Summary of clinical trial and regulatory discussions

Regulatory considerations

- The trial should collect data that could support a “full” regulatory approval of a Lassa vaccine
  - Post marketing data can further support this approval
  - We don’t have information about an immune marker that could be used for a conditional approval
  - An LV vaccine would not currently meet criteria for emergency use

- Success criteria should include 95% lower bound on efficacy in range of 0>LB<30%. An LB around 10-20% may be appropriate. This may allow collection of robust efficacy data in a single season
- Ideally, the trial will support efficacy against all lineages. This will require inclusion of different geographic regions and close collaboration between stakeholders
  - If there are few cases in the trial of some lineages, it may be possible to use an immunobridging approach to further support efficacy against those lineages
    - Immumobridging is more complex because NAbs likely aren’t the main mechanism of protection
    - Immunobridging will require confidence in assays across different lineages
    - It will be essential to collect cross-lineage immune response data before entering phase 3

Regulatory considerations

- Phase 2 studies should be robust
  - General consensus is that phase 2 should include 500-600 participants
  - This should include collection of data on hearing as a key possibly immune-mediated AESI
  - Phase 2 will support full age range in trial
  - We need immune response data relevant to all lineages in phase 2

- It will be most efficient to design trial to address “reactive” setting first

Regulatory considerations

- AVAREF will contribute to trial results evaluation
  - This is another area where collaboration will be critical
- Decisions about vaccine use should consider wide input
  - Community engagement may be needed to promote wider understanding of LV
  - Trial should support decisions about how vaccine will be used
  - Clinical trial endpoints need to support indications for use, which should be focused on clinical disease

Key clinical trial features

- Trial governance agreed in advance, based on a core protocol that facilitates collaboration (but allows for add-on data collection)
- Individually randomized RCT of a single vaccine at a time
- Epidemiological data used to identify locations of expected high transmission
- Vaccine selection to be made by an independent objective prioritization committee that considers all the relevant data
- Age range should include <18 as feasible
- Endpoint: PCR confirmed clinical illness using standardized case definition and a standardized assay that will be performed in each country
  - Malaria can sometimes confound the diagnosis
- Pre-vaccination serology will be important.
- Secondary endpoints: severe disease, infection (recognizing that the trial may be underpowered for severe disease, and vaccine is expected to be less effective against infection vs. clinical disease)
- Exploratory endpoints: possible CoPs, other outcomes including mortality
- Expected trial sizes needed to address efficacy are expected to provide a robust safety database
  - The trial should collect information about pregnancy outcomes
- Duration of follow-up needs to accommodate intensive surveillance for first season after vaccination, plus collect enough information to support subsequent preventive indications