

# NIH and Microbicide Trials Network Activities

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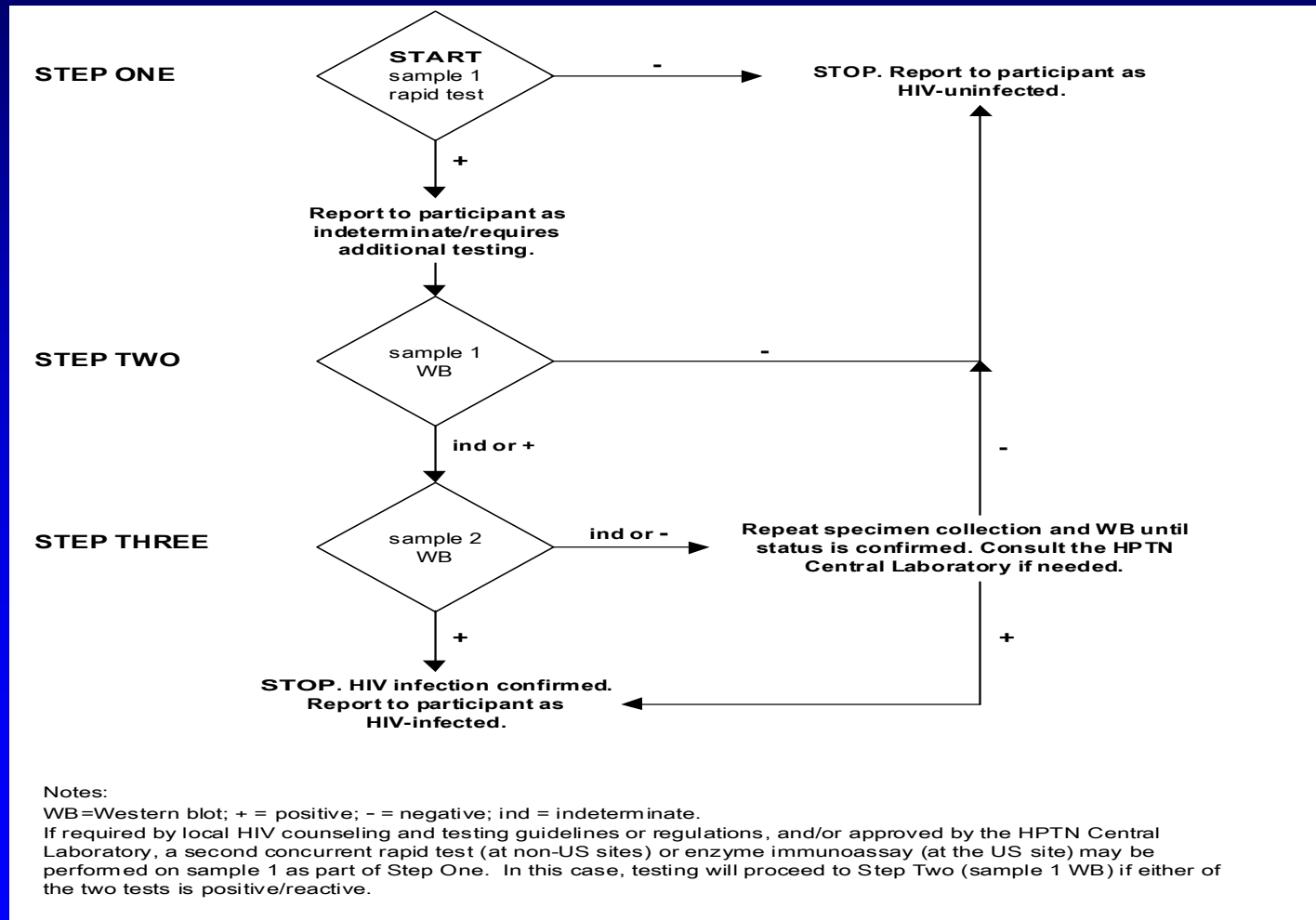
# Overview – NIH Clinical Trials Program in Microbicides

- Estimation of HIV seroincidence
  - » Validation of endpoints at sites and centrally
  - » Preparedness studies to estimate incidence in the context of STD treatment and provision of condoms
- Pregnancy
  - » How have we assessed pregnancy incidences and outcomes in preparation for microbicides effectiveness studies?
  - » How pregnancy incidence is monitored in current effectiveness trials.
  - » What we have learned.
  - » What we plan to do in the future.

# HIV Endpoint Validation

- HIV endpoint integrity recognized as integral to microbicide protocol implementation quality
  - » All site laboratories required to complete validation studies (100HIV+, 100 HIV-) and rapid EIA tests and western blot confirmation tests prior to site activation
  - » HIV testing algorithm for seroconverters developed
  - » All seroconversions and 10% of seronegative women cases confirmed in network laboratory centrally

# HIV Antibody Testing Algorithm for Primary Endpoint Ascertainment at Follow-up Visits



# Estimation of Seroincidence: HIV NET 016a

- 2016 HIV - women enrolled in observational study
- Intense condom counseling provided in 5 sessions over 2 months
- Sites includes Blantyre and Lilongwe in Malawi and Harare, Zimbabwe
- 113 seroconversions; 4.7 per 100 women years of follow-up
- 2,429 woman years of follow-up

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Ref: Kumwenda, et al. Sexually Transmitted Diseases 2006; 33:646

# HIV NET 016a

## Eligibility Criteria

- $\geq 18$  years old
- Willing to give informed consent
- Sexually active
- HIV-1 uninfected
- Willing to adhere to study schedule

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Ref: Kumwenda, et al. Sexually Transmitted Diseases 2006; 33:646

# HIV NET 016a:

## HIV Incidence and Behavior

- HIV incidence among women in Malawi and Zimbabwe high (4.6 per 100 woman-years of follow-up)
- Most women married (93%), and 80% reported vaginal sex in past 2 weeks
- Condom usage low at baseline (16%)
- Any sexually transmitted infection (Chlamydia, Gonorrhea, Syphilis, Trichomoniasis, Genital ulcer) present in only 15%
- 48% using hormonal birth control

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# Multivariate Factors Associated with HIV-1 Seroconversion All Sites Combined

| <u>Factor</u>                         | <u>Hazard Ratio (HR)</u><br><u>(95% CI)</u> | <u>P-value</u> |
|---------------------------------------|---|----------------|
| Age <30                               | 2.1 (1.05, 4.0)                             | 0.04           |
| Some education                        | 1.3 (1.02, 1.7)                             | 0.03           |
| Condom not used<br>with last sex act  | 0.8 (0.5, 1.4)                              | 0.48           |
| Had any STI                           | 2.3(1.4 – 3.8)                              | <.01           |
| Not married or<br>living with partner | 2..59 (1.4, 4.2)                            | <0.001         |

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# What Did HIV NET 016a Teach Us?

- HIV acquisition associated with:
  - » Younger age
  - » MORE education (HR 1.3)
  - » Being unmarried (HR 2.9)
  - » Living with husband/partner rarely (HR 2.8)
  - » Not living with partner (HR 3.1)
- Factors that did not predict HIV seroconversion
  - » STI's at baseline
  - » Condom usage at baseline
  - » Site (Malawi vs. Zimbabwe)



# HPTN 055: Preparedness Study for HPTN 035

## Objectives:

- To describe baseline demographic and HIV risk behavior of women
- To determine baseline demographic factors associated with HIV status among women screened
- To describe the trends in behavioral factors during study duration
- To determine demographic and behavioral factors associated with HIV seroconversion

# HPTN 055 Results

## HIV Prevalence at Baseline

|  | Overall | Durban | Hlabisa | Moshi | Lusaka |
|--|---------|--------|---------|-------|--------|
|  | 32.5%   | 39.5%  | 34.7%   | 14.5% | 38.6%  |

## HIV Incidence

|                                 | Overall            | Durban             | Hlabisa            | Moshi             | Lusaka          |
|---------------------------------|--------------------|--------------------|--------------------|-------------------|-----------------|
| Person years of follow-up       | 744                | 239                | 234                | 193               | 76              |
| Incidence cases (incident rate) | 27<br>(3.6/100 PY) | 12<br>(5.0/100 PY) | 13<br>(5.5/100 PY) | 2<br>(1.0/100 PY) | 0<br>(0/100 PY) |
| 95% CI for IR                   | [2.4, 5.3]         | [2.6, 8.7]         | [2.9, 9.5]         | [0.1-3.87]        | [0.0, 4.9]      |

# Trend in Sexual Behavior Pattern for Duration of Study Period

| <u>Factor</u>                             | <u>Overall</u> |                 |                |
|---|----------------|-----------------|----------------|
|   | <u>Enroll</u>  | <u>Month 12</u> | <u>P-value</u> |
| Mean no. sex partners, past 3 mo          | 1.03           | 0.96            | <0.01          |
| Vaginal sex without condom, past 3 mo     | 83%            | 85%             | NS             |
| Mean no. vaginal sex, past 1 week         | 1.65           | 1.47            | <0.01          |
| With last vaginal sex: used male condom   | 30%            | 20%             | 0.04           |
| With last vaginal sex: douched before sex | 27%            | 2%              | <0.01          |
| With last vaginal sex: douched after sex  | 40%            | 5%              | <0.01          |

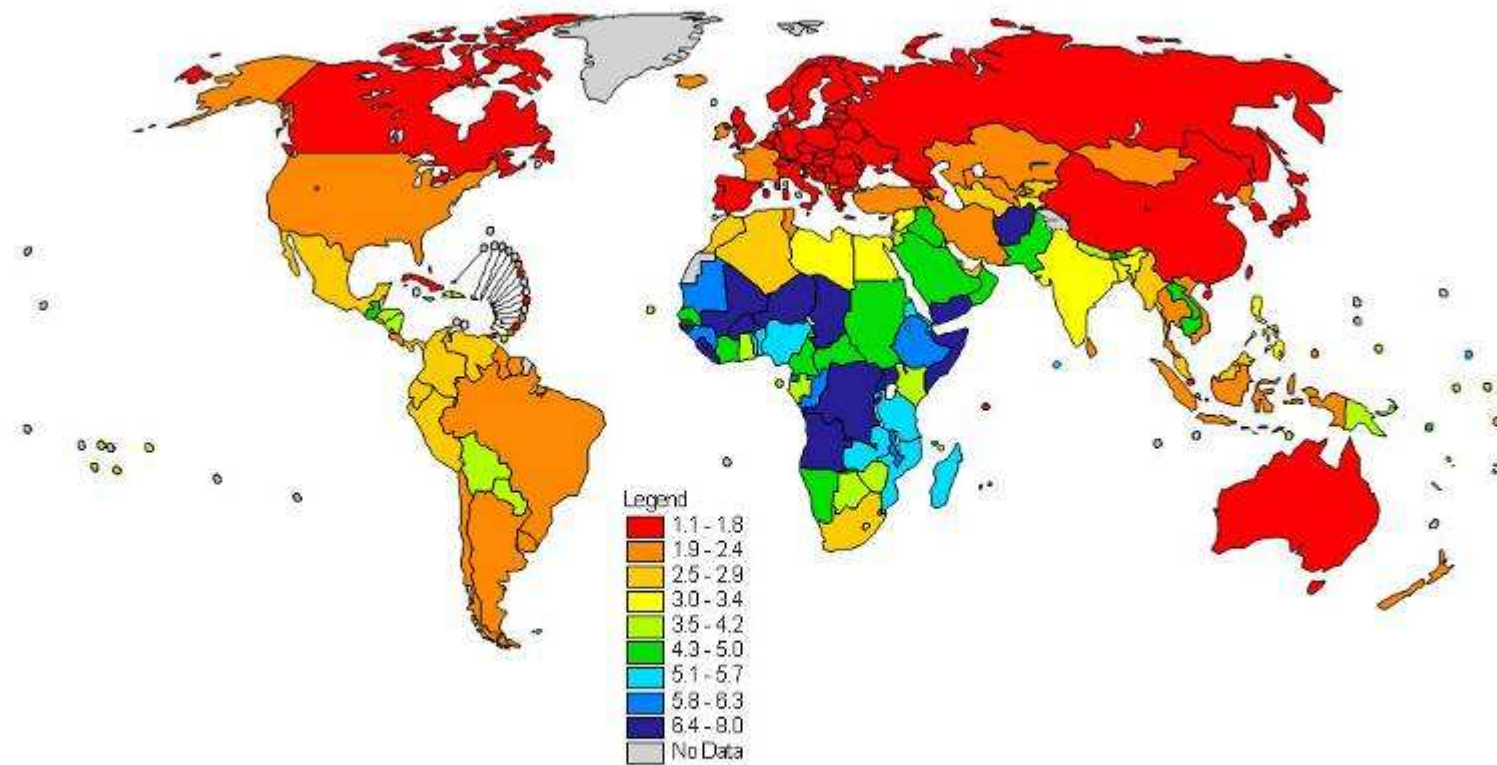
# HPTN 055: Conclusions

- High HIV prevalence at site does not predict high incidence
- Condom use is low and did not increase over study period despite intensive counseling and provision of condoms
- Behaviors under the woman's control (douching, vaginal cleaning) decreased significantly with counseling

# Microbicides and Pregnancy

- Microbicide studies by definition are done in sexually active women, primarily of reproductive age.
- In the US, about 10% of women between age 15 and 44 become pregnant annually; half of pregnancies are unplanned.
- Areas with greatest need for microbicides also have highest fertility rates.
- Once approved, pregnant women will use microbicides whether previously studied in pregnancy or not.

# Fertility Rates: WHO



# Pregnancy: The Myth of the 28 day cycle

- 1935 Menstrual and Reproductive Health Research Program
  - > 35,000 woman-years
  - University of Minnesota students
- 1981 Treloar: mean cycle length 28d
  - Only 1 woman had 28 day cycles

# Frequency of pregnancy outcomes in women attempting pregnancy from 3 longitudinal studies

| Pregnancy Outcomes   | Wilcox<br>n(%) | Zinaman<br>n(%) | Wang<br>n(%) | Total<br>n(%) |
|----------------------|----------------|-----------------|--------------|---------------|
| Total Conceptions    | 198            | 116             | 618          | 932           |
| Chemical pregnancies | 44 (22)        | 15 (13)         | 152 (25)     | 210 (23)      |
| Abortions            | 18 (9)         | 21 (21)         | 49 (8)       | 89 (10)       |
| Deliveries           | 136 (68)       | 79 (68)         | 373 (60)     | 588 (63)      |
| Other                | 1 (0.5)        | 1 (0.8)         | 12 (2)       | 14 (2)        |

Percentages may not add up to 100% due to drop out/lost-to follow up or undetermined pregnancy outcome at the study's conclusion.

Ref: Wilcox, 1988; Zinaman 1996; Wang 2003

## Frequency of pregnancy outcomes in women avoiding pregnancy: HPTN 055

| Pregnancy Outcomes   | N   | %  |
|----------------------|-----|----|
| Total Conceptions    | 105 |    |
| Chemical pregnancies | 18  | 17 |
| Abortions            | 55  | 53 |
| Deliveries           | 32  | 30 |

# Positive Predictive Values of 3 Methods for Diagnosing Pregnancy

| Population                                   | Test Type Used to Diagnose Pregnancy |                                |                               |
|--|--------------------------------------|--------------------------------|-------------------------------|
|  | Protocol 1<br>Monthly hCG*           | Protocol 2<br>Monthly/Weekly + | Protocol 3<br>Missed menses++ |
| Women attempting pregnancy in the literature | 77%                                  | 86-100%                        | 93%                           |
| HPTN 055                                     | 83%                                  | 91%                            | 96%                           |

\*Monthly hCG (based upon calendar day – irrespective of menstrual cycle)

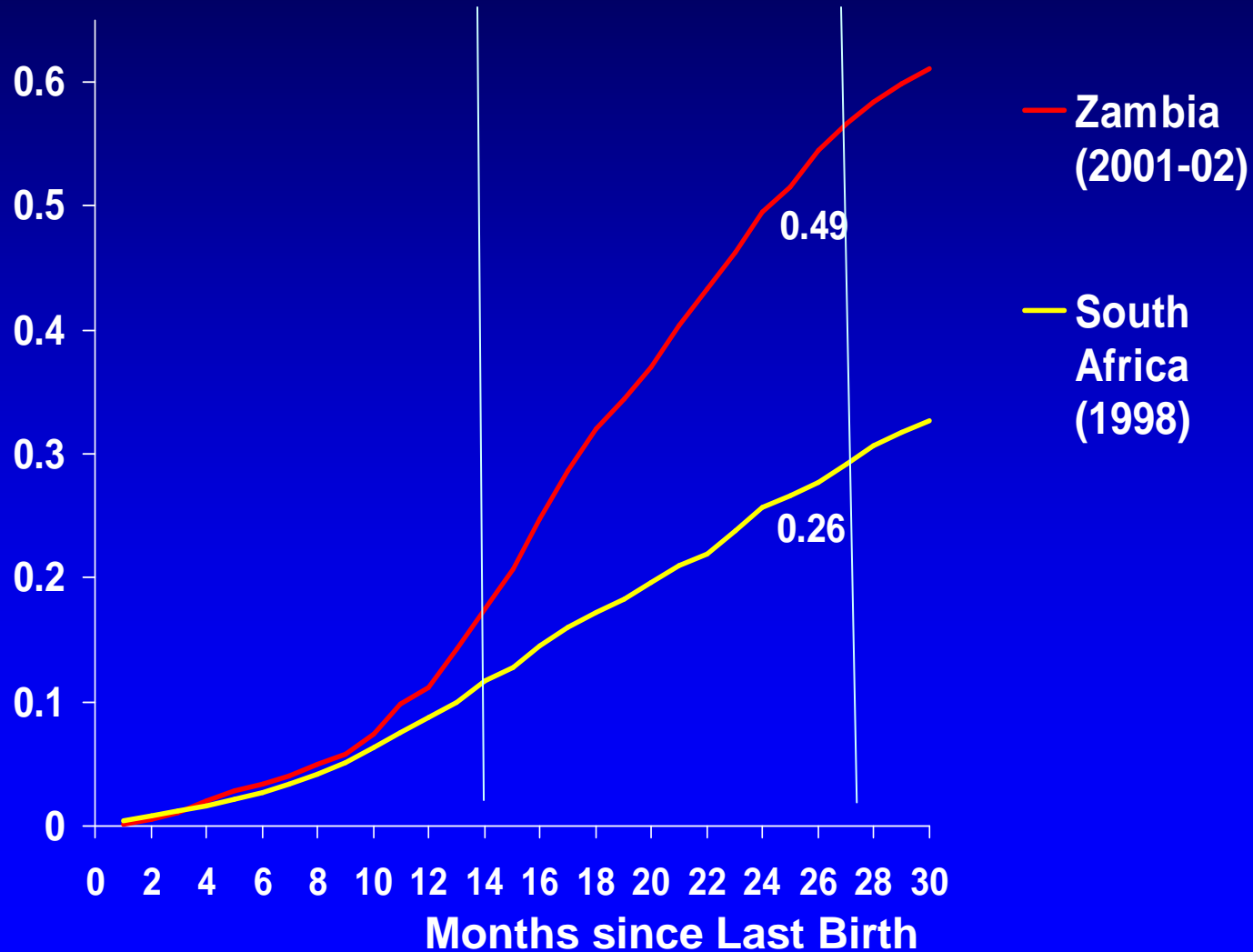
+Monthly hCG with confirmatory follow-up in 1 week if initial test is positive

++ hCG 1 week after missed menses only

# Criteria to Identify Women Most Likely to Become Pregnant

- Age
- Contraceptive use status
- Parity
- Time since last childbirth

# Cumulative Probability of Becoming Pregnant by Months Since Last Birth, by Parity (1-2 Children), DHS



# Primary Infection in Pregnancy

- Pregnant women appear to be more susceptible to acquisition of HIV infection than non-pregnant women.
  - » Uganda: RR 2.16 (1.39-3.37), absolute risk 2.3/100 person years Lancet 2005;366:1182
  - » Malawi: RR 2.1 AIDS 1998;12:197
- Susceptibility may be biologic, behavioral or both.

# Requirements for Including Pregnant Women in Studies

- No specific FDA guidance for inclusion of pregnant women in phase III studies; expect most studies will be post-marketing Pk/PD.
- Pregnancy registries not generally recommended for drugs without systemic exposure.
- Industry considerations
  - » Drug safety and efficacy demonstrated in general population
  - » Significant therapeutic benefit in addition to broad usage in pregnancy
  - » Drug exposure not expected to pose undue risk to the mother and fetus.

# Requirements for Including Pregnant Women in Microbicide Studies?

- At a minimum:
  - » Reproductive (fertility, parturition, lactation) and developmental (mortality, dysmorphogenesis, growth, function) toxicity testing in animals.
  - » Phase I/II safety data in nonpregnant women.
  - » Data on systemic absorption in nonpregnant women.
- Suggest meeting with FDA for additional information/requirements, especially need for data on efficacy in nonpregnant women before studies in pregnancy.

# MTN Plan

- **MTN: Proactively assess formulations in pregnancy**

1. Assess term pregnancy maternal single-dose PK of Tenofovir/PMPA gel
  - ? Altered/increased absorption in late pregnancy
  - Compare to non-pregnant recent historic controls
2. Assess placental transport (fetal exposure) of single-dose Tenofovir/PMPA gel

# MTN Proposal

- Phase I, open label, Pharmacokinetic and safety evaluation
- 10 Healthy term HIV (-) ( $\geq 37$  gestational weeks) parturients
  - Scheduled elective cesarean sections
  - No suggestion of placental disease
    - No IUGR, DM, HTN, CTD, etc.
- Single-site – MWH in PGH

# MTN Proposal Cont'd

- Regimen:
  - » Single-dose Tenofovir (TFV) gel (40 mg)
  - » Placed vaginally in CS Pre-operative holding area
  - » Maternal PK
    - Baseline, 1 hour, 2 hour, 4 hour, 8 hour, 12 hour, and 24 hour
  - » Fetal TFV concentration assessment at time of CS
    - Amniotic Fluid
    - Cord Blood

# Approaches to Dealing with Pregnancy in Microbicide Studies

- Enroll subjects from family planning or postnatal clinics.
- Provide contraceptive services within clinical trial sites
- Allow pregnant women to stay in trial (off product) since many HCG test positives participants do not proceed to clinical pregnancy
- Power studies to account for time off microbicide product due to pregnancy
- Consider developing mechanisms to include pregnant women in microbicide studies

# NIH Funded Clinical Trials Program in Topical Microbicides

- HIV Endpoints
  - » Strong QA/QC and endpoint validation program
  - » Sample size estimates based on measured seroincidence among target population in the context of STI treatment and condom counseling
- Pregnancy
  - » Focus on recruitment from family planning and post-natal clinics
  - » Ensure access to contraceptive services
  - » Support research to assess “chemical pregnancy” outcomes among women in clinical trials
  - » Plan to develop pathway for inclusion of pregnant women in clinical trials