MalVax Alliance

30 June 2026

# Annex A: Technical Scope for Clinical Trial Design and Endpoints Working Group

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| **Relates to** | MalVax Alliance Working Group Terms of Reference (Umbrella TOR) |

## 1. Summary Goal

The MalVax Alliance brings together the malaria vaccine R&D community to efficiently and effectively accelerate progress on urgently needed next-generation vaccines. The MalVax Endpoints & Trial Design Working Group ("Endpoints WG") will harmonise approaches and maximise comparability across future Phase 1-3 clinical trials performed by independent groups; consider evaluation methods that, where possible, assess the full impact/value of next-generation malaria vaccines; and facilitate future regulatory approval and policy guidance.

## 2. Background and Rationale

More than 150 members of the malaria vaccine research and development community met during side meetings of the 2024 and 2025 ASTMH conferences. The meetings identified clinical trial endpoints and design as a key challenge and the need to coordinate early to support comparability, allow translation, and facilitate understanding of the full value of a vaccine.

These two consultations identified a number of key themes that need to be addressed for next-generation malaria vaccines to advance most effectively and efficiently. Among the themes, participants noted that clinical trial endpoints (and design) should be selected for the strategic goal of the vaccine (reducing burden, preventing infection and/or reducing transmission) and that clinical trial designs must adapt as the approved vaccines are rolled out and resources are constrained. They also noted that the complexity of malaria transmission dynamics may require more than one type of vaccination approach, and multiple next-generation malaria vaccine candidates may be useful in different contexts. They went on to conclude that progress will be accelerated by the community and that comparability across studies could be greatly improved (without stifling independent vaccine R&D programs), via a more harmonised approach to clinical trial design and endpoint selection.

In order to advance this harmonisation, the working group will consist of two subthemes, in recognition of the unique considerations, including epidemiology, immunology and regulatory, for vaccines targeting:

- Infants and children under age 5, and
- Children over age 5 and adults.

Endpoints and design of controlled human malaria infection (CHMI) trials are valuable for the development of malaria vaccines, but will be out of scope for this WG in year 1.

## 3. Scope and Priority Deliverables (Feb 2027)

By February 2027, the MalVax Endpoints & Trial Design Working Group deliverables will include:

1. **Practical guidance** document(s) on
   i) the **definition for a range of possible endpoints** for future clinical trials (alongside rationale and value of measuring);
   ii) other **parameters / variables in trial design** that impact inter-trial comparability (alongside rationale and value of measuring and if knowledge gaps exist); and
   iii) **novel approaches to trial design** for emerging endpoints, e.g. control groups; cluster-randomised; platform; non-inferiority/superiority; school-age children (i.e. over age 5); infection-blocking.
2. Identification of **knowledge gaps** associated with trial design and endpoint selection and a **pathway(s) for addressing.**
3. **Linking clinical trial groups** (especially those undertaking or planning Phase 2 trials) to the malaria vaccine Modelling and Assays WGs as relevant.

In order to achieve these priorities, the WG will:

### 3.1. Assess current practice

- **Review current practice** across i) vaccines developed for burden reduction, block of transmission and/or elimination, and ii) field efficacy trials in different age groups (infants through adults).
- Identify, brainstorm and discuss **malaria vaccine efficacy endpoints** including current state-of-play and possible new/exploratory endpoints.
- Based on the assessment, prioritise subsequent deliverables.

### 3.2. Consolidate state of the field on trial endpoints into resources for researchers

- Develop a "**guide" of endpoint options** including reasoning/rationale for use of each (i.e. the "why") and critical caveats / knowledge gaps related to the endpoint. Possibly landing on a minimal recommendation.
  i) This would also include discussion of **refinement and/or best practice** in the hope we move towards community-alignment within the practical guidance document;
  ii) The "why" should include WG assessment of how the **endpoint could add to the assessment of the vaccine candidate's full impact**.
  iii) **Recommendation for prioritisation** of the options (e.g. by defining minimum considerations.)
- **Identify key variables** that may be confounders or have impact on trial endpoints and design (e.g. SMC, drug treatment at time of vaccination, bednet use, etc.) and recommend an aligned approach going forwards, or highlight issues in the "guide", that should be considered in protocol design.
- Identify **knowledge gaps**, highlighted where relevant for each endpoint.

### 3.3. Incorporate modelling insights

- Include **input from malaria modelling community,** such as lessons learnt from R21/RTS,S, experience from clinical trial data collection, and how endpoints are modelled for public health assessment, and regulatory and WHO review.

## 4. MalVax Scientific Conference, February 2027

The following outputs from the WG will contribute to the inaugural MalVax Scientific Conference anticipated in the first week of February 2027:

- **Present progress, discuss and seek feedback** on the emerging "guide" and identified knowledge gaps.
- The WG Co-Chairs will **engage with the MalVax Scientific Planning Committee** to ensure Endpoints and Trial Design topics are well represented in the programme and that the forum concept is introduced to the broader community at the conference.

## 5. Beyond February 2027

Following the Scientific Meeting (Feb 2027), the WG will build on its early work to:

- **Systematically share learnings** that support clinical trial thinking and design across the community.
- **Provide targeted support** on clinical trial endpoints and design when requested and Chair/Co-Chairs determine it is feasible, including within other Working Groups and through joint publications.
- **Expand progressively** with sub-groups, consideration of additional groups such as pregnant women or immunocompromised, CHMI and deeper inclusion of complementary expertise and implementation-focused stakeholders.

The **WG will develop prioritised research questions and activities** for the next phase of the MalVax Alliance's work potentially including:

### 5.1. Aligning on novel study designs

- **Novel approaches to next-generation malaria vaccine trial design** potentially for expansion after February 2027, e.g. cluster-randomised; platform; non-inferiority/superiority; school-age children (SACs); pregnant women; infection-blocking; and cross-cutting ways to accelerate trials.
- Harmonisation of **safety endpoints.**
- Harmonisation of **immunological endpoints,** building on linkages to the Assays WG.
- Endpoints for controlled human malaria infection (**CHMI**) trials in adults in Africa.

### 5.2. Expanding regulatory, policy and implementation considerations

- **Dosing and schedule considerations** by age group.
- **Regulatory strategies and policy implications** of endpoints and trial design for multi-stage or multi-component vaccines, e.g. which endpoints should be prioritised and/or which can add extra data for full vaccine value assessment?
- Alignment of malaria vaccine **trial site network** in Africa to emerging priorities.

## 6. Collaboration

### 6.1. Other MalVax Working Groups

The Endpoints and Trial Design has a cross-cutting role within the MalVax Alliance. It will work closely with:

- **Assays WG:** linking immunological / assay readout considerations, and
- **Modelling WG:** incorporating modelling inputs.

Individuals named as Endpoints and Trial Design subtheme liaisons by the Chair/Co-Chairs will participate in cross-WG coordination meetings, and the WG will share draft outputs with other WGs for comment before finalisation.

### 6.2. Existing Guidance

The WG will take stock of and build on existing WHO guidance and documents from the community, including:

- *Malaria Vaccines: Preferred Product Characteristics and Clinical Development Considerations* (WHO, 2022)
- *Guidelines on the Quality, Safety and Efficacy of Recombinant Malaria Vaccines Targeting the Pre-Erythrocytic and Blood Stages of Plasmodium falciparum* (WHO, 2020)
- Report of an expert consultation on the clinical development plan for a multistage malaria vaccine targeting the circumsporozoite (CS) and blood stage (BS) antigens (PATH/USAID, 2023)
- 2018 malaria vaccine meeting report: Building momentum for malaria vaccine research and development: key considerations (Chitnis, et al, 2020)

WG outputs will be designed to complement, not duplicate these documents, with a focus on practical, community-facing guidance that goes further into implementation and methodology.