NIH Proposal Writing Workshop

DAY 1 | 4.11.2024 | MORNING SESSION

FACENTE CONSULTING
UNDERSTAND • IMPLEMENT • TELL YOUR STORY

Introductions

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Plan for the Morning

1. Types of NIH Proposals
2. Standard NIH Due Dates
3. Proposal Submission: The Big Picture
4. Components of an NIH Proposal
5. How to Structure the Specific Aims Page

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Types of NIH Proposals

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What are standard NIH Due Dates?

- NIH typically reviews proposals in three cycles per year
- The due date can vary by:
  - Award type
  - Whether the proposal is new or a resubmission/renewal/revision
  - Whether the proposal is "AIDS-Related"
- **Always double-check the "key dates" section of the funding opportunity to confirm due dates.**

EXAMPLE for an R01 proposal:

Proposal Type	Cycle 1 Due Date	Cycle 2 Due Date	Cycle 3 Due Date
R01 - new	Feb 5	Jun 5	Oct 5
R01 – renewal, resubmission, or revision	Mar 5	Jul 5	Nov 5
R01 **(AIDS-related)** –new, renewal, resubmission, or revision	May 7	Sep 7	Jan 7

https://grants.nih.gov/grants-process/submit/submission-policies/standard-due-dates

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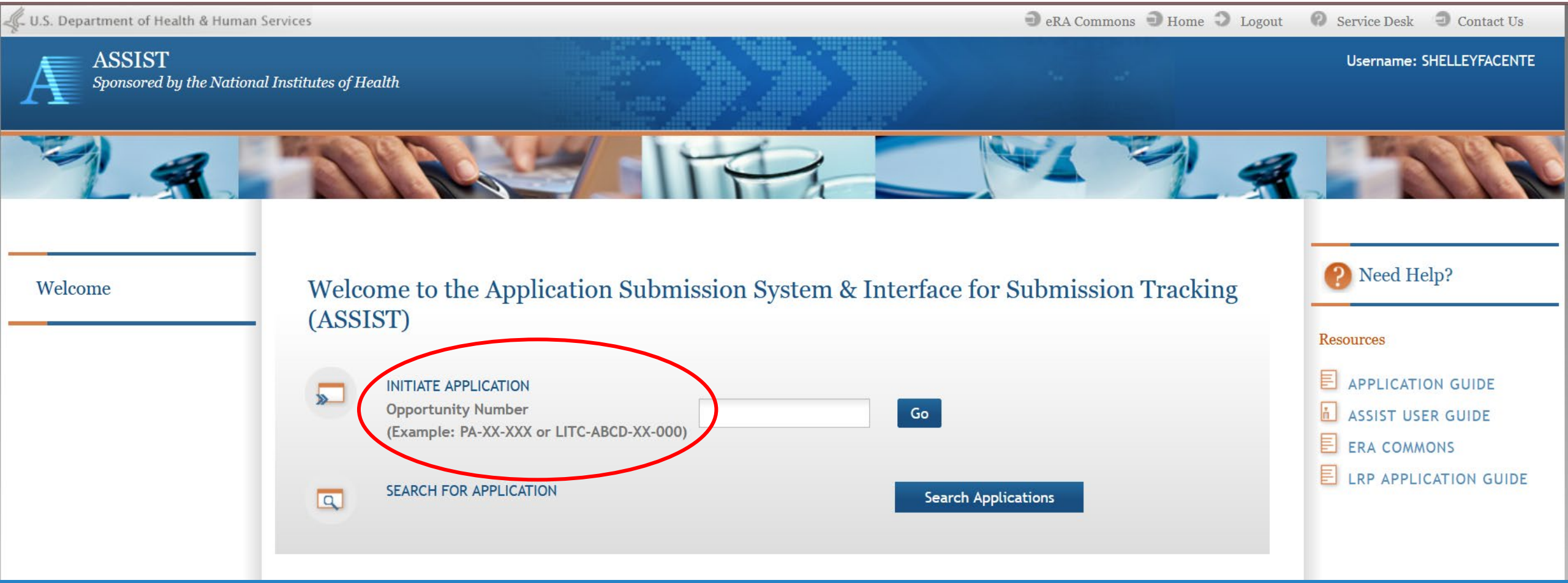
Proposal Submission: The Big Picture

To submit, the prime organization needs:

- A Project Director/Principal Investigator with an eRA Commons username (PI account)
- A DUNS number
- A Unique Entity Identifier (UEI)
- An active SAM registration
- A Signing Official with an eRA Commons username (SO account)

Probably you'll never need to worry about any of these

Proposal Submission: The Big Picture



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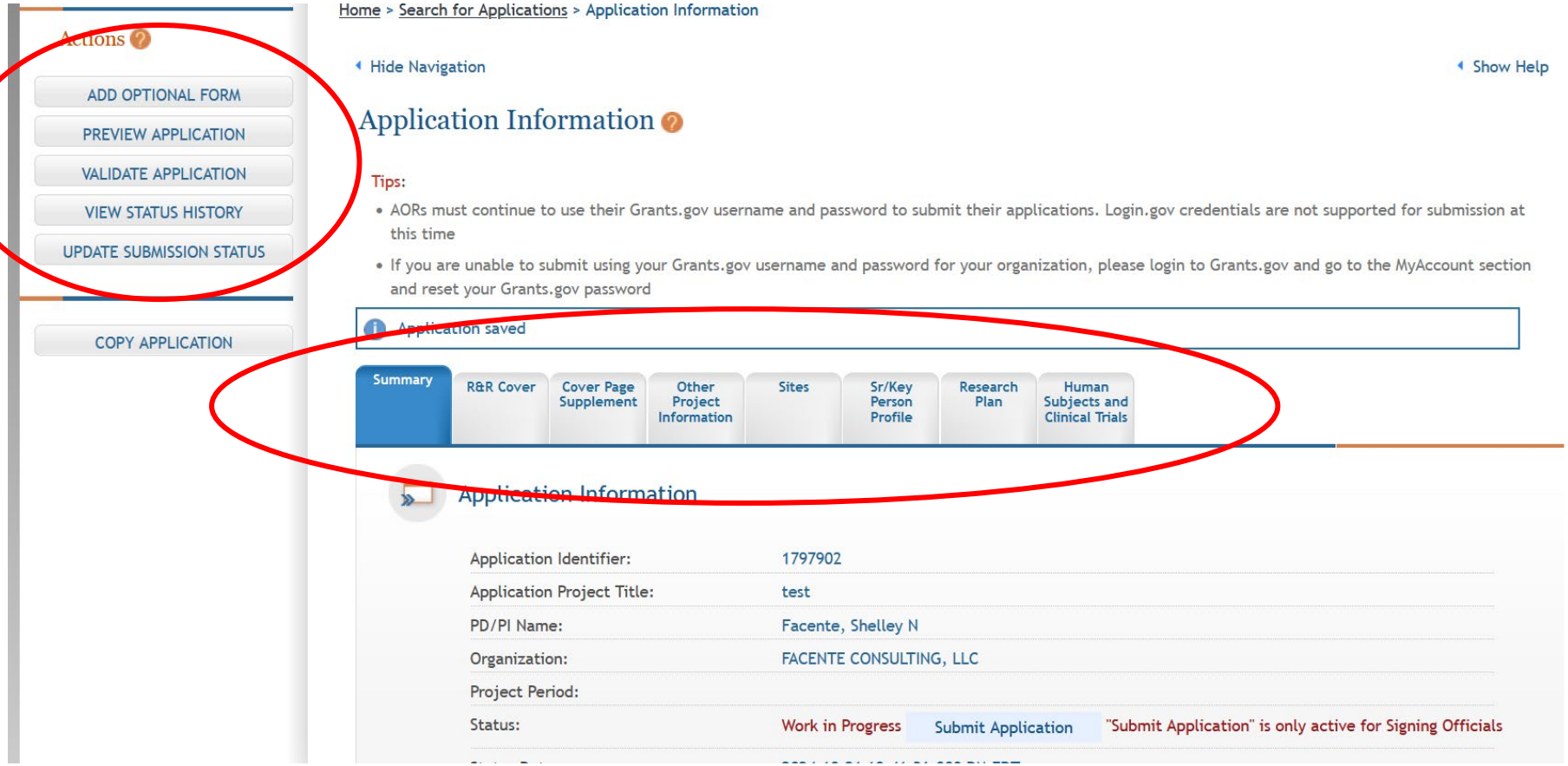

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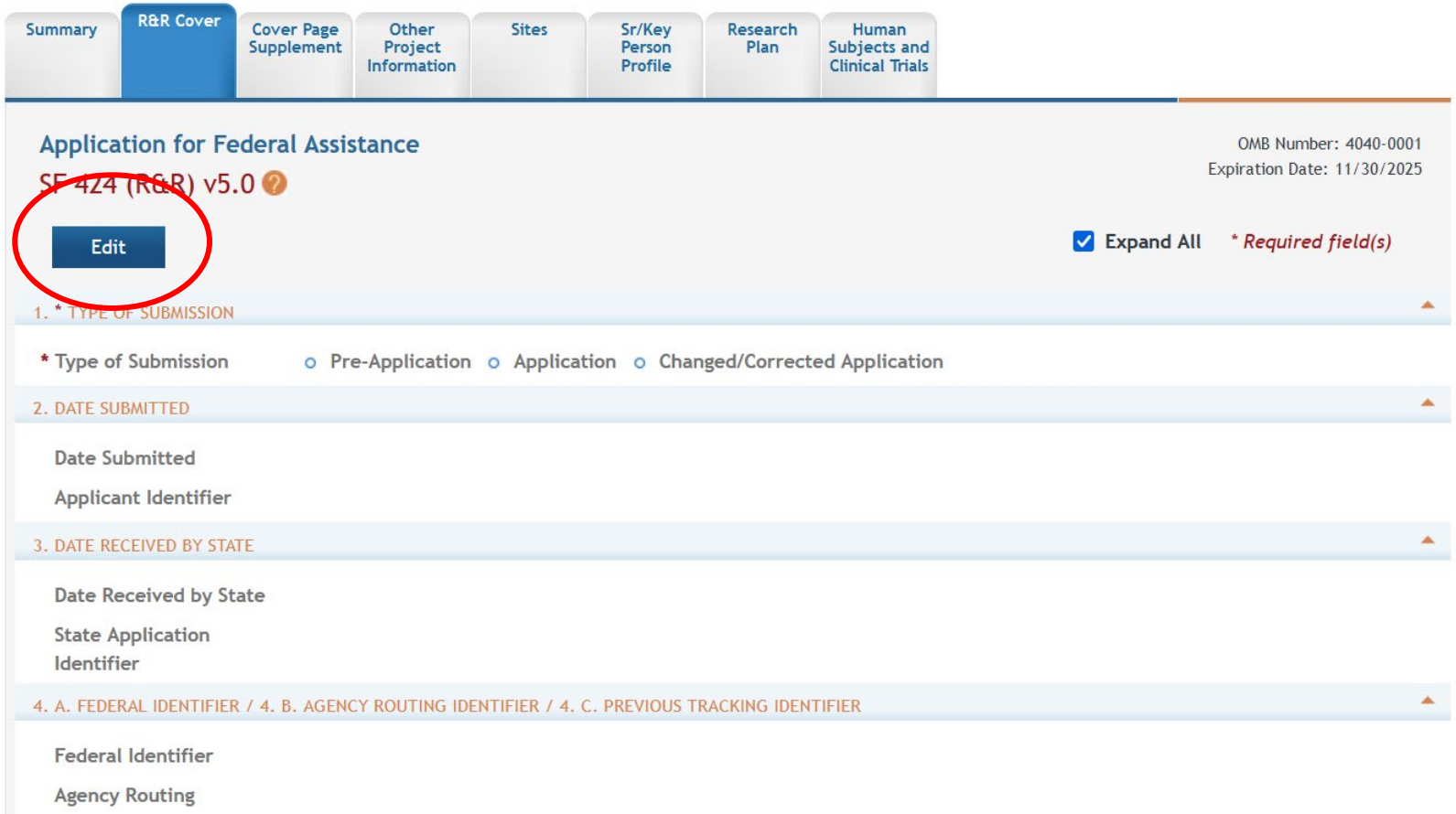

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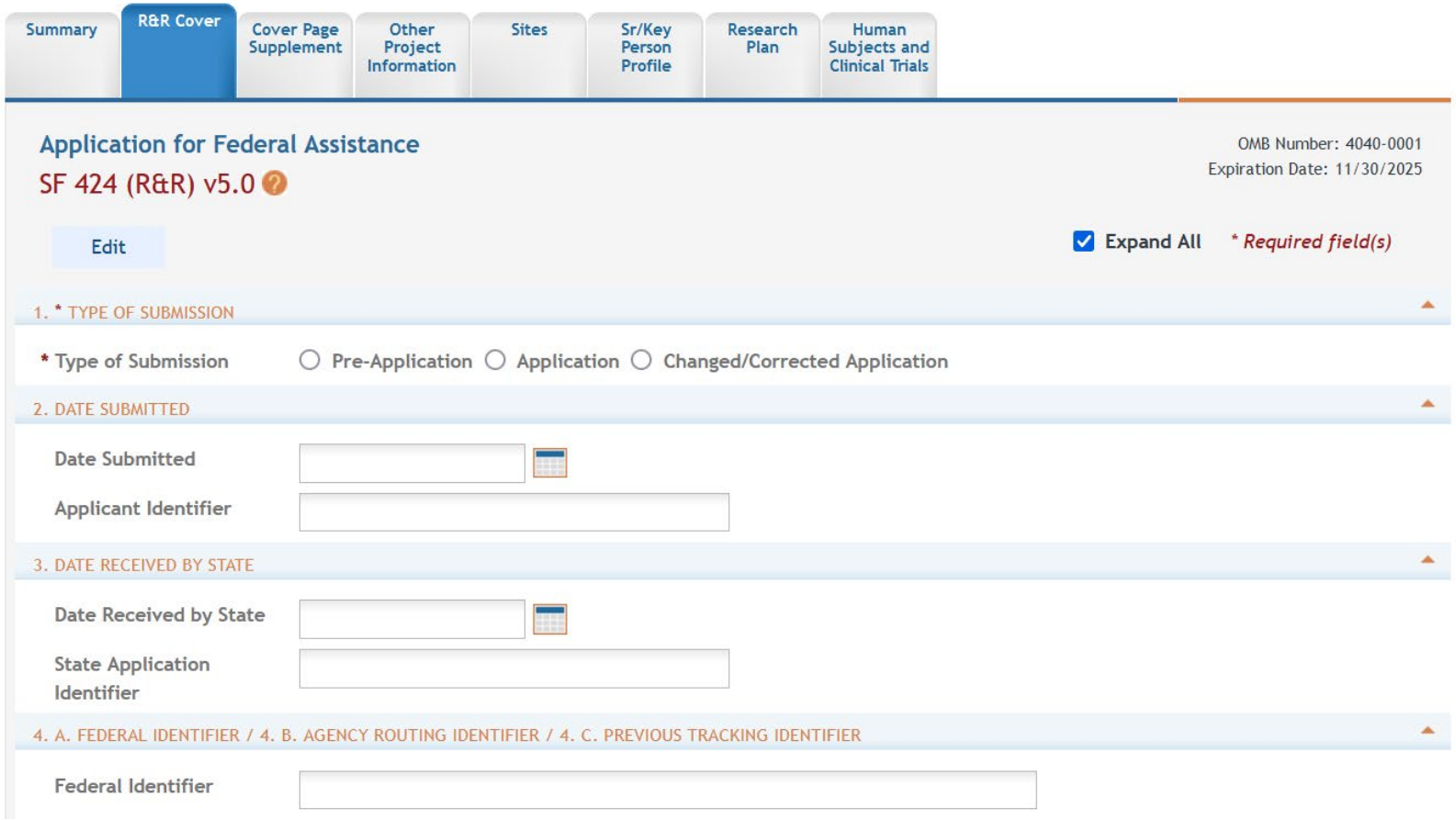

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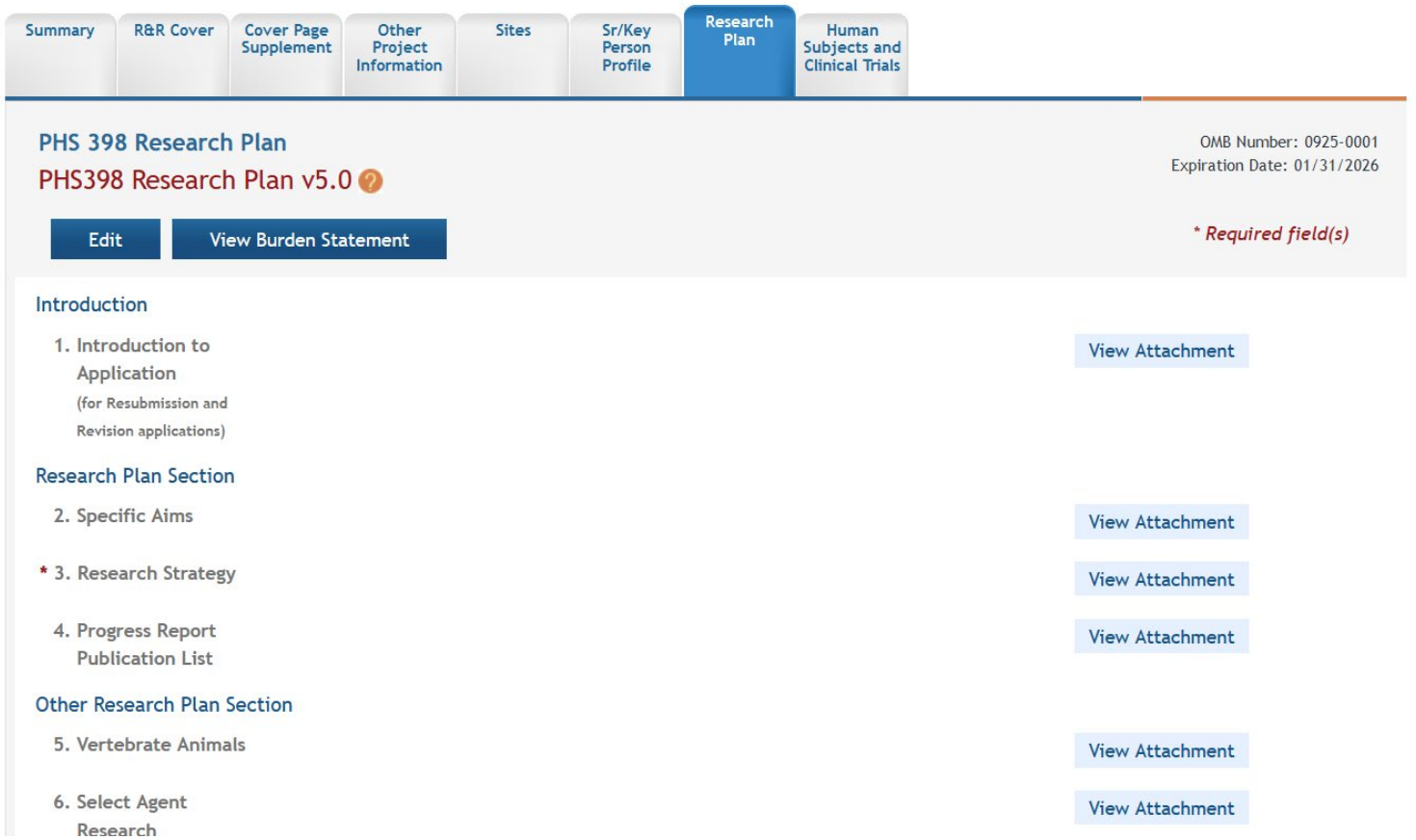

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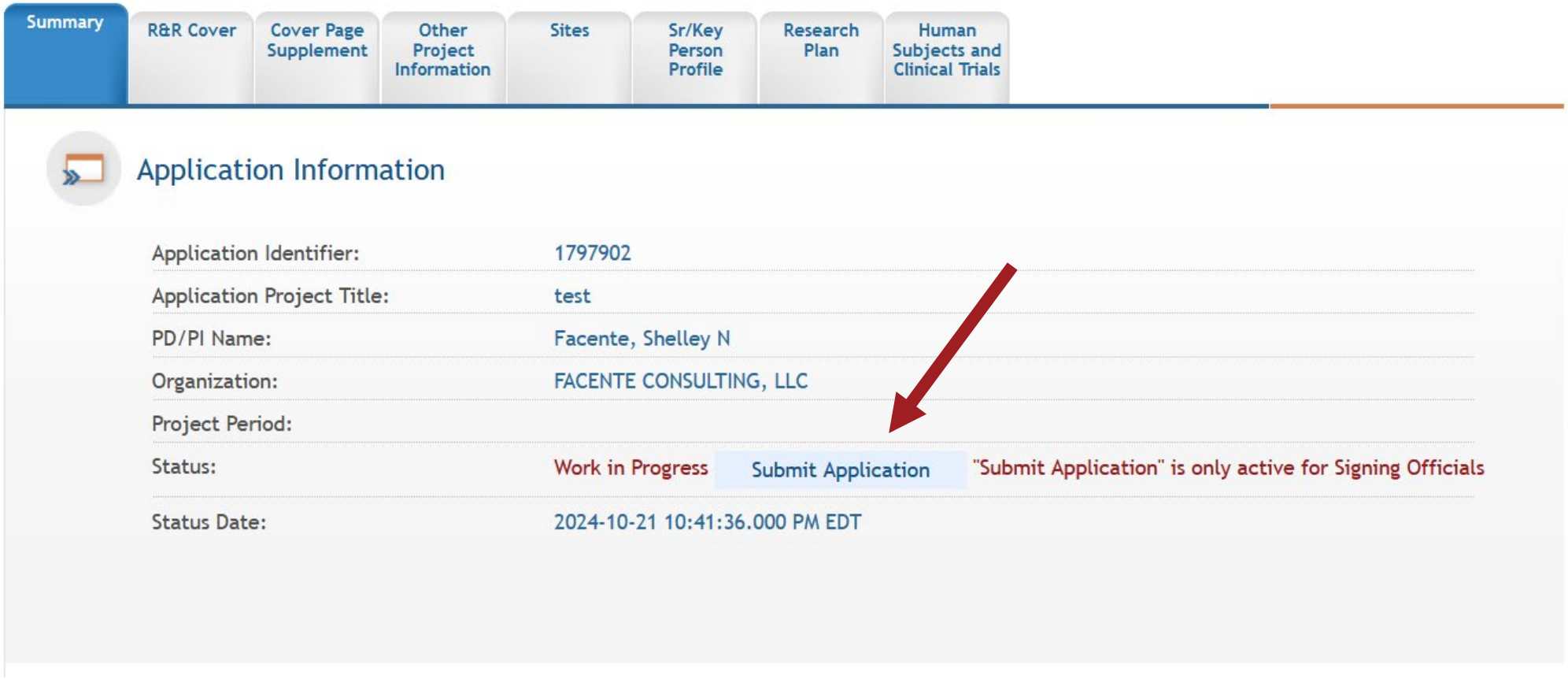

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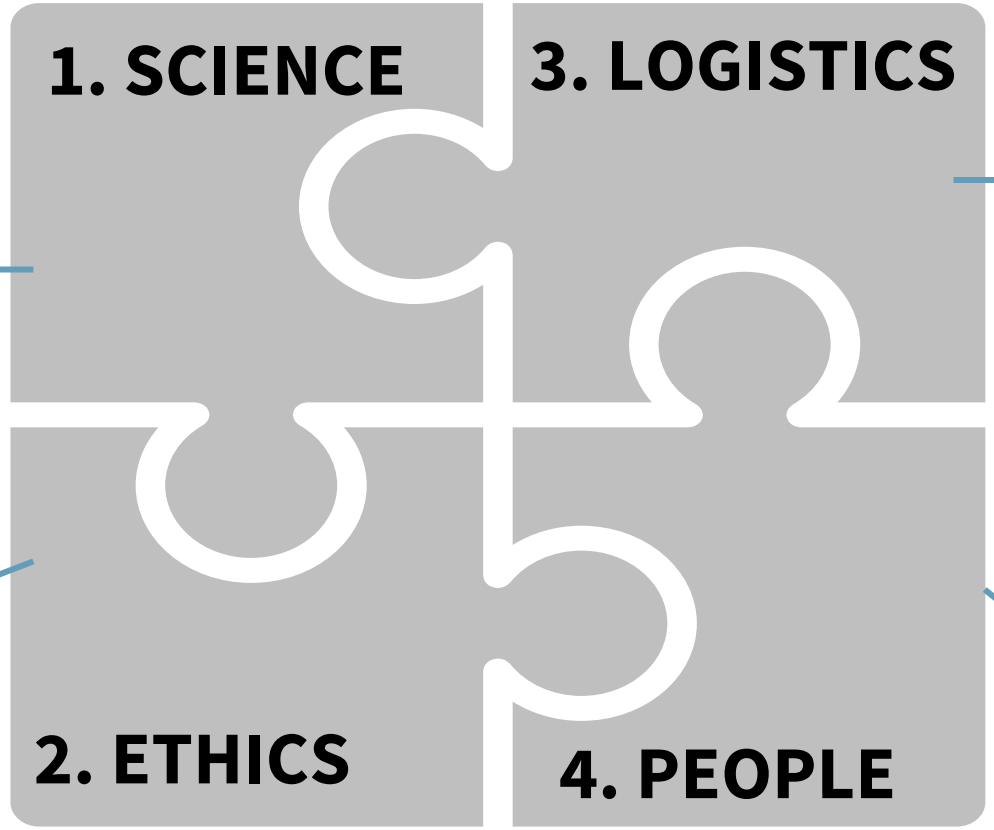
Components of an NIH Proposal

- Specific Aims
- Research Strategy (significance, innovation, approach)
- References

- Human Subjects Package
- Clinical Trials



- Cover letter
- Project Abstract
- Statement of Public Health Relevance
- Budgets
- Budget justifications
- Facilities and Resources
- Equipment
- Resource sharing plan
- Foreign justification
- Multi-PI plan

- Biosketches
- Letters of Support
- Consortium agreements

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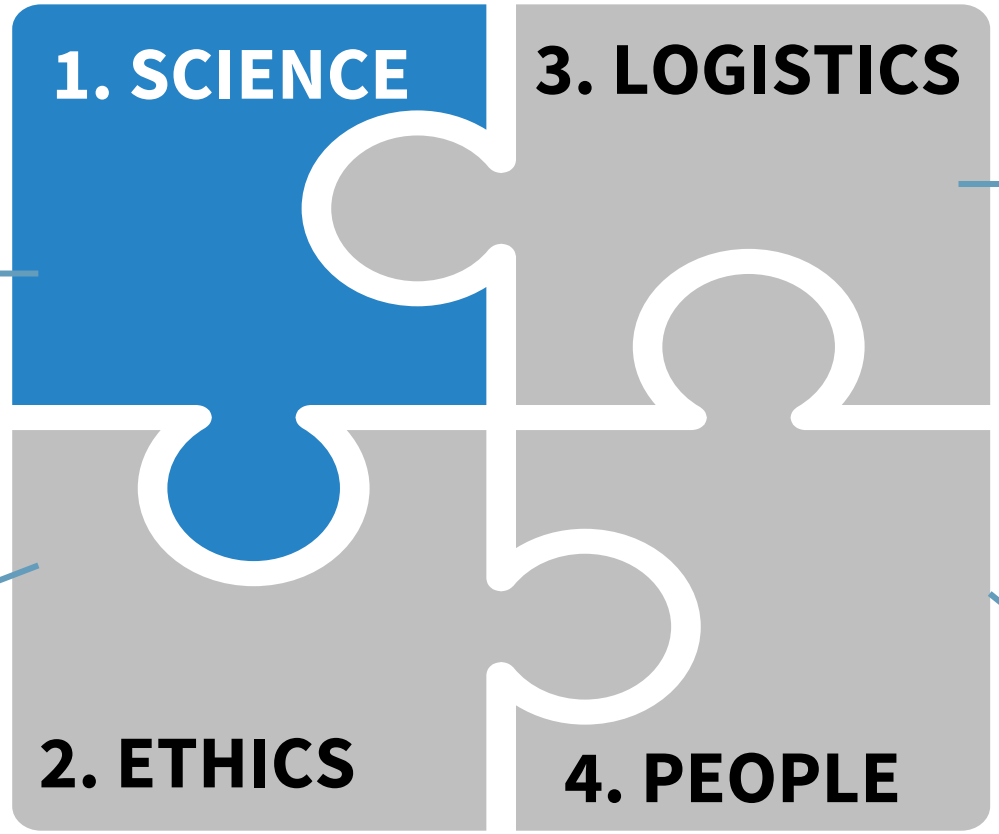

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Three Key Science Docs

SPECIFIC AIMS

- 1 page
- Summarizes the importance and focus of proposal

RESEARCH STRATEGY

- Usually 6 (R21) or 12 (R01) pages
- Describes in detail the significance, innovation, and approach of proposal

BIBLIOGRAPHY & REFERENCES CITED

- No page limit
- References for most of the application

U.S. Letter size paper; 11-inch font minimum for main text; 0.5" empty margin minimum

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Building a Specific Aims Page

- 1 page (no exceptions)
- Summarizes the importance and focus of proposal
- Is typically the thing reviewers read first - and use to form their opinions
- Is densely cited, with citations that continue on to the Research Strategy

Specific Aims should be C.R.I.S.P.

Coherent → Focused around a central theme

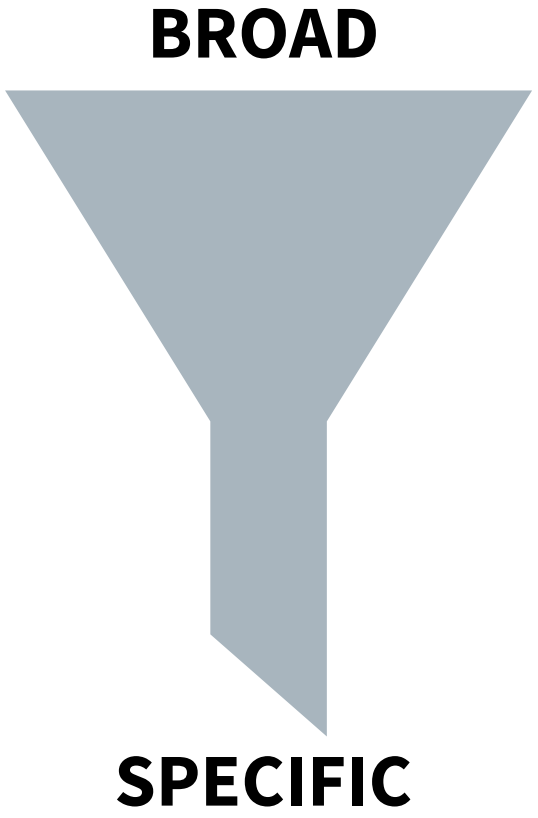
Research-driven → Clearly justified by research landscape

Independent→ Aim 2 should not depend on Aim 1 turning out a certain way

Specific→ Focused hypothesis or goal/outcome for each aim

Plausible → Possible to achieve within grant period

Aims Page: A formula



What is the issue that need to be supported with more research?

How does your proposal contribute to the research gap for this issue?

Aims Page: A formula

1 **State of the ISSUE (1-2 paragraphs):**

a) Description of broad issue & its importance
b) Description of sub-issue and its importance
c) What are the critical research gaps?

2 **Where YOUR WORK fits in (1 paragraph):**

a) Your team's prior work in this area
b) How your study will bridge gaps described

3 **AIMS (list + 1-2 sentences for each aim)**

4 **IMPACT of your work (1-3 sentences)**

Aims Page: A simplified example

1 State of the ISSUE:

a) Description of broad issue & its importance	Syphilis rates are rising. Syphilis causes health problems. Men who have sex with men and people living with HIV are disproportionately impacted by syphilis.
b) Description of sub-issue and its importance	Existing syphilis treatments are suboptimal (need for injection, penicillin shortages)
c) What are the critical research gaps?	Need new treatment alternatives for syphilis; existing antibiotics (cefixime) are safe and promising but have not been systematically studied for efficacy.

Aims Page: A simplified example

2 Where YOUR WORK fits in:

a) Your team's prior work in this area	Literature review suggesting that certain classes of existing antibiotics (like cefixime) are effective against syphilis. Current RCT on using cefixime in early syphilis—pilot study with smaller sample—has initial findings suggesting that cefixime might be effective.
b) How your study will bridge gaps described	Unprecedented, large RCT to understand effectiveness of cefixime in treating syphilis will clarify the potential for cefixime as an alternative treatment in people living with and without HIV.

Aims Page: A simplified example

3 AIMS

Specific Aim 1: Evaluate the effectiveness of cefixime in the treatment of early syphilis when compared to benzathine penicillin G. **Approach:** Conduct a two-arm randomized non-inferiority controlled trial among patients with early syphilis: the experimental arm will receive oral Cefixime 400mg twice a day for 10 days and the control arm will receive benzathine penicillin G 2.4 million units intramuscularly once. **Main outcome:** 4-fold decrease in serum RPR titer at 6 months after treatment completion.

Specific Aim 2: Determine the predictors of syphilis treatment failure among participants. **Approach:** Compare demographic characteristics, syphilis history, adherence to treatment and clinical markers (HIV viral load, CD4 T cell count) of participants by HIV infection status by treatment arm.

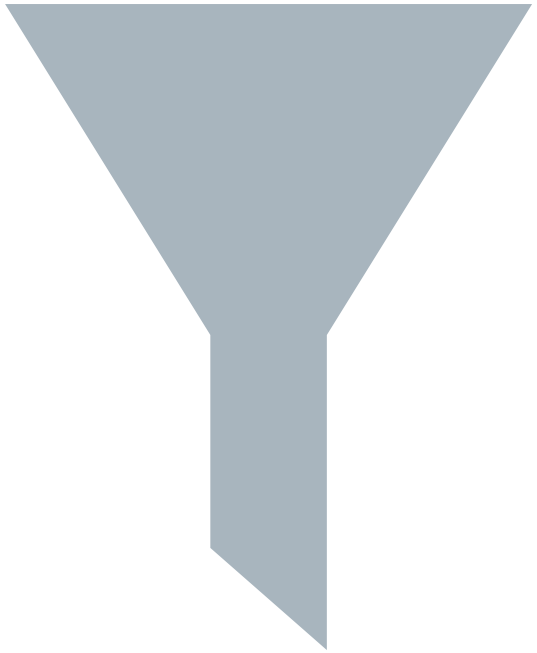
Aims Page: A simplified example

4 IMPACT

- Could find effective alternative to penicillin for syphilis treatment, helping solve penicillin shortage crisis
- Will understand how well it works in PLWH—a subgroup disproportionately affected by syphilis

SPECIFIC AIMS FORMULA

Zooming back out to the big picture:



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3 **AIMS (list + 1-2 sentences for each aim)**

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Crafting the actual Aims language

Let’s look at some real life examples!

PAGE 1

R21 Grant: Prelim Work Feeds into R01

Our proposed R21 project had the following two Specific Aims:

Specific Aim 1: To determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit.

Specific Aim 2: To describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit.

These set the stage for an R01

PAGES 2-3

R01 FIRST draft

Specific Aim 1: Evaluate scalable interventions to decrease the burden of sexually transmitted infections among pregnant women.

Relates to R21 Aim 1 (Page 1)

Specific Aim 2: Describe longitudinal birth and infant outcomes for women screened and/or treated for STIs during pregnancy.

Relates to R21 Aim 2 (Page 1)

Specific Aim 3: Evaluate the cost per pregnant women screened and/or treated, and the cost-effectiveness per STI averted at time of delivery.

PAGES 3-4

R01 SECOND draft (one month later)

Specific Aim 1: Evaluate scalable interventions to decrease the burden of sexually transmitted infections among pregnant women.

Specific Aim 2: Describe changes in the composition and structure of the vaginal microbiome in response to targeted and presumptive antibiotic treatment for STIs.

Specific Aim 3: Describe longitudinal pregnancy and birth outcomes as a function of screening/treatment interventions and the structure and composition of the vaginal microbiome.

R01 THIRD draft (another month later)

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women.

Aim 2: Evaluate the cost per pregnant woman diagnostically screened, and the cost-effectiveness per STI averted at time of delivery and adverse birth outcome.

Aim 3: Investigate the relationship between the vaginal microbiome and STI treatment outcomes.

R01 FOURTH draft (1st Try Submission)

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women.

Aim 2: Evaluate cost per pregnant woman diagnostically screened and treated, cost of adverse pregnancy and birth outcomes, and cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and CT treatment failure in pregnant women.

Impact Score:27 Percentile:15

Summary Statement

RESUME AND SUMMARY OF DISCUSSION: In this application, the Principal Investigator proposes to establish a trial to assess the impact and cost-effectiveness of different diagnostic and screening strategies to decrease the burden of sexually transmitted infections (STIs) in pregnant women. STIs are common globally and have been associated with adverse birth outcomes. The reviewers agreed that the proposed studies are highly significant due to the impact and burden of STIs on birth outcomes in sub-Saharan Africa. The studies were deemed highly innovative as they examine the role of the microbiome on STI treatment outcomes as well as assess means to improve both cost-effectiveness and birth outcomes. Major strengths of the application were the focus on implementation to inform policy on STI testing strategies as well as cost assessment, the well-designed study, and strong investigative team. Enthusiasm was slightly dampened by the concern that syndromic management will impact STI detection since, based on the preliminary data by the investigative team, there is a high rate of asymptomatic infection. Nevertheless, the panel agreed that the proposed studies are highly significant and can potentially have a high overall impact on the management of STIs.

Our Response

Reviewer comment 6: “My enthusiasm is dampened [by] …concern about…a standard of care arm…given that most STIs are asymptomatic” and “…equipoise”

Response 6: Syndromic management is the standard of care in all low and middle-income countries. Demonstrating the impact/cost effectiveness of STI screening v. standard of care with respect to adverse birth outcomes is critical to produce high-level evidence to inform policy change.

R01 (2nd Try, Resubmission)

Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women.

Aim 2: Evaluate cost per pregnant woman diagnostically screened and treated, cost of adverse pregnancy and birth outcomes, and cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and CT treatment failure in pregnant women.

Impact Score:33 Percentile:21

Summary Statement

Reviewer 3

This revision responds to many initial reviewer concerns, providing solid explanation on why HIV+ and HIV- women are included as well as sample size justification, addition of DSMB, PI effort, updating enrollment table, etc. Preliminary data supporting Aim 3 regarding the mechanism have been added, as well as data on the relationship between BV and chlamydial organism load. It remains unclear in this proposed study whether these pregnant women with symptomatic BV will be treated, as clinical guidelines suggest they should be. Previous Reviewer 2 indicates persistent infection and treatment failure are not distinguished, and this remains unclear. For example, what proportion of the not-cleared infections at test of cure occurs *in the absence of* non-adherence/partner re-exposure? As only 55% of women provided male partners with treatment, and adherence in male partners is unknown. Regarding concern about overlapping roles of investigators, this is mostly addressed but there is still some lack of clarity on the roles of biostatisticians. Overall, the investigative team is excellent, the environment is strong, and the goal to reduce adverse birth outcomes through STI testing and treatment is of public health and clinical relevance, and the aim to determine impact of vaginal microbiome on chlamydia treatment outcome is innovative. However, the trial methodology is not innovative, and the potential magnitude of the impact of VMB on CT treatment outcome is uncertain.

PAGES 9-10

R01 (3rd Try, New Submission)

Aim 1: Evaluate different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women.

Impact Score:43 Percentile:25

Summary Statement

Overall

weaknesses. The reviewers raised some concerns on the STI testing result interpretation, the handling and analysis of the data collected, as well as the lack of clarity on male partner role. Furthermore, the reviewers questioned, give the teams preliminary data, whether the syndromic management arm is necessary. Overall, this is a well written application that has the potential to inform standard of care. However, the panel agreed that the weaknesses raised mostly in the experimental approach lowered overall impact to moderate.

Reviewer 3

persistent Chlamydial infections in pregnant women. The investigator team is strong, the study design is innovative, and the environment is supportive however my enthusiasm is tempered by the use of a syndromic approach arm in this study given the both the preliminary data from this team and data from other studies which clearly demonstrate inferiority of this approach.

Reviewer 4

Do not think that the syndromic management arm is necessary given the preliminary data (HPTN 040) and data from other studies clearly show increased MTCT of HIV in the presence of maternal STI as well as historical data on the fetal and neonatal complications of STI (the are

PAGE 11

Impact Score:27 Percentile:10

R01 (4th Try, Resubmission)

Aim 1: Evaluate three different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and disability-adjusted life-year (DALY) averted.

Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women.

FUNDED!

Take-home points

- ✓ Process of creating your Specific Aims is iterative and messy!
- ✓ Opportunity to learn from reviewer feedback
- ✓ Often takes multiple submissions to get it right
- ✓ Keep trying; persistence is key!
- ✓ Sometimes you have to change the grant to satisfy reviewers, but then do what you want to once the grant is funded (like the syndromic arm)

Practice!

Start working on your own Specific Aims, remembering what you just learned. We are here to help you think it through!

What we've done this morning

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