abbreviations used in your report. Please add your abbreviations to the list below.

CP: Critical Path
LMIC: Low- and Middle-Income Countries
MPT: Multipurpose Prevention Technology
NPR: New Project Request form
SAG: Scientific Advisory Group
SSA: Sub Saharan Africa
TA-D1: Technology Accelerator Domain 1
TA-D2: Technology Accelerator Domain 2

New Project Request (NPR) Template

Submission of New Project Requests (NPR) must be preceded by an invitation by the MATRIX PRIME with USAID concurrence to submit the NPR. Permission to submit an NPR does not imply approval to start the project.

1. **New Project Identifier**
   The new project identifier should describe the product or activity to be conducted in the new project, i.e., Development of XXX drug for long-acting HIV prevention, Development of a highly sensitive point of care measuring device, Development of a novel in situ detection method for implanted long-acting HIV prevention strategies, etc.

   Date: Date of submission of the NPR to MATRIX

   Date of Invitation to submit a NPR:

   Date of Scientific Advisory Group (SAG) Evaluation:

2. **Group/Organization:** Entity submitting the request. Can be an individual investigator, lab, or institution. New projects may be proposed by SSA investigators, investigators already in MATRIX or invited investigators.

3. **Relationship of group to MATRIX:**
   External to MATRIX/Internal to MATRIX, residing in the US, SSA or other

4. **USAID Priorities addressed: (100 words)**
   Describes how the new project addresses the overarching USAID priorities of developing HIV prevention strategies or multipurpose prevention technologies (MPT) that are acceptabile, affordable, scalable and /or deliverable to young girls and women in LMICs. Ideally new projects will incorporate attributes that enable each of the 4 product factors.

   Briefly describe anySSA or LMIC capacity building activities of the proposed new project (100 words):

5. **Proposed Duration of Project:**
   For all new projects, the performance period can be no longer than the base MATRIX award (November. 30, 2026).

6. **Briefly Description of the New Project:**
   Brief description (500 words or less) of the proposed new project.

   Describe the proposed experimental design and identify critical outcomes of the proposed research.

   Specific outcomes of the project should be described .

7. **Describe any New Human Capital Created by the New Project (100 words or less)**
   Will the project be part of a mentoring or training program for a Sub Sharan Africa investigator? What will the investigators gain from participating in the new project? Will the new project enhance existing or create new infrastructure in the labs or institution it is carried out in? What new infrastructure will be created, e.g., new methods and assays to test anti-HIV drugs.

8. Impact of New Project (200 word of less)

Describe how the work fills a gap within MATRIX or adds to the HIV prevention field. Provide sufficient reasoning for the activity to be brought on/into MATRIX.

For new projects derived from terminated CP or Domain 2 projects the impact statement must also identify the specific value of the "rescued" project to USAID.

9. Required Supporting Appendices

Depending upon the type of new project and scope of the activity, the following appendices may or may not be used.

Provide the appropriate information or attach the appropriate documents in the indicated appendices. For appendices not used –Label the appendix "Not Required."

Appendix 2 Targeted Product Profile.

Appendix 3: Product Descriptor

Appendix 4: Gantt Chart

Appendix 5: Product Specifications

Appendix 6: Decision Tree or Selection Algorithm

Appendix7: Proposed Hub Involvement (if any)

Appendix 8: Proposed Clinical Trial (if any)

Appendix 9: Milestones

Appendix 10: USAID Microbicides R&D Assessment

Definitions for timeline, milestone, benchmarks and Go/ No-Go can be found in Appendix 1.

Requirements for new CP projects

The minimal following documents are required:

- 1 page milestone and benchmark Gantt chart (Appendix 2)
- 1 page TPP (Appendix 2)
- 2 page Project Descriptor (Appendix 3) that discusses the following
    1. Pre-clinical/Clinical development plan
        a. Lead(s) drug substance (Active Pharmaceutical Ingredient(s) API(s))
        b. Drug delivery system
        c. Product manufacturing plans and options
    2. Regulatory strategy and timing
    3. Product cost evaluation
    4. Plans for key consumers/end-users' and stakeholders' input:
        a. Acceptability and user preference considerations
        b. Affordability, scalability, product delivery considerations
    5. Status of technology and technical approach (include R&D benchmarks)
    6. IP and patents considerations
    7. Key risks and unknowns
    8. Value added and relevance
- Gantt chart (Appendix 4)
- Product Specifications (Appendix 5)

- Decision tree(s)/selection algorithm(s) (Appendix 6)
- Proposed Hub Involvement (Appendix 7), if appropriate
- Proposed Clinical Trials(Appendix 8), if applicable
- Milestones (Appendix 9)
- Budget (Appendix 10)
- USAID Microbicides R&D Assessment (Appendix 11

10. Budgets and personnel

Provide a budget as indicated in Appendix 10

New CP project require a detailed year 1 budget and a predicted total budget for subsequent years.

TA-DI projects will provide a detailed budget for the duration of the project.

11. USAID Microbicide R&D assessment

Fill out the USAID microbicide R&D assessment.

SAG recommendation

To be filled out by the PRIME after concurrence of USAID with the SAG recommendations. The SAG may recommend approval or disapproval of the new project on-boarding request. In all cases, the new project will not be officially implemented until concurrence is received from USAID.

The SAG review of new TA-D1 projects that are not derived from a terminated Domain 2 or CP will be a courtesy review to familiarize the SAG committee with the project and to establish the required project *documentation. The SAG will be asked if they concur with the proposed onboarding by the MATRIX PRIME and USAID of the project.*

Appendix 1: Definitions

Timeline: A chronological arrangement and identification of critical events in their order of their occurrence during product development. Usually provided as a graphical representation of time and events.

Milestone: A research milestone is a measure of progress. Milestones identify critical junctures/steps in the research process that must be accomplished/completed in order to successfully complete the proposed research and development. Milestones are associated with the achievement of product specifications, e.g., release rate, duration, etc.) that are critical for creating the envisioned product. Milestones must be time specified and contain a defined and measurable Go/ No-Go criterion.

Example of a Milestone
Complete rat vaginal irritation and PK study by XX (date) with irritation scores of no greater than XXs and a Plasma Drug concentration of at least XX.

Benchmark: A point of reference that can be used to judge progress, usually toward a milestone. Benchmarks composed of the steps required to complete a project can be used to measure progress of the project.

Example of Benchmarks.
In order to complete the Rat Safety and PK study milestone I need to Identify a CRO to perform the study, write a protocol, get IACUC approval for the protocol, make drug product to test, perform the study and analyze the study. Each of these steps can be considered a benchmark and measure progress toward the milestone.

Go/ No-Go Criteria: These are critical decision points stated as absolutes in the development pathway of a product. Go and No-Go can be applied to Milestones and benchmarks. Go is a decision to continue development. No-Go is a decision to stop development. A single milestone or benchmark may have multiple Go/ No-Go criteria depending upon its complexity.

Example of a Go and No-Go
Milestone complete Safety and Rat PK study
Go: There are no safety issues and the prespecified PK Parameters were met
No-Go. There are safety concerns and/or the PK parameters were not met.

Appendix 2: TPP

Requirement:
Efficacy Estimates should not be made versus placebo.

TPP efficacy estimates used must be directly linked to known clinical efficacy of licensed HIV drugs i.e., cabotegravir CP projects to CAB LA, vaginal film to Dapivirine IVR. For products without an established clinical efficacy an appropriate standard that reflects the current landscape for prevention and MPTs should be used. All TPP efficacy estimates for MPTs, should include a comparison to a relevant licensed contraceptive., e.g., MPT LNG to LNG use to prevent pregnancy.

The TPP should be in tabular format and should minimally contain the following elements. Additional elements maybe added by the PD as required.

	Item	Preferred Target	Minimum Target
1	Primary Indication		
2	Other indication(s)		
3	Target population		
4	Anticipated clinical efficacy		
5	Preparation		
6	administration /removal		
7	Safety, tolerability		
8	Contraindications		
9	Product attribute/s		
10	Dosing frequency		
11	Disposal/waste		
12	Drug product shelflife		
13	Distributor storage conditions		
14	Packaging		
15	Regulatorystrategy		
16	Anticipated post licensure COGs for 1 person/year		

Appendix 3: Project Descriptor (2 pages)

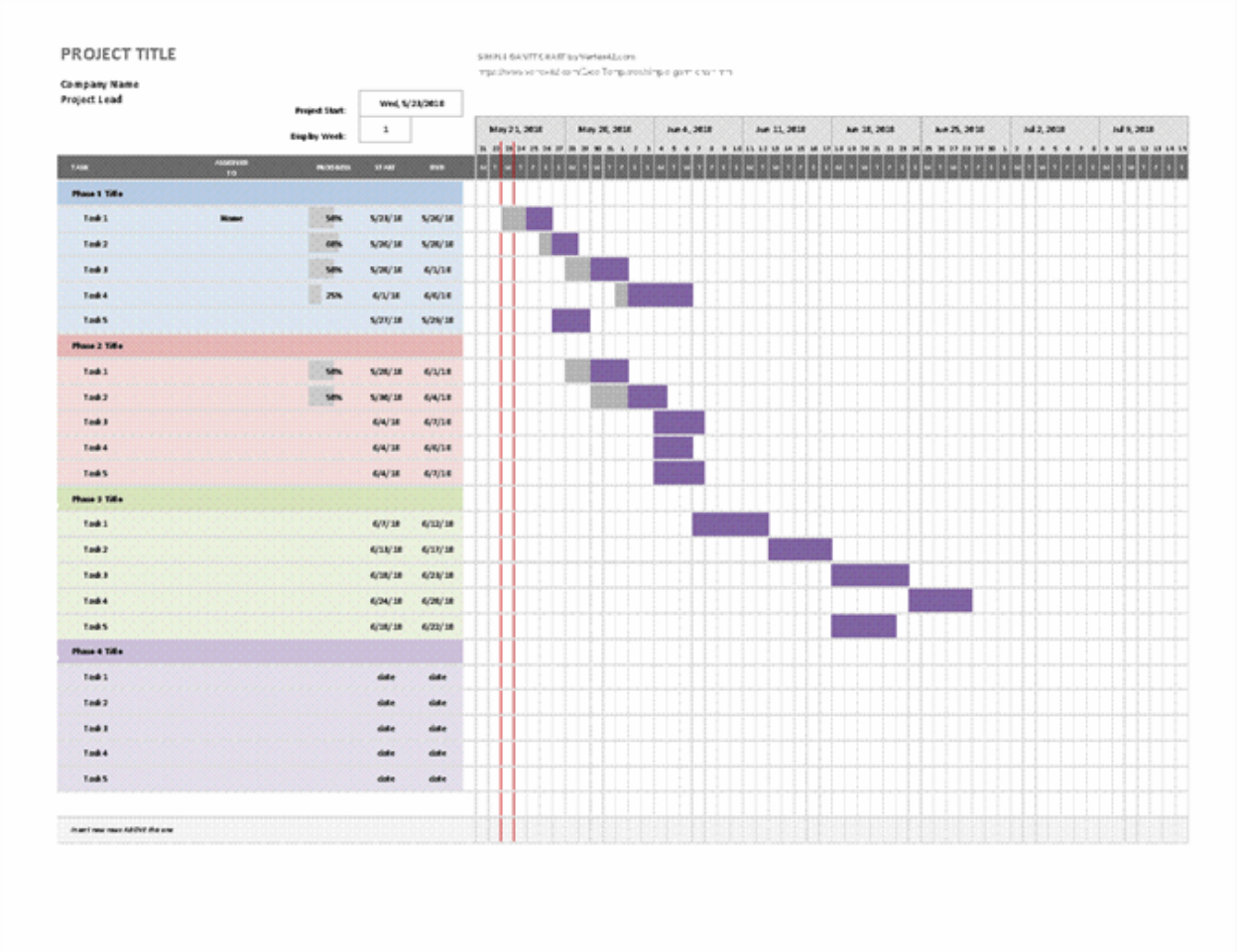
All new projects must address the following issues

1. Pre-clinical/Clinical development plan
    a. Lead(s) drug substances/ API(s)
    b. Drug delivery system
    c. Product manufacturing plans and options
2. Regulatory strategy and timing
3. Product cost evaluation-
4. Plans for key consumers/end-users' and stakeholders' input.
    a. Acceptability and user preference considerations
    b. Affordability, scalability, product delivery considerations
5. Status of technology and technical approach (include R&D benchmarks)
6. IP and patents considerations: describing freedom to operate.
7. Key risks and unknowns
8. Value added and relevance

Appendix 4: Gantt Chart

Gantt chart should be an. Industry standard Gantt chart—see example below

This is a Microsoft Office Simple Gantt chart https://binaries.templates.cdn.office.net/support/templates/en-us/tf16400962_win32.xltx This is provided as an example –It is NOT a requirement to use this template



Appendix 5: Product Specifications

If the new project is working toward developing a new, drug, drug delivery system or instrumentation then a product specification must be provided.

Product specifications should be in a table format.

Parameter	**Product specifications**
Duration	
Release Rate	
Storage condition	
Duration of Tail	
Include other parameters as appropriate	

Example

Please provide the parameters you are targeting for your final product. This may include physical, rheological and other targeted properties.
Product specifications must include targets for duration and release rate.

Parameter	Product specifications
Water content	0%
Stability	100% 37C mo
Physical description	White powder
Storage conditions	TBD
Duration	6 months
Release rate	2mg/day
Purity	99%
Other parameters, e.g. oxidation, contaminates, depredated products. Etc.	

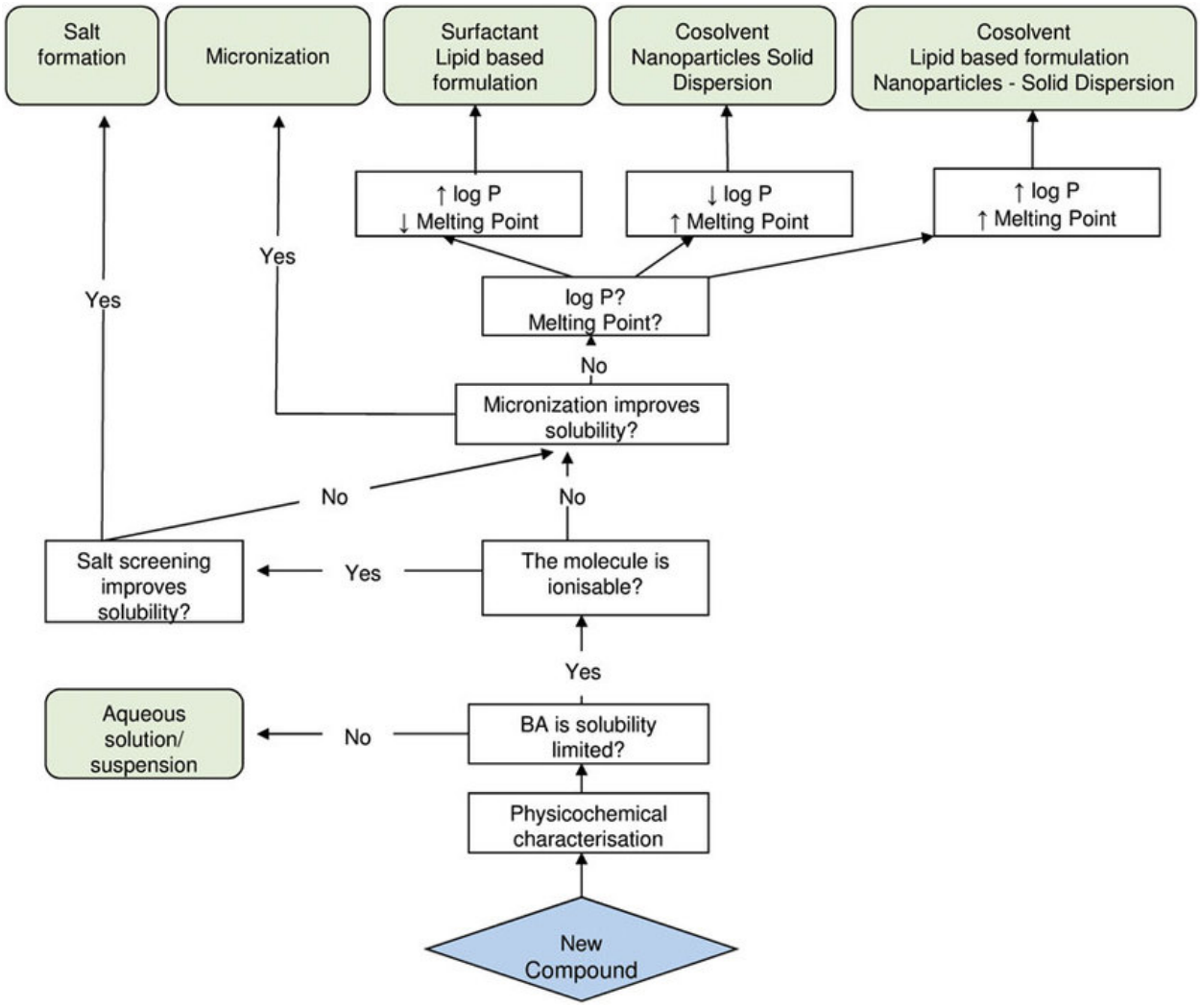
Appendix 6: Decision Tree/Selection Algorithms

Please provide decision trees for both your CP project target product and any decision trees being used to optimize products for the overarching decision trees, i.e., prototype selection. You can use a separate page for each decision tree/selection algorithm being used.

Overall CP Project Decision Tree:

Prototype Optimization Decision Tree(s):

Example



Appendix 7: Proposed HUB Involvement

Use a separate page for each HUB activity, if appropriate. Each Hub activity interaction description should not be more than 1 page in length.

Hub: Identify the Hub you are proposing to work with. Multiple Hubs maybe identified.

Title of activity e.g., end user studies of X to support final protype development, business case development, etc.

Description of Activity (200 words): Briefly describe the activity and its objective(s).

Impact of Activity on MATRIX award:
Provide a brief statement for how the Hub activity will support the critical path and proposed product development. The statement may be either impact on the CP project and/or impact on the operations of the Hub. Please identify what overarching objective this activity supports.

Appendix 8: Proposed Clinical Trials

Use a separate page for each clinical trial being proposed.

The provided clinical trial information may be in draft form. It is recognized that the schema and objectives may not be final. The goal of this requirement is to provide the SAG with an understanding of the need for and scope of proposed clinical activities and it is acknowledged that early schemas may change dramatically as the proposed clinical trial is developed.

Proposed or actual start date:

Projected completion date:

Proposed Sites
US:_____.
SSA: _____.

Section A

Insert draft schema of the proposed clinical trial

Section B

Proposed primary objectives:

Proposed secondary objectives:

Proposed exploratory objectives:

Appendix 9: Milestones

Note the format of the milestone report is landscape view: Section breaks have been used to allow use of landscape presentation in this section.

If a work plan has already been negotiated with USAID use the milestones created for that work plan.

Milestones should be provided for the duration of the new project.

Milestone Table

# Project Specific Activity	Milestone	Type*	Projected Completion (Date)	Go Criteria	No-Go Criteria

Product specific activity describes the activity being conducted, i.e., Antiviral testing, animal study, formulation assessment, etc.

* Milestone type
O= overarching
S= Supporative

Appendix 10: Budget

For new CP projects provide a detailed first year budget of personnel, equipment, and reagents to conduct the new project. For subsequent years provide a projected total.

I am aware of the USAID Equipment tracking requirements and will follow the required procedures. _____Initials

If equipment is requested, please indicate that you are aware of the USAID requirements for tracking of equipment during and after awards. If you are not aware of these requirements, please contact the PRIME for further information. Equipment is defined as an item costing US$5,000 or more **and** having a useful life of more than one year. Note: At USAID's discretion, equipment may need to be returned at the end of the award period.

The following table is a suggested format only, If you have another format that addresses the budget areas below you may use it,

Category	Item	Budget	Justification
Personnel			
Equipment			
Reagents			
Animals			
Travel			
Miscellaneous			

Appendix 11: USAID Microbicides R&D Assessment

This report will only be required for onboarding of new CP projects
Instructions for the R&D assessment will be provided separately.