An Update on FACTS 001

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FACTS Protocol Chair

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FACTS 001

A Phase III, Multi-Centre, Randomised Controlled Trial to Assess the Safety and Effectiveness of the Vaginal Microbicide 1% Tenofovir Gel in the Prevention of HIV-1 Infection in Women, and to Examine Effects of the Microbicide on the Incidence of HSV-2 Infection

Rationale for confirmatory study

HIV Protection	• Confirm CAPRISA 004 results i.e. 39% (CI: 6,60), p=0.017
Safety	• Safety of tenofovir gel when used as BAT 24 regimen.
Generalizability	•CAPRISA 004 included 899 women in KZN. Effectiveness in diverse populations required.
HSV-2	• Confirm CAPRISA data on effectiveness for prevention of HSV-2

The FACTS Consortium

WITS REPRODUCTIVE HEALTH & HIV INSTITUTE

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FACTS sites in South Africa
Soshanguve
GaRankuwa
Rustenburg
Tembisa
Soweto
Yeoville
Ladysmith
Pietermaritzburg
Cape Town

Primary objective

- To evaluate the safety and effectiveness of 1% tenofovir gel applied intravaginally in preventing sexually transmitted HIV-1 infection in women.

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Secondary objectives

- To evaluate the effectiveness of 1% tenofovir gel applied intravaginally in preventing sexually transmitted HSV-2 infection in women
- To ascertain the impact of 1% tenofovir gel on pregnancy outcomes
- To investigate the effectiveness of 1% tenofovir gel according to levels of gel and condom use
- To seek evidence of incident HIV-1 infections unmasked by product withdrawal
- In women who become infected with HIV-1 during the trial:
  - To assess the impact, if any, of 1% tenofovir gel on HIV-1 viral load set point
  - To assess tenofovir resistance

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Protocol changes V3 to V4

- 2200 women aged 18-30 years enrolled at 6 sites in South Africa
- 88 endpoints
- Minimum 15 months on product maximum 24 months

- 2900 women aged 18 – 40 years (approx. 300 women aged 31-40 for safety)
- 118 endpoints
- This will increase the power of the study to detect an effect, at 1-sided alpha=0.025, of 90% for a 45% reduction in risk for active gel relative to placebo gel
- Minimum 16 months on product maximum 27 months

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Version 4 approval

- Submitted to MCC April 2012
  - Responded to queries July 2012
  - Further responses submitted
  - Approval pending

- Submitted to all EC
  - All approved

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Achievements to date

- Rapid initiation of 9 South African sites
  - 295 staff across all sites
  - 18 staff in CORE
- Accrual initiated October 2011
- Version 4 training complete
- Additional training: social science, VIRA, adherence, adherence IDI, GPP
- Adherence focus

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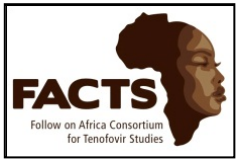
Accrual

Data provided by ACRO from sites 21 September 2012			
Site Name	Number Screened	Number Enrolled	Screen failures
AURUM RTB	339	144	143
AURUM Thembisa	356	134	207
DTHF	227	153	74
MATCH	309	176	123
Medunsa	200	100	100
PHRU	664	280	250
QM	237	133	88
Setshaba	466	316	142
WRHI	467	259	189
TOTAL	3265	1695	1316

Accrual expected to complete March-April 2013

Enhancing and Measuring Adherence in FACTS001



Focus on Adherence

- Optimise gel use and gel use assessment
- Reduce factors which dilute adherence viz. pregnancy, missed visits

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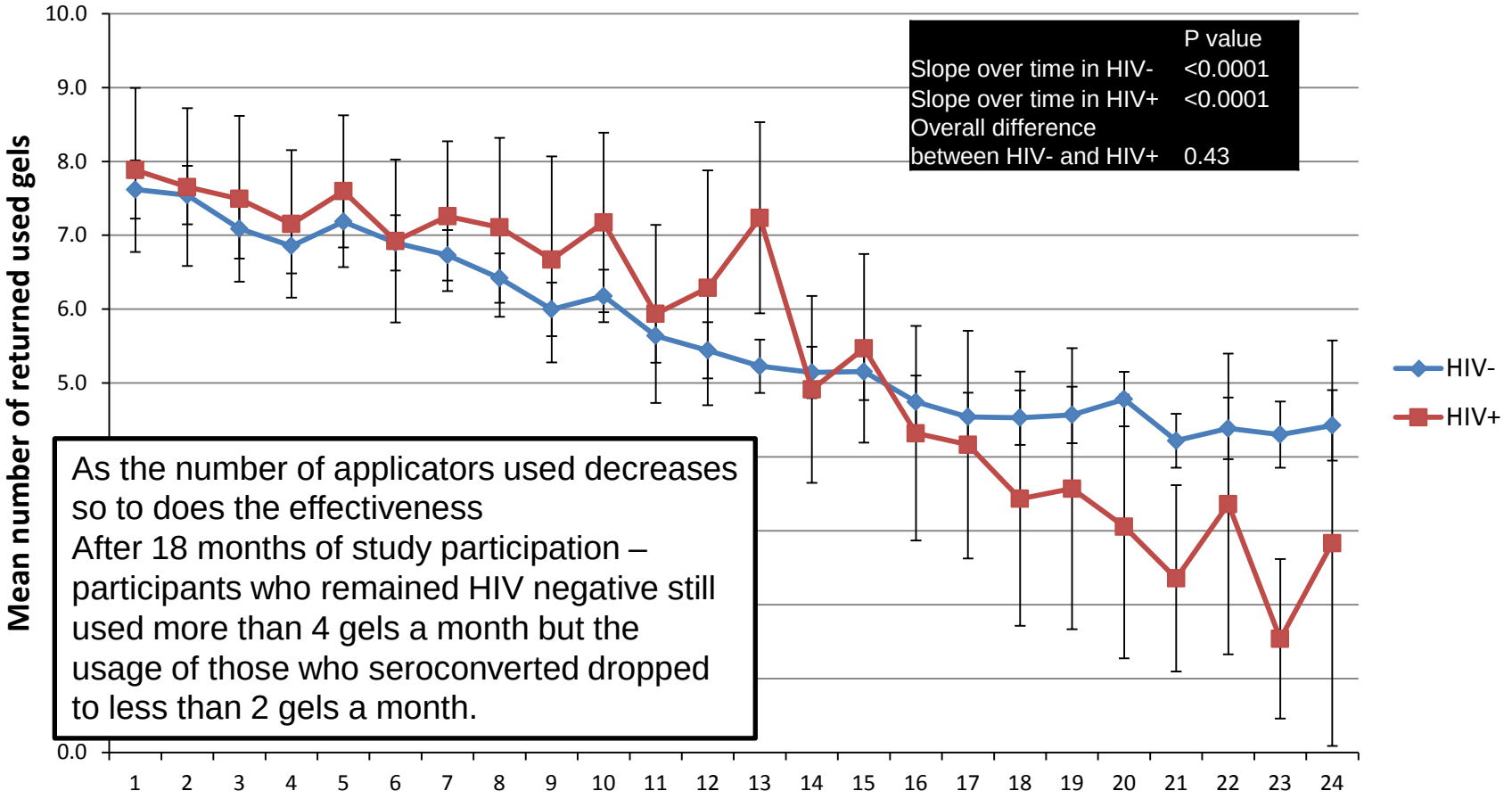
Relationship between effectiveness & mean number of returned empty applicators



Effectiveness **47%** **50%** **47%** **39%**

What is our approach informed by?

- CAPRISA: Visual inspection of returned applicators (VIRA)
- MDP301: Coital Diaries, gel returns, CRFs,
- VOICE C: serial in depth interviews on adherence and barriers to use

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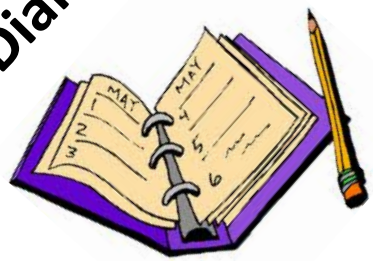
FACTS 001 Adherence Measurements

3. Triangulation Interview

1. Pharmacy: Visual Inspection of Return Applicator

2. Sex Diaries



Adherence checks

- Coital Diary
  - Sex, Gel and Condom use and timing
  - Reviewed at monthly visits
  - Assists in the Sexual Behavior and Gel Use CRF
- IDI
  - Purpose: Explore adherence, barriers and facilitators, experiences of clinical trial and gel use, partnerships
  - Random sample of 145 participants
  - Interviewed 3 x during the trial (M3, M6, Exit)
- All administered by social science interviewers

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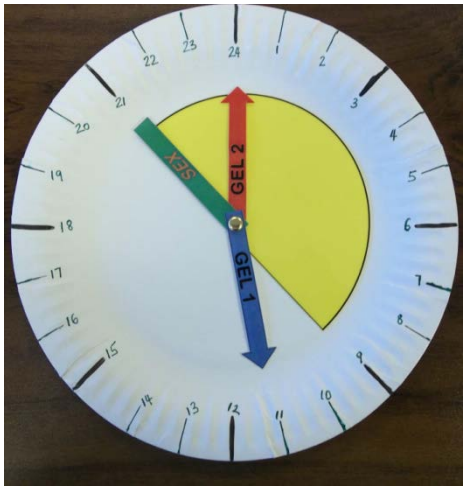
Supporting Adherence



- **Client-Centred Counseling (motivational interviewing)**
  - Participant-centred, counsellor directed approach with feedback loop to support adherence to product use
- **Waiting Room Observations**
  - Identify issues, rumours and concerns of participants—to facilitate development of messages and responses as needed
- **Practical tools to support gel use and dosing understanding**
  - Eg. Paper plate 24-hour clocks made by participants to use at home and reinforce understanding of BAT 24 dosing
- **Motivational Text Messages (In planning phase)**

Visual Inspection of Returned Applicators (VIRA)

- **Why visual Inspection of Applicators ?**
  - Participants return used and unused applicators
  - May feel an obligation to show use even if not used
  - Visual inspection will contribute to verifying use
- **How?**
  - Used applicators counted and entered onto the Study Product Returns Inventory Log
  - Returned used product immediately sent for visual inspection and documentation of visual inspections procedures by trained inspector
  - Counts from the visual inspection
  - QC checks by pharmacist

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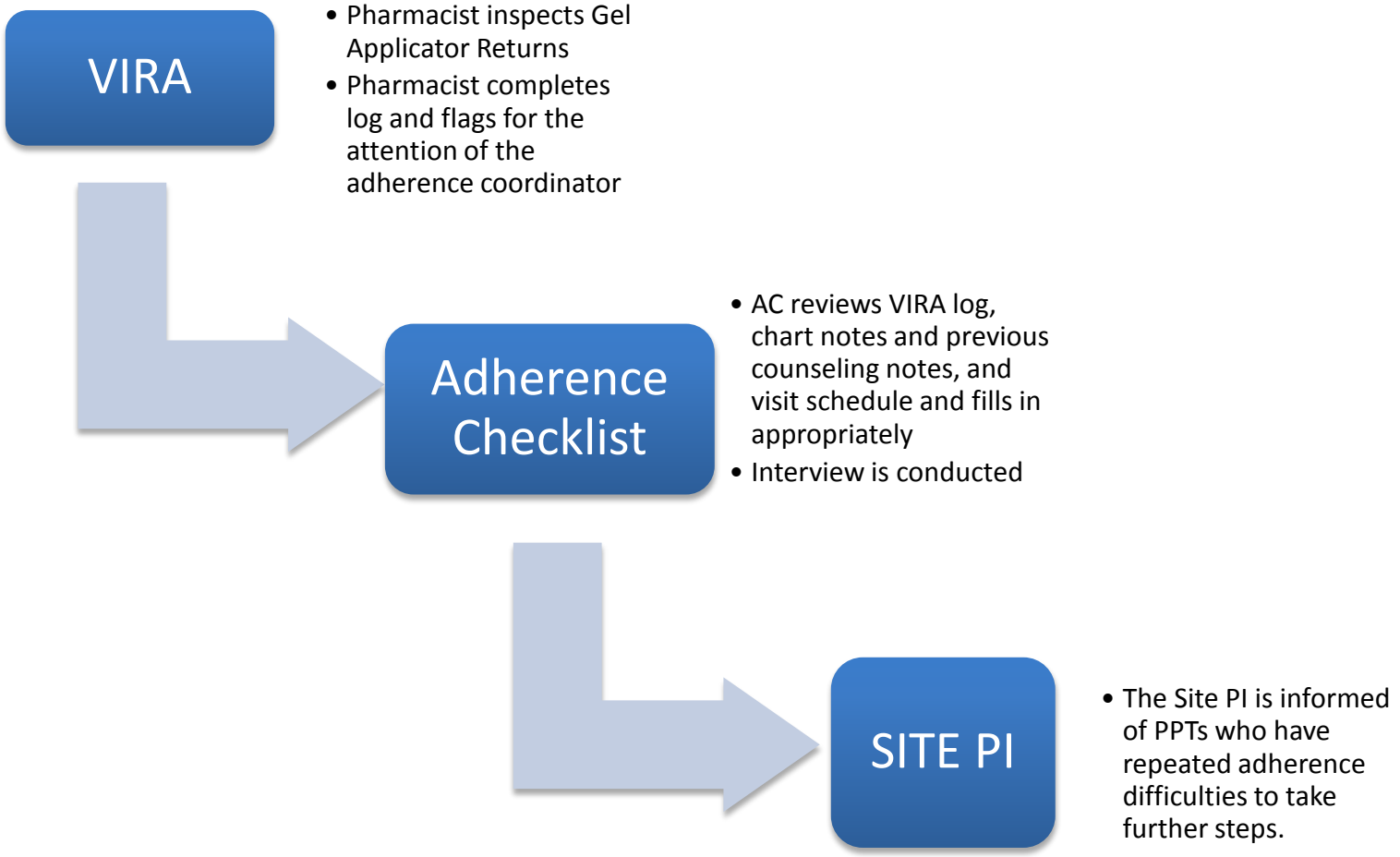
What's appears used?

Challenges

- Wiping and washing
- Sniff test
- Blood stained
- Gel only at tip of applicators

Feedback Loop



UVL: The Concept

‘UV light inspection of applicators had the highest accuracy in correctly assessing applicator insertion status’.

Thomas R. Moench et al. (2012). Evaluation of Microbicide Gel Adherence Monitoring Methods. *Sex Trans Dis*

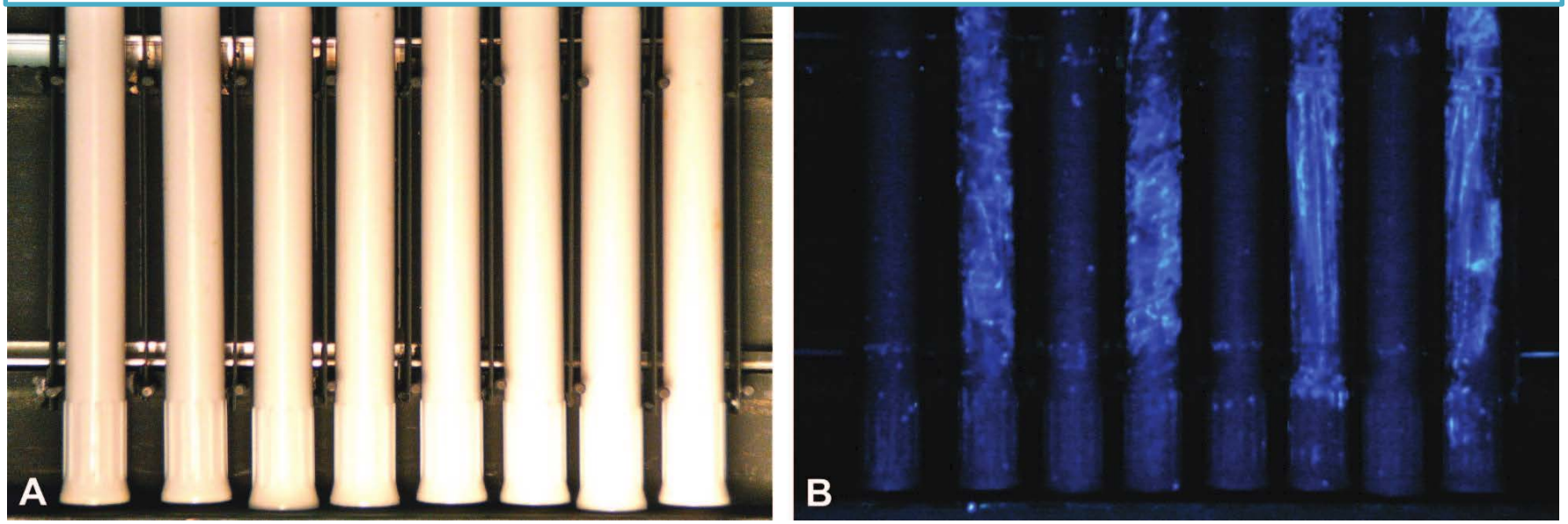
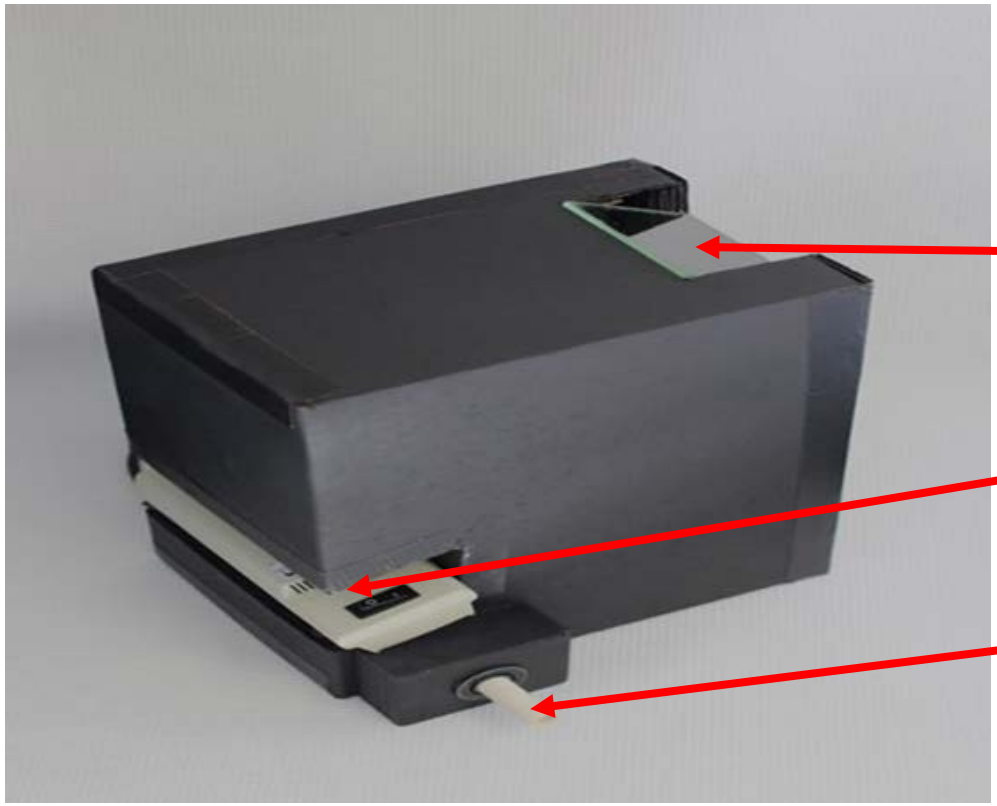


Figure 3. Sham-inserted applicators alternating with vaginally inserted applicators obtained during consecutive daily applications of HEC gel. A, Visible light illumination. B, Ultraviolet light illumination.

How does it work?

- Body fluids fluoresce when viewed using ultraviolet light (cervicovaginal secretions, semen, blood)



Viewing filter

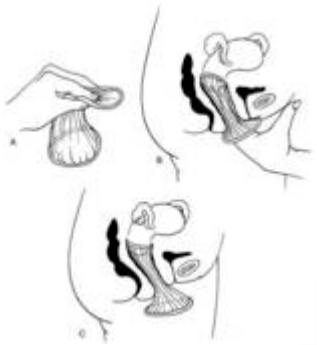
UV Light

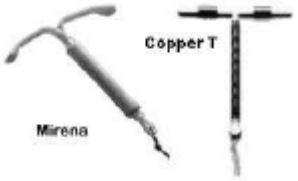
Applicator inserted for viewing

Summary of FACTS 001 adherence activities

- Strategies for enhancing adherence
  - Motivational Interviewing (counselling)
  - Checklist and feedback loop integrating VIRA

- Strategies for measurement and monitoring
  - All participants CRF monthly
  - All participants VIRA monthly
    - UVL pending – start date 2013 (?)
  - Coital diaries monthly as additional detailed check measure
  - IDI on a sample





Pregnancy and Contraception in FACTS 001

Limited method mix – implications for trials

Total no. of pregnancies	COC	Injectable
37	35	2

CSC report 21/09/2012

- Suggestion that women are being offered COC because of concerns of HIV risk with injectable, but consequence is increased pregnancies on COC

- Did participants understand the requirement not to fall pregnant – many are choosing to keep baby
  - 19 currently ongoing (51%)

Impact on trial

- Pregnancy incidence 7% currently

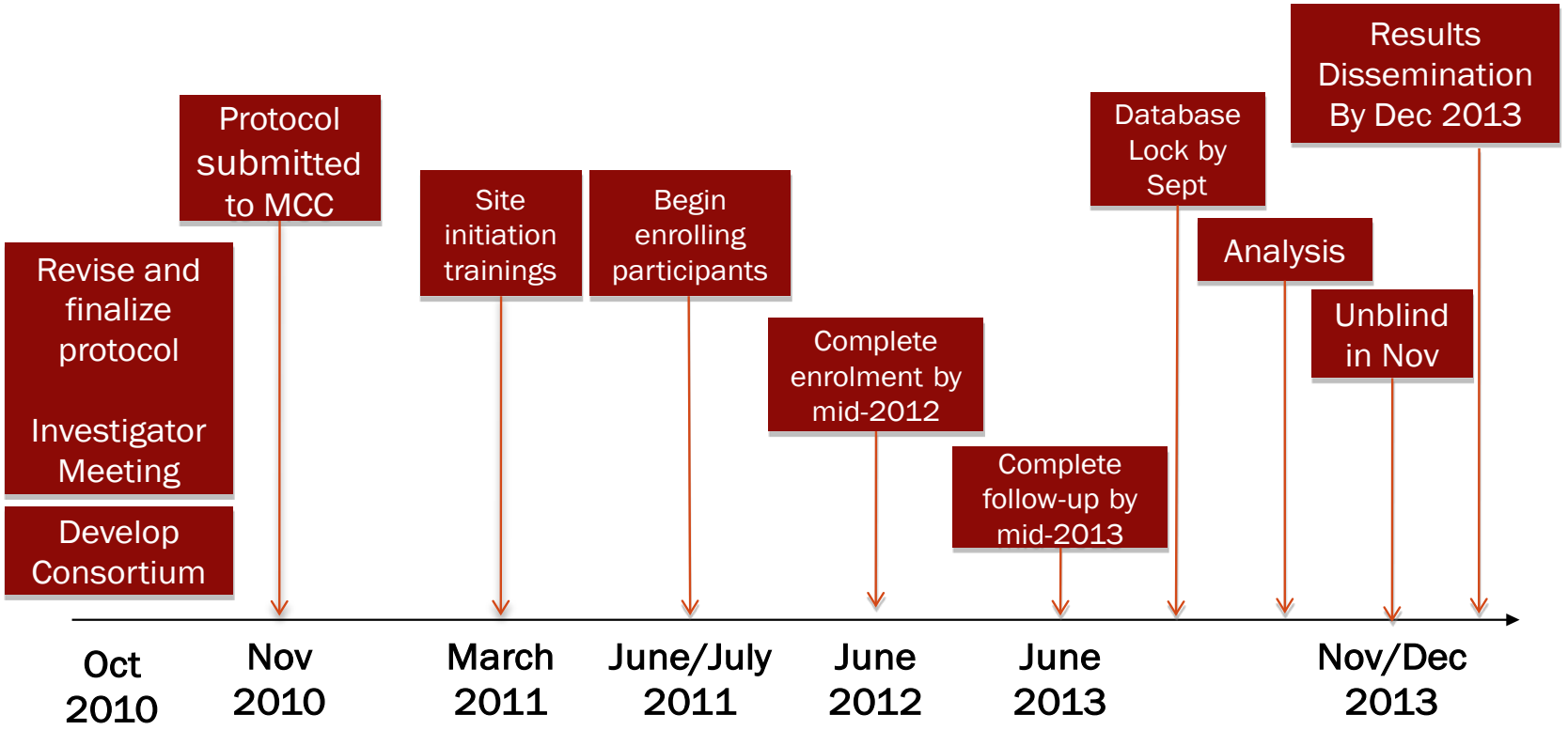
- Time off study product
  - Mean 50 days off product for those that have resumed following pregnancy (n=10)
  - Mean 104 days for those continuing their pregnancy (n=21)

Expanding contraception options

1. Sites provided with contraception counselling guidelines
2. Sites asked to update pregnancy prevention SOP to define strategies beyond contraception for reducing pregnancy in the trial
    - Take into account screening assessments, fertility intentions, as well as contraceptive methods
3. IUCD training for all sites
    - Start with sites with large number of pregnancies and/or high numbers of COC
    - Educate participants on IUCDs
    - Offer IUCDs to all eligible participants
    - Train all clinical staff

Last Reflection

Original FACTS 001 timeline



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Thank you

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