Overview of Study Design Options Being Proposed for the Implementation of the Ebola Therapeutics Trial: Scientific, Statistical & Ethical Considerations & Implementation Challenges

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Conflicts of Interest

• None
Overview

• Phases of Development & Scientific, Ethical and Statistical Design Considerations
• Trial Operations/Implementation Challenges/Solutions
Core principles of science and ethics in conducting clinical research should not change during an epidemic

RCTs ethical and appropriate: most efficient, reliable way to determine safety and efficacy

Clinical research studies must have
- Scientific and social value
- Respect for/engagement with affected communities
- Post-trial access to candidate products proved safe/effective
### Outbreak Unknowns
- Where?
- When?
- Pathogens?
- Available Research capacity?
- Duration: average 4 weeks
- ? Epidemiology: SARS
- ? Pathogenesis: Ebola
- ? Predictive Animal Models

### Known EID Challenges
- Variable cultural context
- Establishing collaboration
- Establishing Trust
- Preparedness
  - EOC
  - Surveillance
- Rapid trial operation
- SMC/GPP
- Vulnerable populations
**Normative Design Elements:**

**Outbreak Therapeutics Study Designs**

<table>
<thead>
<tr>
<th>Goal: Fastest way to assess safety and efficacy with advanced plans to scale effective therapies</th>
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</table>

- Randomized
- Equitable
- Rapid/Simple
- Adaptive
- Flexible
- Continuous
- **Efficient**
  - Rigorous
    - Safety
    - Efficacy
- Ethical
  - Equipoise
Designing the 2018 Ebola Therapeutics Trial: 3 Phases

Aug. 10 - Aug. 23
• WHO R&D BP Ebola Therapeutics WG
• Goal: Develop Concept

August 28 - Oct. 2nd
• Protocol team: DRC MOH/INRB, NIAID, WHO, MSF, ALIMA, IMC, Companies
• Goal: Regulatory & Ethical approval of protocol version 2.0 (NIAID Oct. 2, DRC Nov. 20)

Oct. 11th - Ongoing
• Oct. 11 Ad hoc consultation to review design—Summary released Nov. 9th
• WHO reassess composition protocol team with NIH, no companies, 2 reps per group
• Goal: Rapidly revise protocol to align with outcomes in Nov. 9th meeting summary

13 days
36 days
NIH/FDA Approval +48 days
DRC IRB approval
48+ days
Design Elements Agreement 8/10:
- No oSOC only arm
- NHP safety data needed before combination therapy in people
- Agreement on ZMapp as control. Preference for two arms ZMapp vs Remdesivir, DRC Preference to include mAb114
- Randomized, multi-outbreak
- NIAID agreed to write a concept for 8/17

August 10th

August 17th

- Draft Concept: RCT, ZMapp vs. Remdesivir vs. mAb114
- Primary EP: 28 day Mortality
- Adaptive, multi-outbreak
- Superiority with secondary non-inferiority end of each outbreak,
- Close DSMB oversight, flexible Adding and dropping of arms
- Against: Some strongly favor oSOC only arm
- Arguments against secondary non-inferiority

August 23rd

- Compromise on two Options for control arm: 1) Zmapp + oSOC or 2) oSOC only
- DRC chooses Zmapp control arm over oSOC only
- NIAID agreement to develop protocol team & have revised draft protocol by Sept. 10th
In PREVAIL 2 ZMapp did not reach accepted level of certainty regarding efficacy (p=0.18 not usual P< 0.05) and is not therefore an established standard of care for EVD.

A higher mortality in an oSOC control arm would have a smaller sample size to determine efficacy of investigational agents.

Ethical to use oSOC only arm when there is no proven therapy.
Collective evidence from: Prevail 2 trend towards efficacy 2 sided $p = 0.18$ combined with NHP data and plausible MOA together suggest an impact on mortality.

EVD unlike other diseases: high mortality, vulnerable population

oSOC only is not ethical based on Principle of Beneficence

oSOC acceptability challenges
Developing the Protocol Team

**Preparations**

- Separate Telecons with key partners: DRC/INRB/WHO, MSF, ALIMA
- Meeting with the DRC MOH reps
- Informal FDA concept review suggested increasing type I error rate above usual 0.05
- Separate Telecons with:
  - Gilead
  - MappBio
  - VRC

**Aims**

1. Aim to ensure all partners were comfortable with a three arm RCT: comparing remdesivir and mAb114 to Zmapp control before first protocol team call
2. Asked each partner to identify one member for he team
Protocol Development: 7 team calls, (NIAID IRB 30 d, +49d DRC IRB Approval)

Protocol Distributed for Comment v .4
Back to WHO Ebola Thx WG

MSF Design Call

Consensus Developed on Concept

Operations Call: Pharmacy, Regulatory, Site Development, Training etc.

FDA Submission

Start in Beni

Protocol Team Reps
- DCR/NIAID
- DRC MOH/INRB
- MSF (Brussels/France)
- WHO-R&D BP HQ/FIELD
- ALIMA
- IMC
- VRC
- MappBio
- Gilead Sciences
- BARDA (added later)

SMC Call WHO/UNICEF

Scientific Pre-Review

Scientific Review & Approval

Submission to NIAID IRB

NIAID IRB Approval

Start in Beni

NIAID IRB Review

FDA Submission
Various views among team on many issues

- Concern not feasible—112/arm (N=336)
- Some favor addition of 4th arm with regeneron
- Some opposed articulating regeneron similar to Zmapp, citing increase in sample size
- Disagreement on ethics of continuation of MEURI at RCT sites

- Strong disagreement on what constitutes “optimized” standard of care on outcomes
- Concern Zmapp as control arm promoting Zmapp
- Concern that 50% reduction (30%-15% not feasible)
- Advocates for more than 2 stratification variables
195 written comments were received, and 137 were formally addressed in written responses back to the team.
Key Design Features: A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease (Version 2.0)

General

- 2 Options for control arm: ZMapp + oSOC vs. oSOC only
- Multi-Outbreak
- Close interim monitoring to introduce new arms, allow early stopping for: futility, efficacy, or safety.
- Comparisons of safety and efficacy will be based on data from concurrently randomized participants.

DRC

- Randomized: 1:1:1 to ZMapp, Remdesivir, mAb114
- N= 336 (112/arm)
- Study Population: Patients with known acute Ebola virus infection having symptoms of any duration
- Primary endpoint 28 day mortality
Proposed Design

EVD Patients
- +EBOV RT-PCR < 3 days
- Consent
- Contraception
- No other study first 28 days
- Agree to be randomized

Stratification CT < 22 vs CT > 22 -ETU

Day 1
- ZMapp
- Remdesivir
- mAb114 Day 1

Days 1, 4, 8
Once daily 10-14d

Day 28
Primary Endpoint Day 28 Mortality

Day 58
Semen collection (ETU discharge & day 58)

Data Collected Daily while in ETU
- Current symptoms, any new or worsening (S)AEs compared to baseline or last prior status, with focus on: targeted symptoms, organ dysfunction, failure, or possible drug toxicity
- Vital signs & oSOC received
- Laboratory: Creatinine, K+, Na+, AST/ALT, Ebola virus RT-PCR with CT
Objectives(1)

Primary Objective
• To compare the mortality in patients with Ebola virus disease who receive one of two different investigational therapeutics with those who receive ZMapp in the control arm.

Secondary Objectives
• To evaluate the safety and tolerability of investigational therapeutics relative to the control arm.
• To compare the change in viral load between study arms.
• To compare mortality rates among patients whose baseline predictors of disease place them in high-risk versus low-risk categories for disease severity.
• To compare mortality rates of investigational arms to the control arm up to 58 days after randomization.
Objectives(2)

Secondary Objectives (con’t)

- When possible, to evaluate the presence of Ebola viral RNA in the semen of male survivors at ETU discharge or Day 28 (whichever comes first) and Day 58.
- To assess the relationship between change in viral load over time with survival.
- To compare time to successful discharge from the ETU between participants receiving investigational therapeutics, relative to the reference control arm.
- To compare time to death of participants receiving investigational therapeutics, relative to the control arm.
- To collect data on the oSOC available in each participating ETU and, when possible, on the oSOC provided to each participant. (WHO, INRB)

Exploratory Objectives

- To assess comparative ease both of preparation and administration of the individual study agents.
- Pharmacokinetic assessments of investigational agents, when possible.
- Assessment of viral resistance over time, when possible.
Statistical Issues

- Sample size is based on an expected mortality rate of 30% by day 28 in the ZMapp arm, with a 50% relative reduction in the experimental treatment (i.e., rate of 15%).
- 85% power using a one-sided type I error rate of 0.05.
- No multiplicity adjustment

- A mortality rate of 30% for ZMapp is based, in part, on a meta-analysis (Dodd, L.) of eight clinical studies conducted during the 2014-2016 West African Ebola outbreak. indicated that the mortality rates within PREVAIL 2 (22.2 & 37.1) were lower than other studies across both treatment and control arms.
† Potential drug shortage. Randomization will become 1:1 during shortages. Comparisons will be relative to concurrently enrolled subjects.

In this schema drug A is dropped based on poor performance during an interim analysis. A determination about adding a new drug, “Drug C,” will be made. If a decision of superiority is made, the control arm may change, and comparisons would be based on concurrent enrollments relative to the new standard. Note that if a stopping boundary is not crossed, drug A will continue and drug C will not be substituted.

‡ In this schema drug A is dropped based on poor performance during an interim analysis. A determination about adding a new drug, “Drug C,” will be made. If a decision of superiority is made, the control arm may change, and comparisons would be based on concurrent enrollments relative to the new standard. Note that if a stopping boundary is not crossed, drug A will continue and drug C will not be substituted.
October 11th WHO Ad Hoc Consultation: Design Consideration

- Zmapp as control arm debated
- Arguments for oSOC control revisited
- Consensus around adding 4th arm regeneron
- WHO revise protocol team composition

- Proposed strategy trial—DAA vs. pool mAbs
- Revisiting desire for combination therapy design 2X4 (DAA vs. mAbs +/- DAA) 7 arms. Consensus need NHP data before moving in this direction
- Drug class effect approach proposed (i.e., combining mAbs)
### Proposed Strategy Trial: DAA vs mAbs

**Pros**

- Two arms - smaller sample size
- Includes all therapeutic candidates past phase I
- For some: Removes Zmapp as the control
### Proposed Strategy Trial: DAA vs mAbs

#### Cons

- mAbs may have different safety and efficacy profiles, and regulatory agencies advise against pooling.
- Combining arms implies particular mAb does not matter.
- Risk of combining arms with different mortality rates:
  - One could falsely conclude that a given antibody works even with no effect.
- Statistically challenging to show mAbs are similar. To rigorously prove this is a non-inferiority hypothesis test, which is challenging with a small sample size. Alternative to argue arms are similar in the absence of a significant difference is problematic.
- Interim monitoring is problematic due to small sample sizes.
Addition of Regeneron: Statistical & Sample Size Implications

- Zmapp vs. mAb114, remdesivir, regeneron
  - 3 comparisons, with two-sided type I error of 0.10 and no multiplicity adjustments leads to 24% chance of erroneously rejecting null hypothesis

- Therefore advising the following:
  - Increase in two sided type I error to 0.05, no multiplicity adjustments
  - Increase sample size 10 -13 per arm (112 to 125)
  - Total sample size for 4 arm vs. 3 arm: 500 vs. 336
  - Changes decrease chanced of erroneously rejecting null hypothesis to 12.5%
Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI): Conditions for Use

1) No proven effective treatment exists
2) It is not possible to initiate clinical studies immediately
3) Data providing preliminary support of the intervention’s efficacy and safety are available, at least from laboratory or animal studies...favorable risk benefit ratio for clinical trials
4) The relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;
5) Adequate resources are available to ensure that risks can be minimized;
6) The patient’s informed consent is obtained; and
7) The emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community.
ETHICAL RATIONALE MEURI

**Ethical basis for MEURI** — MEURI is justified by the ethical principle of respect for patient autonomy — i.e. the right of individuals to make their own risk–benefit assessments in light of their personal values, goals and health conditions. It is also supported by the principle of beneficence — providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival.

**Effective resource allocation** — MEURI should not preclude or delay the initiation of clinical research into experimental products. In addition, it should not divert attention or resources from the implementation of effective clinical care and/or public health measures that may be crucial to control an outbreak.
Transitioning from MEURI to RCT

- DRC IRB concerned about two protocols being in place at the same time.
- INRB leadership explained the need to phase in RCT at ETUs over time.
- INRB explained the need to continue MEURI for a patient who has already signed the MEURI consent.
- DRC IRB designated that MEURI would stop at an ETU once the RCT had started.
Response Research - Requires Integrated Science and Operations

Monitoring:
- Capacity Assessment
- Protocol Monitoring Plan
- Safety Monitoring Plan

Pharmacy:
- Randomization
- Capacity Assessment
- Drug Storage
- Cold-chain management
- Supplies
- Pharmacy staff training

Site Management:
- Capacity Assessment
- Patient Flow
- Site Staff Training

Social Mobilization:
- Capacity Assessment / and Local Situation Analysis
- SMC plan

Bio-statistics:
- Data Analysis Plan
- DSMB Reporting

Laboratory:
- Capacity Assessment
- Supplies
- Equipment
- Lab staff training

Regulatory & Ethics:
- Local Capacity Assessment
- IND & Local Reg Submissions
- IRB submissions
- Consent Form

Data Management:
- Capacity/Resource Assessment
- Case Report Forms
- Data Management System
- Data Table / Reports

Study Design

Scientific Decisions → THE PROTOCOL

MCM Selection

Clinical Assess Schedule
Implementation at the ETU-Overview

- INRB led with ALIMA support
- Study team, with specific roles and responsibilities works in parallel to Clinical team.
- Study team responsible for randomization, CRFs, follow-up, reporting to oversight bodies
- Clinical care comes first and study team should not impede clinical care.
- Study team and CRFs do not need to go into the hotzone
- Site activation check list to ensure site is ready
- Three weeks of training for the first team-off and on site
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<thead>
<tr>
<th>Role</th>
<th>Responsibility</th>
<th>Number Needed</th>
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<tbody>
<tr>
<td>Site PI</td>
<td>• Ultimately responsible for the conduct of the study</td>
<td>Currently 2</td>
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<tr>
<td></td>
<td>• Study oversight</td>
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<td></td>
<td>• Required to fill out Eligibility, SAE and End of Study CRFs</td>
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<td></td>
<td>• Obtains informed consent and required documentation</td>
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<tr>
<td>Study Coordinator</td>
<td>• Organizes study flow and operations</td>
<td>Currently 1</td>
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<td></td>
<td>• Facilitates study communications</td>
<td></td>
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<td></td>
<td>• Completes study CRFs</td>
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<td></td>
<td>• Works with data management and study team to resolve study queries</td>
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<td></td>
<td>• Maintains Delegation log</td>
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<td></td>
<td>• Submits contents to eRegulatory Binder</td>
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<td></td>
<td>• Obtains informed consent and required documentation</td>
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<tr>
<td>Study Staff Physician (currently listed as “Clinician”)</td>
<td>• Provide back-up to the Site PI and Study Coordinator</td>
<td>1</td>
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<tr>
<td></td>
<td>• Performs study assessments</td>
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<tr>
<td></td>
<td>• Completes study CRFs</td>
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<td></td>
<td>• Obtains informed consent and required documentation</td>
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<tr>
<td>Study Nurse</td>
<td>• Assists with collecting data and filling out CRFs</td>
<td>3</td>
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<tr>
<td></td>
<td>• Supplement Clinical Team as needed to continue the research</td>
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<tr>
<td>Study Pharmacist Supervisor</td>
<td>• Oversees the study pharmacy activities including randomization, preparation of study agents,</td>
<td>1</td>
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<tr>
<td></td>
<td>cold chain and drug supply</td>
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<td></td>
<td>• Back-up to Study Pharmacist for Randomization</td>
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<tr>
<td>Role</td>
<td>Responsibility</td>
<td>Number needed</td>
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<tr>
<td>Assistant Study Pharmacy Supervisor</td>
<td>• Quality Control of Randomization and Drug preparation procedures</td>
<td>Currently 1</td>
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<td></td>
<td>• Oversees all study pharmacy documentation</td>
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<td></td>
<td>• Back-up to Pharmacy Supervisor</td>
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<td></td>
<td>• Back-up to Study Pharmacist for Randomization</td>
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<tr>
<td>Study Pharmacist</td>
<td>• Randomization Procedure</td>
<td>Currently 1 – need to confirm</td>
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<tr>
<td></td>
<td>• Communicating Randomization Assignment to Study Nurse (drug preparer)</td>
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<td></td>
<td>• Maintenance of Randomization study documents</td>
<td></td>
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<td></td>
<td>• Cold Chain storage/monitoring</td>
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<tr>
<td>Study Pharmacist (currenty listed as psychosocial counselor)</td>
<td>• Socializes participant to study in the holding center</td>
<td>Currently 2</td>
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<td></td>
<td>• Provision of study flip book to participants</td>
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<td></td>
<td>• Continuous follow-up of participants throughout the study</td>
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<tr>
<td>Drug preparer (study nurse)</td>
<td>• Prepares study drug</td>
<td>Currently 3 – need to confirm</td>
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<td></td>
<td>• May also assist in study drug administration (as discussed in Kinshasa)</td>
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<tr>
<td>Study Psychosocial Specialist (currently listed as psychosocial counselor)</td>
<td>• Oversight of study data collection and scanning at the site</td>
<td>Currently 1</td>
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<tr>
<td>Study Data Manager</td>
<td>• QC of CRFs</td>
<td>Currently 3 – need to confirm</td>
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<tr>
<td>Study Data Management/Assistant Clinical Research Associate</td>
<td>• Scan CRFs to Huddle/ICC</td>
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<td></td>
<td>• Maintain record of scanned documents</td>
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<td></td>
<td>• Organize query responses and send corrections to Huddle/ICC</td>
<td></td>
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<tr>
<td>Study Lab Supervisor (currently listed as Lab Supervisor)</td>
<td>• Responsible for study lab results and required study documentation</td>
<td>Currently 1</td>
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<td></td>
<td>• Responsible for communicating and providing documentation of study lab results to ETC study staff</td>
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<tr>
<td>CTE Lab Technician</td>
<td>• Responsible for study lab results</td>
<td>Currently 1</td>
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<tr>
<td></td>
<td>• Available to assist with study lab processing</td>
<td></td>
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<tr>
<td>Data Lab Technician</td>
<td>• Responsible for study lab results</td>
<td>Currently 1</td>
</tr>
<tr>
<td></td>
<td>• Responsible for accurate recording of all study lab results on CRFs</td>
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<tr>
<td>IT Assistant/Logistician</td>
<td>• Provide IT support to the site related to connectivity and devices</td>
<td>Currently 3</td>
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Site Activation Requirements

Reg Binder

- Signed and Dated Form FDA 1572 (Original) (IND studies only) OR Investigator Agreement (IDE studies only)
- Federal Wide Assurance Number (FWA #, IRB#, IORG)
- Investigator’s Brochure (IND studies only) / Package Insert/ Report of Prior Investigations (IDE only)
- SRCP OR signed TORO (IND studies only)
- Copy of the IRB/EC approval letter(s)
- Copy of the IRB/EC approved protocol(s) and amendment(s)
- Copy of the IRB/EC-approved informed consent(s) and translations (if applicable)
- PI CV (must be signed and dated and current within the last two years)
- PI Medical License (must be current)
- Authorized Representative Sheet/Delegation Log

Training

- 3 weeks total for study team plus overview for the ETC Clinical team
  - GCP
  - Role Specific training
  - Pharmacy
  - Data management
  - Multiple dry runs
  - Review SOPs
Site Activation Requirements

Additional Key Essential Documents Required During the Study

- Current IRB(s)/EC(s) Membership List/IRB/EC Roster(s)
- Laboratory Certifications for all laboratories performing clinical laboratory tests
- Laboratory normal reference ranges for all clinical laboratory tests to be performed in the study protocol or a note to file to the applicable web sites (if a historical list is maintained)
- CVs (signed and dated and current within the last two years) for:
  - IND- all Sub Investigators listed on Form FDA 1572
  - IDE- all staff listed on the Investigator Agreement
  - Non-IND at the Clinic Center- the lead SC or AI only
  - All other Non-IND- any other clinician (MD, NP, PA, etc.) that are delegated to obtain consent AND either evaluate subject eligibility OR AE/SAE assessment
- Medical Licenses for all staff as listed above for CVs.
- Screening/Enrollment Log
- Communication from Site to Sponsor
- Protocol Amendments and ICF amendments and their corresponding approvals
- IRB/EC Continuing Review approvals
- Final CRF pages and corresponding instruction set
- Study Manuals
- Monitoring Plan (signed original)
- Protocol Signature Pages
- Site SOPs/Procedures
- Drug Accountability information and documents
- Randomization Log
- Sponsor Confirmation and Follow Up Letters for all Site Visits
- Protocol Deviations
- Data tables/pulls
Social Mobilization, Communications, and Community Engagement (SMC) and Psychosocial Teams

• Psychosocial team and SMC team will work collaboratively to follow survivors, facilitate integration back into community, clinical care, address counseling needs etc.
Implementation Ongoing Support/Oversight

• Daily calls with the field to review challenges, questions
• Monitoring
• DSMB
• NIAID IRB
• U. Kinshasa IRB
• Development of WHO governance structure
Summary

Numerous scientific, ethical, statistical operational challenges but collective good will to rapidly advance an ethical, scientifically rigorous study while building capacity within the DRC to conduct clinical research.