

Section 3. Participant Accrual and Retention

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3. Introduction

This section provides information on requirements and procedures for recruiting participants in MTN-042. Information on required screening and enrollment procedures are included in Section 5 of this manual. This section also presents information related to definitions, requirements, and procedures for participant retention.

3.1 Pre-Screening Procedures

Sites are encouraged to implement pre-screening procedures for MTN-042 as part of their DELIVER recruitment strategy. Pre-screening approaches and materials used during the pre-screening process should have input from community outreach workers and must be IRB approved.

During pre-screening, staff may explain MTN-042 to potential study participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. No information collected from participants during prescreening may be used for publication purposes unless written informed consent is provided from potential participants.

Note: PTID assignment should not occur until after the participant provides written informed consent at the screening visit.

It is recommended that pre-screening cover key eligibility criteria, such as (but not limited to):

- Age
- Gestational age (confirmed by ultrasound)
- Willing to be randomly assigned to and use the dapivirine ring or oral Truvada
- Plans to deliver at a health center or hospital
- Willing to enroll their baby in the study

Participants found to be presumptively eligible may also be provided with the study informed consent or other IRB approved IC materials for review prior to their screening visit as part of the pre-screening procedures. Study staff should accommodate participants who want to involve their partners or other loved ones in their enrollment decision by offering group information sessions or individual information sessions for partners or couples.

The **MTN-042/MTN-043 Study Enrollment Decision Tool** will be a required exercise for all participants that must be completed before signatures are obtained on the ICF Instructions and a

worksheet for documentation purposes are available on the MTN-042 study implementation materials website. The MTN-042/MTN-043 Study Enrollment Decision Tool materials will guide site staff through an exercise with potential participants aimed at helping them think through the pros and cons of study participation. If used during pre-screening, staff should first educate the potential participant about the study requirements and assess presumptive eligibility. Afterward, site staff should use the decision tool to help each potential participant think through what the positives and negatives of participating might be for her and her infant.

Site staff should familiarize themselves with the tool and decide when and how to implement it. One option is to implement this tool as part of the pre-screening process for the study, with a check-in during the IC session prior to asking the participant to sign. Another option is to complete the tool for the first time as part of the informed consent process. Some sites may choose a hybrid approach, where the exercise is introduced to participants at prescreening for them to think about prior to the screening visit, but the worksheet is not completed until the informed consent session.

Sites should think critically about which staff members are best suited to facilitate this exercise, keeping in mind that remaining neutral, curious, and respectful of participants' decisions is key. At the end of this exercise, potential participants will decide whether they want to continue pursuing enrollment in the study. Some potential participants may indicate that they are not ready to make a decision; in this case, participant needs (e.g. time, input from friends/family, additional information) should be identified and formal screening for the study should be delayed until the participant feels confident about joining DELIVER.

The MTN-042/MTN-043 Study Enrollment Decision Tool worksheet should be used to document these conversations. Any worksheets completed during pre-screening should be stored securely at the study site and incorporated into the PTID binders (or name file, depending on site preference) for all enrolled participants.

When a potential participant comes to screen for MTN-042, site staff should confirm if an enrollment decision making worksheet was completed as part of pre-screening. If so, staff should conduct a brief check-in with the participant about the exercise after review of the informed consent form(s), but before signatures are obtained. Staff should document this check-in on the original worksheet, making note of any significant changes since the participant first completed the exercise. If a participant did not complete the decision-making exercise as part of pre-screening (e.g. a participant was missed or the site decided not to incorporate the exercise into prescreening activities), it should be conducted as part of the informed consent session (after review of the consent(s) and completion of the comprehension assessment, but before signatures are collected). Regardless of whether the decision-making tool is administered at pre-screening or screening, sites must have a completed worksheet on file for all participants prior to collecting signatures on the informed consent form.

3.2 Participant Accrual

3.2.1 Study Accrual Plan

Approximately 750 pregnant women, 18-40 years old (inclusive), as well as their infants, will be recruited across four sites. At enrollment, all women must have evidence of a viable, intrauterine, singleton pregnancy with sonographic confirmation of gestational age that fits within the limits of the currently enrolling cohort, as follows:

- **Cohort 1:** 150 women 36 0/7 weeks-37 6/7 weeks
- **Cohort 2:** 150 women 30 0/7 weeks-35 6/7 weeks
- **Cohort 3:** 150 women 20 0/7 weeks-29 6/7 weeks
- **Cohort 4:** 300 women 12 0/7 weeks-19 6/7 weeks

Collectively across sites, the study will aim to enroll cohorts 1-3 within approximately 4 to 5 months of each cohort opening to accrual (i.e. date of first enrollment at first site), and cohort 4 within 7 to 9 months. Rather than having site-specific accrual targets, all sites will work cooperatively to reach the overall accrual goals for each cohort. While there are no site-specific targets or maximums, the minimum number of enrolled participants at each enrolling site is 18 participants per cohort. Accrual and other quality indicators will be monitored closely by the MTN-042 management team according to the MTN-042 Risk Mitigation Plan. Should key indicator targets not be met, site-specific or study-wide

recommendations may be made to adjust the pace of accrual (e.g. to slow, pause, or discontinue) until improvement is demonstrated. For Cohort 1, accrual will begin after all applicable approvals are obtained and a Site-Specific Study Activation Notice is issued by the MTN Leadership and Operations Center (LOC) (FHI 360).

Note that overall study duration – from first enrollment through closure of all follow-up – may be longer than planned if temporary site closures due to the COVID-19 pandemic cause delays or pauses in enrolling participants at one or more research sites. The MTN-042 Management Team acknowledges that accrual-related indicators in the MTN-042 Risk Mitigation Plan may be triggered due to COVID-19 and, therefore, may forgo the requirement for sites to conduct the indicated corrective/responsive actions.

Screening and enrollment data will be captured on case report forms (CRFs) and entered into Medidata Rave as per SSP Section 12. The Inclusion/Exclusion Criteria CRF will be completed for all participants once they are enrolled at the Enrollment Visit or have screened out of the study at the Screening Visit or the Enrollment Visit.

The MTN SDMC will provide information on the number of participants screened and enrolled based on data received and entered into the study database. See Section 14 of this manual for more details on SCHARP Enrollment Reports.

3.2.2 Cohort-Specific Accrual

Receipt of the MTN-042 Study Activation Notice indicates that a site has met all requirements necessary to begin accrual for Cohort 1. The Study Activation Notice is only required at initial onset of MTN-042 and will not be required for commencement of each subsequent cohort, but sites will be required to complete cohort-specific readiness checklists. Accrual within each cohort will continue until the overall accrual target for the cohort has been met or the site receives notice from the management team that accrual should stop (e.g. if the cohort needs to be ended early or accrual at one site needs to slow or stop to allow another site to contribute more data to the cohort).

As each cohort nears full accrual, the management team will contact sites to discuss when accrual for that cohort should cease and how to manage any participants still in the screening process. Additional communication will go out to site teams upon full enrollment of each cohort. At this point, the study will pause accrual to allow time for the last women enrolled in the cohort to have their pregnancy outcomes, and for the Interim Review Panel (IRP) to conduct a safety assessment. Accrual pauses are expected to range from 3 to 8 months (with shorter pauses for earlier cohorts). Study sites are encouraged to message about these pauses during stakeholder engagement and community outreach. While no screening or enrollment visits should take place during accrual pauses, prescreening activities may continue, if site staff feel it would be beneficial. Potential participants who are prescreened during this time should be informed that accrual into the next cohort is dependent upon the recommendation of the IRP.

Once the IRP has made a recommendation regarding the subsequent cohort, the management team will communicate this recommendation to site teams in accordance with the IRP SOP. Communication to site teams may include conference calls as well as written communication of the decision. If the recommendation is to begin accrual into the next cohort, an Operational Guidance document that includes an implementation date when sites may open the cohort to accrual will be issued.

3.2.3 Accrual Tips and Reminders:

Before initiating accrual, sites should develop methods for tracking accrual, including monitoring the expected screening to enrollment ratios and how these change over time.

Recruitment methods and venues should be assessed on an ongoing basis. The usefulness or “yield” of various recruitment sources should be tracked over time. Team meetings should be held to identify recruitment sources of participants who screen and enroll and methods for timely evaluation of the usefulness of recruitment methods and venues.

In addition to tracking accrual and recruitment methods, sites should also monitor early screening and enrollment visits for flow, participant comfort and visit length. Accrual pacing should allow for enough time to adjust techniques as necessary to maximize participant retention and buy-in.

Staff responsibilities include the following:

- Designate a Recruitment Coordinator who is responsible for tracking accrual rates and managing recruitment efforts over time. The Recruitment Coordinator, in collaboration with the IoR, should also assist/advise in pacing accrual to ensure that enough time is allowed between participant visits to make any necessary refinements to visit flow in support of participant comfort and efficient visits.
- Hold regular meetings among staff involved in accrual activities – community educators, recruiters, outreach workers, peer educators, others – to discuss current and ongoing strategies
- Engage community representatives on accrual issues and strategies throughout the accrual period

Continue to discuss as a team, over time, the following characteristics of “good candidates” for study participation:

- Likely to be retained for the duration of the study
- Likely to use study product as indicated for the duration of the study

3.2.4 Participant Accrual SOP

Site staff members are responsible for establishing a study-specific participant accrual plan in the form of a Participant Accrual standard operating procedure (SOP); and updating the SOP and recruitment efforts undertaken if needed to meet site-specific accrual goals. The accrual SOP should contain, at minimum, the following elements:

- Methods for tracking accrual
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3 Participant Retention

3.3.1 Retention Definitions

The term “retention” generally refers to completion of follow-up visits and procedures as specified in a study protocol. For MTN-042, two retention measures are planned to be used. Additional retention measures may be defined and used during the study if desired by the Protocol Chairs and/or Protocol Statisticians.

- During the study, retention for each regularly scheduled follow-up visit will be defined based on whether participants complete the visit within the visit window. Participants who complete a regularly scheduled visit within the visit window will be considered ‘retained’ for that visit.
- Overall study retention is calculated as the percentage of the total number of visits completed by all participants (within their allowable visit window) divided by the number of visits expected for all participants. A visit is considered expected for a participant once the allowable window closes, regardless of whether or not a participant is lost to follow-up or terminated early from the study.

As indicated above, participants who do not complete a particular scheduled visit within the allowable window, but then complete the next scheduled visit (including any required make-up procedures that were missed), will not be considered retained for the missed visit. However, they will be considered

retained for the next scheduled visit. Thus, retention rates can fluctuate over time and across visits. Importantly, retention shortfalls can be made up by ensuring that participants return for their next scheduled visit after missing a visit. Aside from the PPO visit, missed visits in MTN-042 are not expected to be made up. More detail on missed visits is available in SSP Section 5.5.5.

The MTN SDMC will post reports on their ATLAS portal presenting retention rates for key study visits designated by the Protocol Team. The SDMC also will generate a final end-of-study retention rate after the study is completed.

3.3.2 Retention Requirements

Each study site will target retention of at least 95% of enrolled study participants for each scheduled follow up visit. The purpose of the 95% retention target is to ensure the accuracy of study results by minimizing bias that can be caused by missing data.

Low retention rates can have serious impacts on the accuracy of the study results because it is unknown whether participants who do not return for scheduled study visits used the study product, liked the product or had adverse effects resulting from use of the product. Low retention is also closely linked with low adherence to the study product. If a participant misses her regularly scheduled visit, she may not have access to the vaginal ring or tablets for the coming month(s). Poor adherence makes it harder to evaluate study objectives. To avoid these problems, and thereby avoid bias in the study results, high participant retention rates must be maintained throughout the study.

3.3.3 Retention SOPs

Site staff members are responsible for establishing a Participant Retention SOP to meet the study retention goal of 95%. This SOP should be re-evaluated and modified in response to lower than anticipated retention rates, or at any other time when retention strategies are modified. It is recommended that this SOP contain the following elements:

- Site-specific retention goals
- Methods for tracking actual retention versus retention goals
- Procedures for completing and updating participant locator information
- Site-specific definition of "adequate" locator information (for purposes of determining participant eligibility)
- Visit reminder methods and timeframes
- Methods and timeframes for identifying when a visit has been missed
- Planned retention methods (e.g. what outreach/locator efforts are taken within 24 hours, 1-3 days, 1 week, or 2 weeks after a missed visit)
- Methods for timely evaluation of the utility of retention methods
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

3.3.4 Obtaining and Updating Locator Information

Successful retention begins with collection of locator information from each study participant. All study participants will be asked to provide locator information during the study screening process, and to continually review/update this information during follow-up. Provision of "adequate" locator information during screening is a study eligibility requirement and each site must specify its definition of adequate locator information in its Participant Retention SOP.

Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention.

Potential locator items include:

- Participant's full name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; work address; work phone number; or e-mail address; daytime and nighttime locations, meeting places and hangouts.
- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.

Note: Although contact information for a participant's current primary partner will likely be useful, contact information for other contacts also should be collected, since the participant's relationship with this partner could change during the study. Locator forms that include partner contact information should also include an indication of whether the participant gives permission to contact the partner.

During the informed consent process and when collecting locator information, study participants must be informed that their locator sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when locator sources are contacted. Arrangements agreed upon with the participant should be documented on the locator form.

Study staff should view every participant contact as an opportunity to update the participant's locator information. When updating locator information, site staff should ascertain whether the information is still current (i.e., rather than simply asking "Has any of your information changed since your last visit?") and also probe for additional information that the participant was not able or willing to provide at previous visits.

Study staff should document on the visit checklist or chart notes that they reviewed the locator information with the participant at every visit. Any updates to the locator form should use standard GCP corrections with initials and date of the staff member making the changes.

3.3.5 Use of a Participant Tracking System

Implementation of a participant tracking system will assist sites in accurately assessing participant retention in the study. This system may be paper-based, or an electronic database. The system chosen must be able to provide the site with a listing of all participants who have missed scheduled study visits.

It is expected that each site will have specific staff members designated to retention efforts and the maintenance of this system to track participant visits from the day that accrual starts.

The participant tracking system should be able to inform the site team of the following:

- Number of participants who are expected in the next week/day (to allow for visit reminders to be made in the timeframe specified in site Retention SOP).
- Participants who have missed their scheduled visit and are still within the visit window (ideally so that participants whose window is about to close can be prioritized for tracing).
- Participants who have missed their scheduled visit and need study product(s) to be replaced.
- Participants who have missed their scheduled visit and the window has closed (and a missed visit CRF is needed).

3.3.6 Retention Tips

Some general strategies for maximizing participant retention are as follows:

- Emphasize the value of the participant's involvement in the study during the study informed consent process and subsequently at follow-up visits. When a participant completes scheduled visits, acknowledge and compliment her commitment, time, and effort devoted to the study.

- Create and maintain a mother/baby friendly clinic space to ensure a comfortable space for participants while attending clinic visits.
- Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary. Make use of all information collected on the participant's locator form. Even if a locator source is not useful/successful on one occasion, try it again later.
- Schedule all follow-up visits up to her planned delivery date at the participant's Enrollment Visit. Schedule all post-pregnancy outcome visits at the PPO. At each follow-up visit, confirm the scheduling of the next visit and give the participant an appointment card with the scheduled visit date and time noted. When the participant is getting close to her delivery date, make a plan to check in often with the participant.
- Prepare a calendar of scheduled visits for each enrolled participant, or offer a planner/calendar as an incentive and note all study appointments in the planner/calendar. Note the dates of all scheduled visits in the participant's file for easy reference.
- Strategize ways within the clinic to ensure efficiency of study visits; keeping visits short and at a time that is convenient. Formal visit flow assessments should be used periodically to identify inefficiencies.
- Provide snacks and activities to keep the participants entertained while waiting for visit procedures.
- Provide childcare for participants when needed.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits earlier in the allowable visit window to allow maximum time for re-contact and re-scheduling if needed.
- Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window. Organize daily caseloads and work assignments based on these priorities.
- Make use of all available contact methods (e.g. Whatsapp/text messages, phone, mail, home visits, street outreach, e-mail/internet).
- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study.
- Inform local service providers who interact with the local study population about the study, so that they also can express their support for the study.
- Host gatherings, parties and/or other social events for participants. Host social, educational, and/or other events for participants' partners and/or other family members.
- Use tracking systems to identify when participants' scheduled visits are due and/or overdue. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits, such as SMS messages or phone calls.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the Participant Retention SOP until contact is made.

3.3.7 Participants Who Voluntarily Discontinue Study Participation

If a participant wishes to discontinue participation in the study, her wishes must be respected. The participant should be advised that she is always welcome to come back if she wishes. Refer to SSP section 5.11 (Voluntary Withdrawal of Study Participation) for procedures to be followed for participants who prematurely discontinue study participation.