MTN-042 Operational Guidance #05:
Initiation of Cohort 3 Accrual

This operational guidance document provides instruction to sites regarding initiation of Cohort 3 accrual (i.e., enrollment).

The MTN-042 Interim Review Panel reviewed safety and primary outcome data from MTN-042 Cohort 2 in June 2022. The IRP noted no safety concerns and recommended that the study proceed with enrollment of the next gestational age cohort as planned. A summary that includes these recommendations from the IRP has been issued with this Operational Guidance document and should be submitted to IRB/EC(s) and Drug Regulatory Agencies that are overseeing the conduct of MTN-042.

Cohort 3 will enroll 250 women in the gestational age range of 12 0/7 weeks – 29 6/7 weeks, and their infants once born. Per protocol, accrual of Cohort 3 should be complete within 7-9 months of the date of the first Cohort 3 enrollment at the first site.

Once all items on the site's MTN-042 Cohort 3 Readiness Checklist have been completed and a signed checklist is issued by FHI 360, the site may initiate enrollment of participants for Cohort 3. Note that prescreening or screening activities may take place prior completion of the readiness checklist, but no Cohort 3 enrollment visits should take place prior to receiving a signed checklist.

Potential Cohort 3 participants should be informed verbally of the Cohort 2 IRP safety review and their recommendations before enrollment. Furthermore, maternal participants in Cohort 2 should be informed of the outcome of the Cohort 2 IRP safety review. This can be completed at the next routinely scheduled infant visit (i.e., the Month 6 or Month 12 visit) or over the phone, per the discretion and preference of the site.

Below are suggested counseling messages to provide verbally to participants. Should sites want to develop supplemental written materials to facilitate provision of this information, please notify FHI 360. As to not delay availability of this information, sites should proceed to counsel participants verbally while waiting on IRB/EC approvals of any written materials. Sites should document provision of this information to participants on visit checklists and/or chart notes.

Cohort 2 IRP Safety Review - Counseling Messages

- The MTN-042 Interim Review Panel (IRP) reviewed safety and pregnancy outcome data from the 2nd group of women enrolled in the study (Cohort 2) in June 2022. This was a planned review that is part of the study design.
- The IRP is an external group of subject matter experts from North America and Sub-Saharan Africa. There are 7 members from the fields of obstetrics/gynecology, pediatrics, public health, ethics, and statistics.
- **The IRP noted no safety concerns and recommended that the study move forward as planned to enroll the next group of women (Cohort 3).** Women in Cohort 3 will be slightly earlier in their pregnancy at enrollment, between 12-29 weeks.
- Additional details about Cohort 2 and the safety data reviewed are as follows:
    - Women in Cohort 2 were between 30-35 weeks pregnant when they enrolled. The review included safety data through the time of their delivery.
    - Cohort 2 enrolled 157 participants across 4 study sites:
        - Kampala, Uganda: 42 participants

        - Johannesburg, South Africa: 28 participants
        - Chitungwiza, Zimbabwe: 47 participants
        - Blantyre, Malawi: 40 participants
    - A total of 106 participants were randomized to the dapivirine vaginal ring and 51 to oral PrEP (Truvada). Women used the study products they were assigned until delivery.
    - Pregnancy outcome data was available from 154 women enrolled in Cohort 2.
        - Most women had live births (99%). There was one stillbirth.
        - There were 10 preterm births (i.e., delivery before 37 weeks).
        - The frequency of stillbirth and preterm birth was lower than the rate generally observed in the communities where the study is being conducted.
    - Overall, pregnancy complications were rare and lower than the rate generally observed in the study communities.
    - All serious maternal and infant events were considered not related to the study products by investigators.
    - The rate of confirmed congenital anomalies is similar to what is generally observed in the study communities.
- In summary, in this second cohort of pregnant women using the dapivirine vaginal ring or oral PrEP (Truvada) late in pregnancy, adverse pregnancy outcomes, pregnancy complications, and adverse infant outcomes were uncommon and were similar to or lower than rates observed in the communities where the study is being conducted and were comparable to rates observed in the first cohort where study product was initiated in late pregnancy.
- What questions or concerns do you have?

All Operational Guidance documents must be printed and filed with study essential documents.

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