# MATRIX Investigators Meeting Griffithsin Fast Dissolving Insert

Population Council
Center for Biomedical Research
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PEPFAR

USAID
FROM THE AMERICAN PEOPLE

MATRIX
Advancing R&D of Innovative
HIV Prevention Products for Women

POPULATION COUNCIL
Ideas. Evidence. Impact.

# What Are We Aiming For?

## On-demand Non-ARV Product


- Option desired by users
- Reduced stigma
- Low risk of HIV resistance
- Minimal healthcare system burden
- Complement HIV prevention products available and under development

**ASPIRATIONAL GOAL** → Alternative to condoms
De-medicalized prevention

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# Why and What is Griffithsin (GRFT)?

- Non-ARV with broad antiviral properties
- Protein discovered in algae — now bioengineered
- Promising preclinical and early clinical data
- Highly potent against HIV — effective at sub-nanomolar concentrations
- Topically-active/non-systemic
  - Likely safe during pregnancy/breastfeeding
  - Anticipate few to no side effects
  - Less concern about resistance

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# Why Fast-dissolving Insert (FDI)?

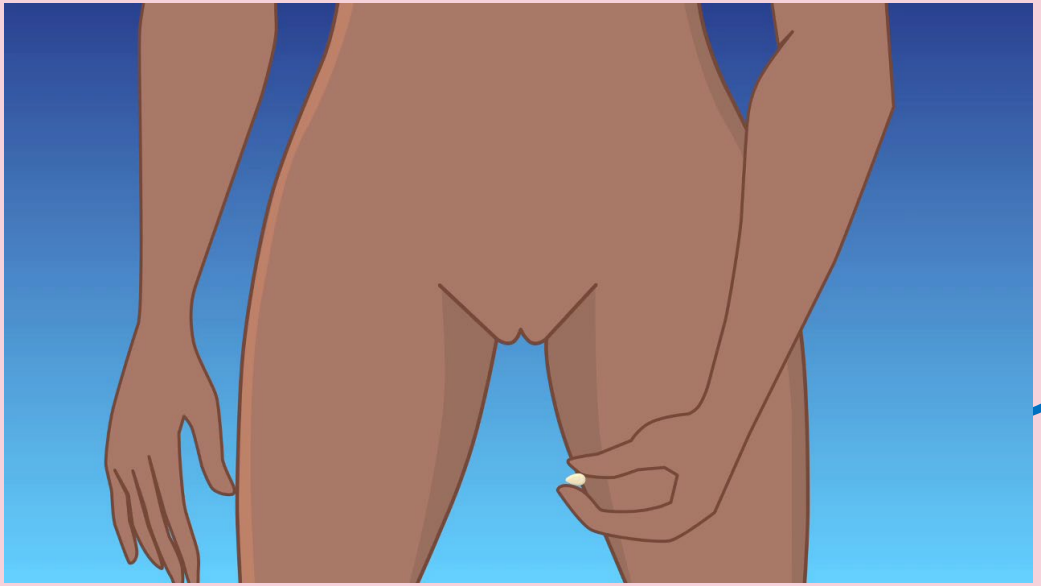
## User Acceptance

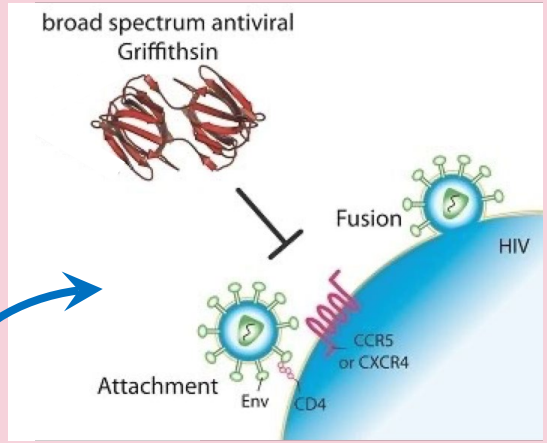
- Endorsed as highly desired by end-users
- Discreet, easy to use, portable
- Anticipate minimal impact on vaginal discharge → lower risk of partner detection

## Product Characteristics

- Relatively simple manufacturing and capacity to scale-up production
- Optimal for wide distribution

# How Does It Work Exactly?






*Lusvarghi et al. 2016*

**GRFT binds irreversibly to the outside of HIV and prevents entry into healthy cells**

Preclinical studies suggest GRFT also inhibits Herpes Simplex virus (HSV-2) and Human Papillomavirus infection (HPV)

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# Our Product

- Quick onset (<20 minutes)
- **12+** hours duration of protection
- Portable, stable at room temperature
- No inserter
  - Discreet placement with finger
  - Reduced waste/cost
- Could possibly use with other prevention methods
- Ideal for eventual distribution over the counter

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# GRFT FDI Development Prior to MATRIX

## What We Did

4mg GRFT gel

- Completed necessary preclinical safety/ toxicology studies
- Conducted first-in-human trial of daily dosing for 14 days

4mg FDI

- Developed FDI prototype
- Tested FDIs in non-human primates (NHPs) 14 day

## What We Learned

- 4mg GRFT gel appears safe and tolerable with no systemic absorption when used daily vaginally for 14 days
- Clinical, animal and laboratory studies suggest protection for at least 4 hours after insertion
- GRFT FDIs manufactured to rapidly disintegrate

# GRFT Fast Dissolving Insert Project Overview

Year 1 | Year 2 | Year 3 | Year 4 | Year 5

- Goals within MATRIX
  - Secure methods for scalable GRFT production
  - Produce FDIs for preclinical studies and clinical trials
  - Evaluate higher GRFT doses to extend window of protection
  - Complete needed safety/toxicology studies to enable advancing to human studies
  - Conduct Phase 1 clinical trial of vaginal insert in US and SSA for HIV prevention

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# GRFT FDI Progress To Date Under MATRIX

Year 1 | Year 2

## What We Did

To support preclinical studies:

- Manufactured FDIs
- Conducted stability testing
- Developed analytical methods

Completed* pre-clinical studies:

- Non-GLP FDI disintegration, rabbits
- GLP 28-d repeated dose toxicity, rats
- Non-GLP single administration, NHPs

*in process of completing sample analysis

## What We Learned

- FDIs stable for up to 3 months under accelerated conditions
- FDIs disintegrate rapidly in preclinical studies
- No safety concerns with higher dose formulations (up to 12mg clinical dose equivalent)

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# NHP Single Administration Study

**Median GRFT concentrations in macaque CVLs**

| Time point | GRFT FDI | Median (6 animals/group/ time point) |
|---|---|---|
| 1h | 1mg GRFT | 180356 |
| | 3mg GRFT | 695175 |
| 4h | 1mg GRFT | 121208 |
| | 3mg GRFT | 436900 |
| 8h | 1mg GRFT | 40146 |
| | 3mg GRFT | 103359 |
| 12h | 1mg GRFT | 5528 |
| | 3mg GRFT | 119239 |
| 24h | 1mg GRFT | 1461 |
| | 3mg GRFT | 23096 |
| 48h | 1mg GRFT | 141.8 |
| | 3mg GRFT | 80.95 |
| 72h | 1mg GRFT | 171.9 |
| | 3mg GRFT | 408.6 |

*above concentration associated with protection against SHIV challenge in prior NHP study (> 51559 ng/mL)

For 3mg FDI (equivalent to 12mg clinical dose): GRFT CVL concentrations at 12 hours post-insertion above concentrations associated with efficacy in NHP

→ Suggestive of ≥**12 hours** of protection

Preliminary Plasma GRFT concentrations 1–72 hours post FDI insertion all below level of quantification

→ Suggestive of **minimal** systemic absorption

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# Challenge: Quality GRFT source

- Our initial batch of GRFT produced by bacterial fermentation was highly oxidized (17%)

→ Secure new high-quality supplier to reduce risk

- Conducted renewed GRFT supplier search
- Redesigned preclinical rat toxicity study to include both plant and bacterial-sourced GRFT
- Paused several activities and extended project timeline to ensure GRFT source is secured prior to any further clinical study preparations

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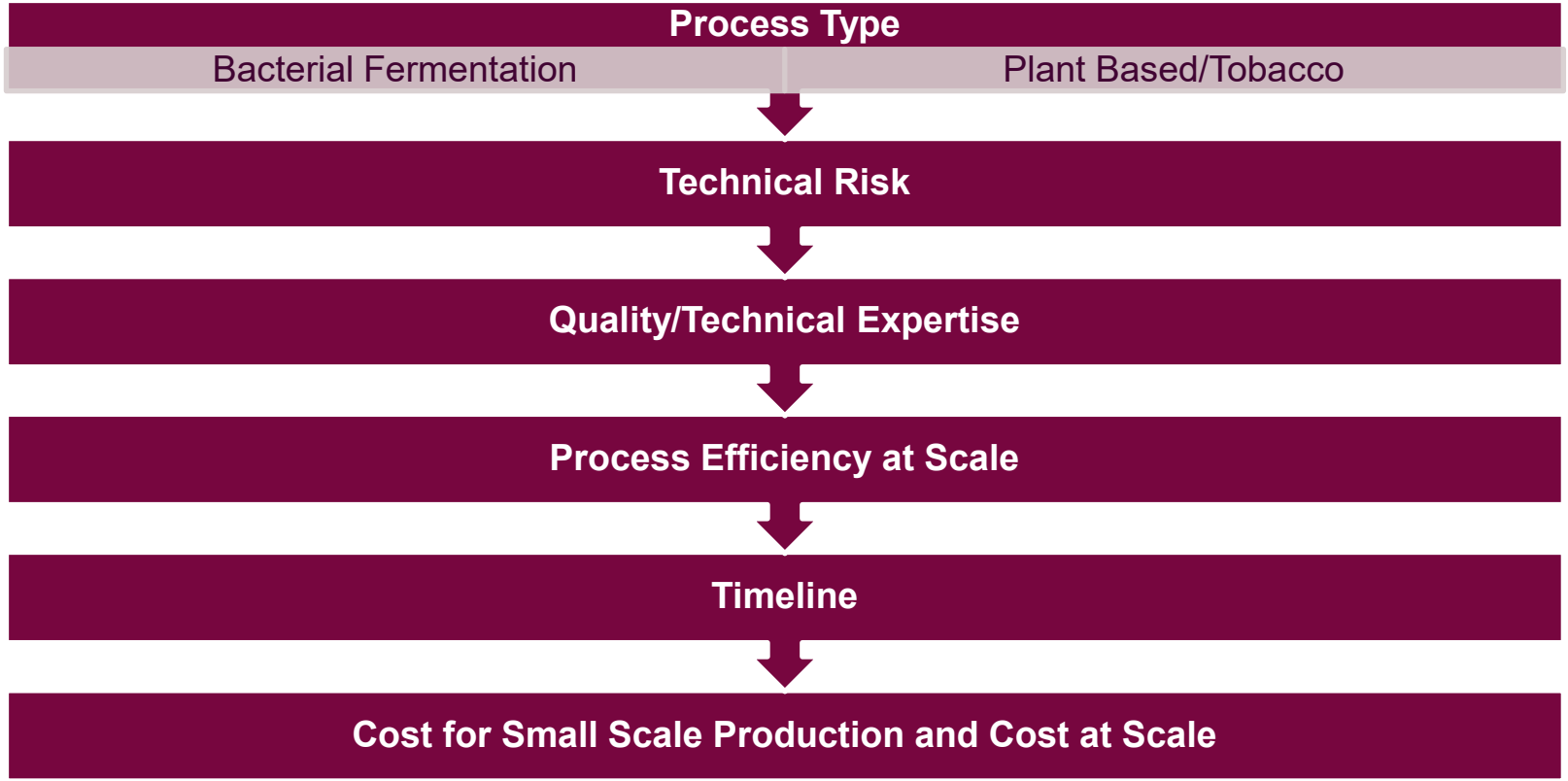
# Algorithm for Determining GRFT Supplier

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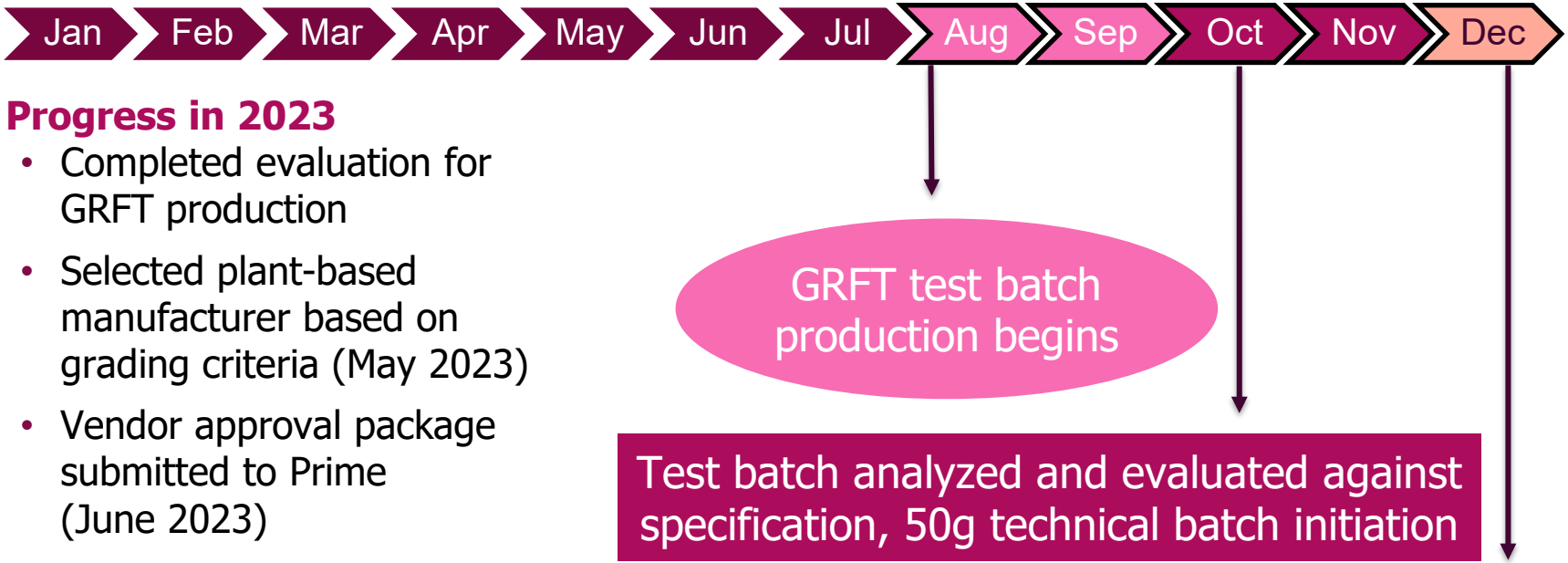
# Procurement of GRFT




**Progress in 2023**

- Completed evaluation for GRFT production
- Selected plant-based manufacturer based on grading criteria (May 2023)
- Vendor approval package submitted to Prime (June 2023)
- Received USAID vendor approval for procurement and contract executed (August 2023)

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# GRFT FDI Next Steps

- → Manufacture and confirm quality of GRFT from new supplier
- → Complete safety/toxicology evaluation (rabbit vaginal irritation study)
- → Produce FDIs and prepare protocol for Phase 1 clinical trial
- → Submit to FDA

**START PHASE 1 TRIAL**
**Q4 2024**
**→ PK, Safety, Acceptability**

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# Acknowledgements

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*The contents in this presentation are those of the presenter and do not necessarily reflect the view of the U.S. President's Emergency Plan for AIDS Relief, the U.S. Agency for International Development or the U.S. Government.*