MATRIX-002 Operational Guidance # 03

Operational Guidance Category:

☒ Clinical Procedures ☐ Pharmacy ☐ Laboratory ☐ Other, specify:

Brief Description:

This Operational Guidance outlines the MATRIX-002 Management Team's decision **not to allow film replacement for participants who experience film expulsions**, and the rationale thereof.

Background:

- At the fully enrolled Pitt site, 11 out of the 20 enrolled participants reported at least one instance of film expulsion (2 persons reported 2 instances each).
  - No replacement film was provided to any of the participants that reported expulsions.
- At the KEMRI site, 1 of 6 participants enrolled to date reported film expulsion.
  - No replacement film was provided.
- At the Wits RHI site, 1 of 3 participants enrolled to date reported film expulsion.
  - Study staff, in consultation with protocol co-chair, provided a replacement film for the participant to insert due to concerns about potential inability to collect adequate/sufficient data on acceptability endpoints.
- Most expulsions occurred early on (i.e., within the first couple of days of product use).
- Important questions arose from the instance of expulsion described above for the Wits RHI site, which warranted the MATRIX-002 Management Team to discuss how best to handle this across all MATRIX-002 sites. The discussion took place on 19 Apr 2024 and is detailed below.

Decision considerations:

- Protocol provision for replacement film to participants
  - Not explicitly prohibited, but neither is allowed (explicitly or implicitly).
    - Primary and secondary objectives: "To assess acceptability and safety when administered vaginally once monthly for two months."
    - Section 6.1: "Each participant will receive one dose per month for two consecutive months, for a total of 2 doses of placebo vaginal film."
    - Per SIC - Key Information section: "You would be randomly assigned to one of the two films and asked to use (self-insert) the assigned film two times (approximately one month apart)"
    - Per SIC - Why is this research being done?: "This study will allow participants to use one of the placebo vaginal films twice during their participation."
- Ability to achieve the study objectives if participants experience film expulsion within the first couple of days of product use
  - Film expulsions are only explicitly tied to one exploratory endpoint of acceptability.

        - Exploratory acceptability endpoint: "Experience and comfort with inserted vaginal film (e.g., expulsions, leakage, awareness of film during daily activities)"
        - Per Sections 7.6.1 and 10.3, exploratory acceptability endpoint data on "concerns and comfort with film use" collected at 24-72hr, 1-week and 2-week visits.
    - Per SBR report, participants at the Pitt site who experienced film expulsions early still provided rich qualitative data.
        - SBR CRFs have been modified to add skip patterns applicable to ppts who experience film expulsions, with an Expulsion Log added to REDCap (see SBR Operational Guidance #2).
- Product Developer guidance
    - Due to the dissolving nature of these vaginal films, some dissolved material will remain in the vagina even if expulsion occurs early. While only placebo, this can confound the secondary safety endpoint data unless the "extra" material can be accounted for.
    - There is limited product supply, so there is a risk of not having enough film for the study if film replacement occurs unless the current process is revised.
- Allowing provision of replacement film would need to be implemented as a protocol amendment, not as a clarification memo or through SSP/SOP revisions and would add considerable operational complexity.

Conclusion/Site Guidance:

Given the above considerations, the following was determined: Sites should **not** provide participants with replacement film in case of expulsion (regardless of time passed after insertion).

- If a participant reports a film expulsion, continue with study visits/procedures per protocol
- SBR Operational Guidance #2, Implementation of the PRN Expulsion Log offers additional details.

Operational Guidance memos, once signed, must be distributed to MATRIX sites via email. Sites are responsible for ensuring that appropriate staff review and understand the content of each memo and file the memo with their essential documents. Operational Guidance memos must also be posted to the appropriate MATRIX webpage. As per SSP section 13, the memos are official study documentation and will be considered an official part of the MATRIX SSP Manual. The Operational Memo becomes effective the date it is signed.

DocuSigned by:

Nyaradzo Mgodi

Signer Name: Nyaradzo Mgodi
Signing Reason: I approve this document
Signing Time: 5/1/2024 | 12:52:54 AM PDT

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5/1/2024

Nyaradzo M. Mgodi, MBChB, MMed
Protocol Co-Chair

Date