CONDUCTING PHASE 3 MPT STUDIES
CONSIDERATIONS FOR
DEMONSTRATING CONTRACEPTIVE
EFFICACY AND SAFETY

Clinical Trial Evaluation Workshop for MPTs:
Strategic Steps to Ensure Success
Washington, DC
September 14, 2016

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Population Council
IOM Restates the Obvious

“Unprotected intercourse can result in both unintended pregnancy, HIV infection & other STIs.”

. IOM- New frontiers in Contraception: A blueprint for action. 2004
The Quest for an MPT

- **1992** - Cates & Stone\(^1\); Cates & Steiner\(^2\)
  
  “In the midst of the global epidemics of both unintended pregnancy and sexually transmitted, research to prevent unintended pregnancy should not be done in isolation from research to prevent ID, including HIV and other STIs.”

- **1993** - FDA lifts ban on participation of women with childbearing potential in early phase clinical trials
  
- **1993** - FDA approves first female condom; barrier contraceptive offering limited protection against STIs

- **1994** - CDC expands definition of AIDS to include invasive cervical cancer; publishes first recommendations for prevention of perinatal HIV transmission
  
  1994 -FDA approves first drug for prevention of HIV transmission from infected pregnant women to fetus; Organizes inter agency/extra mural task force to examine effects of spermicides in HIV transmission

- **2009** - FDA approves a second-generation female condom for preventing pregnancy, HIV/AIDS, & other STIs

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Numerous Countries in SSA & SA with High Unmet Need for MPTs

A MPT: A Complex System

Complex systems are highly sensitive to slight changes; small alterations can give rise to strikingly great consequences.

Development of drugs with 2 mechanisms is complex, time-consuming and costly.

Developing MPTs is challenging, both synthetically and clinically.

Keeping Our Eye on the Goal
NDA Submission & Approval by a SRA
Introduction where Needed Most

Preclinical Demands
CMC Challenges
Clinical Realities
COMPLEXITIES OF MPT DEVELOPMENT INCREASE DEPENDING UPON WHETHER API COMPONENTS ARE REGISTERED

Brady M, Tolley E. Aligning product development and user perspectives: social–behavioural dimensions of multipurpose prevention technologies. BJOG 2014; 121 (Suppl. 5): 70-78
Demonstrating Clinical Safety & Efficacy for the Contraceptive Component of the MPT Phase 3 Requirements
Phase 3 S & E Evidence Preceded by Completion/near Completion of Non Clinical Studies

Pharmacology, general toxicity studies

Toxicokinetic & nonclinical PK studies;

Repro & genotoxicity studies

Biocompatibility with delivery system, e.g. ring

Carcinogenic potential (drugs with special cause for concern or intended for long duration of use)

Other nonclinical studies, e.g. immunotoxicity,

For MPT, each API and combination of APIs must be well characterized

Utilizing a NCE requires additional expertise, budget & time

69 non clinical studies completed for Nestorone® (NES), a NCE

• Long term studies subject to changes in regulatory requirements, during development, e.g. reproductive toxicology.

• Some studies completed while Phase 3 trials are ongoing
  — 2-year carcinogenicity mouse study with intravaginal dosing

Current MPT candidates utilize LNG for contraception (well characterized progestin, not an NCE).

May require additional drug-drug interaction studies (non clinical & clinical)
CMC Issues Complex for Long-Acting MPTs Containing Two or More APIs

- Characterizing API release integral to S & E expectations during clinical trials, especially for Phase 3 trials.

- CMC issues for a long acting formulation require expertise r/t release, stability, and establishing a quality control system
  - Combination of 2 or more APIs can affect release of APIs individually & overall, e.g. NES affects release of EE; DPV affects release of LNG
  - Inclusion of > 1 API creates regulatory and budgetary hurdles for manufacturing
  - Be prepared to defend registration batches in relation to Phase 3 product
    » Scaling up technology best determined prior to Phase 3
  - Distribution questions- e.g. will time to first use in clinical trial be consistent with time to first use for commercial product

![Diagram of Nestorone/Ethynyl Estradiol core and Nestorone core with dimensions and labels: channels 3 x 25 mm, 8.4 mm in cross section, 56 mm in diameter]
Demonstrating Contraceptive Efficacy & Safety in Clinical Studies

Clinical studies completed prior to Phase 3

- substantiate API dosage(s) & regimen of contraceptive component of MPT
  » TPP to articulate efficacy goals;
  • local and/or systemic effects to achieve contraceptive effect;
  • bleeding pattern expectations
  • duration of action e.g.
    • 1, 3, 6, 13 cycles; 30, 60, 90 days.
What is the Contraceptive Efficacy Goal?

Local Effects- Cervical mucous changes to inhibit sperm transport
Low dose of P has local effects

Systemic Effect- Ovulation suppression in 90-95%* of cycles/ intervals of time

Ovulation = follicular rupture (measured directly by Vag US; indirectly by P levels ≥ 10 nmol/L in 2 consecutive samples)

Serum levels of progestin evaluated as an indication of efficacy

For LNG need serum levels > 2 nmol/L (> 625 pg/mL)
For NES need serum levels > 0.25 nmol/L (> 90 pg/mL)

Reports of pregnancy (if Phase 2 protocol(s) calls for inclusion of women at risk for pregnancy)
PK Profile Identified Early in Development: Serum Levels of a New Progestin (NES) for 1-Year Use

Burst effect on Day 1 Needs to Be Controlled & Steady State Identified
SAFETY

Safety Measurements

• Reports of SAEs, AEs, physical & laboratory parameters;
  • Safety signals?

• LNG (or other progestin) without estrogen add back may result in menopausal symptoms

• Local effects of MPT, e.g. Vaginal Microbiome; Endometrium
Demonstrating Contraceptive S & E in Phase 3
MPT Clinical Studies

Hormonal contraceptives containing a NCE.
NDA must include data from \( \geq 20,000 \) treatment cycles & 400 women who complete 13 cycles (1-year) of use.”

MPT containing well-studied compounds, but used in combination with another API may have similar regulatory requirement

Safety Reports will be critical; Risks vs. Benefits

The Pearl Index (PI)- Primary Measure of Efficacy

\[ PI = \frac{\# \text{ pregnancies} \times 1300}{\# \text{ on-therapy cycles}} \]

• Based on 28 day cycles in one year, hence 13 cycles
• # of unintended pregnancies in 100 woman-years of exposure (e.g. 100 women over 1-year of use)

Alternative approach to defining unit of exposure during continuous use of contraceptive over 1-year;

– Determine for each woman the no. of days of use for the MPT
– Add up all woman years of use in the trial and divide the no. of pregnancies by 100 woman years

\[ \# \text{ Pregnancies} / \text{Total number of days} \times 365.25 \times 100 = PI \]
Ethical Concerns Associated with Design & Implementation of Late-stage MPT Trials for HIV/Pregnancy Prevention

Primary efficacy outcome is the PI in women < 35 years of age & for whom no backup contraception is used, e.g. condoms

Cycles cannot be counted when condoms or other contraceptives are used:

* Raises numerous ethical concerns associated with design & implementation of late-stage MPT trials for HIV/pregnancy prevention & our moral mandate to protect the diverse community of participants*

Minimizing Risks & Promoting Benefits

− Clarity on actual risks associated with MPT
  • Participant educational materials developed with focus on literacy & comprehension

− Frequent testing for pregnancy & HIV

− Tracking pregnancy outcomes
  • Further research on HIV drugs in pregnancy

− Access to optimal care & treatment regimens for participants who become pregnant or sero-convert

“Acceptability”
Specific Characteristics of an MPT Will Affect Adherence, Method Continuation & Goals of Product Development

Domains of NES/EE CVR Use

- Ease of Use + Side Effects
- Expulsions + Feeling CVR
- Sex and Intercourse
  - Intimacy
  - Physical Effects

Satisfaction

Adherence (ring removals for > 2 hours)
Continuation

Development of an MPT is complex and chaotic, but it is achievable and a worthy goal.

Thank You