2nd IABS RWE workshop
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Alternative Approaches to Phase 3 Clinical Trials for Vaccine Efficacy and Licensure: the role of Real-World Evidence

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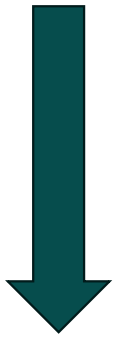
Day 1 – Summary

- Challenges of vaccine development in low-incidence diseases (GBS)
- Overview of vaccines licensed without Phase 3 RCT efficacy data
- Insights on alternative evidence:
  - **Animal models**
  - **Human infection models**
  - **Correlates of protection**
- Panel discussion on managing uncertainty at initial approval
- Role of **Real-World Evidence** from observational and pragmatic studies
- RWE case studies across multiple vaccines: Mpox, MenB, Ebola, Chikungunya, Dengue, Pneumococcal, COVID-19
- Increasing need for flexible, science-based pathways integrating multiple evidence sources

Day 1 – Key takeways

RCTs not always feasible

Observational studies prone to bias



Pragmatic trials may provide a solution: reduced bias through randomization

PT as a lean RCT, minimalistic data collection

No one-size-fits-all: portfolio of study designs to show efficacy/effectiveness

Day 2 – Summary

- Several very informative examples of pragmatic trials for various vaccines:
  - High-dose vs. standard-dose influenza vaccines
  - RSV vaccine effectiveness against hospitalizations
  - RSV correlates of protection from South Africa
  - Finnish experience using probe-based pragmatic trials
- Panel discussion: barriers, enablers, and requirements for pragmatic trials
  - Relatively new kid on the block: not all regulators aware, need training and information, share experience and align between regions
  - Ethics: generally, not a concern, as pragmatic trials will only be done for approved vaccines (phase 4) but only if supply issue and/or not recommended – IC is key
  - Answering questions unanswered in the RCT is a strong rationale : new data is in everybody's interest.
  - Needed between licensure and recommendation
  - cannot be done in a lot of countries. Could be done in Africa for ex through a CRF (minimalist data collection)
  - PH institutes best placed to conduct?
  - Generalizability
  - The impact of open-label design?
  - How to get PT-derived data into the SMPC?
  - Cannot be used for original licensure yet

Breakout 1

Theme: When are alternative approaches needed?

Limits of Phase 3 trials

Rare diseases / low incidence

Urgent public health needs

Breakout 2

Theme: What alternative approaches exist?

Immunobridging

Correlates of protection

RWE-supported approaches

Adaptive/platform designs

Break-out 1

Alternative scenarios:

- Registration of combination vaccines
- well designed pragm post-licensure could lower the pivotal bar
- additional antigens
- for viruses on the same family (next Filo)
- CHIM for conditional approval followed by pragm trial

Hurdles:

- alignment between the regulators: things are moving forward (PAHO, AVAREF, EMA)
- Generalizability of the data
- Industry could drive the regulators harmonization need a mechanism

Break out 2

- Sc 1: outbreak response using investigational products
  - Rwanda for Marburg : decided by local regulators for their population
  - Need animal or immune, validation of biomarker, minimal safety data (Ph1/2, 3M Follow-up)
  - Scarce amount→ PT, cluster design, human challenge, validation of biomarker
  - Self-controlled risk interval , TNCC

- Sc 2: Roll-out under EUA:
  - Randomized allocation (ring vaccine type) ASAP.
  - Robusntess of data : the more severe the disease, the less robust. Trend to insist on more robust data for poorer countries.
  - EMA M4all (art 58) mechanism unique
  - Depends if limited vaccine supply: case for randomization easier. If lot of vaccine → TNCC + collect blood samples for CoP

- Sc 3 Post-marketing commitments when alternate approaches were used:
  - Scientific justification for commitments (eg pregn registr for travel vaccine) more guidance is needed
  - Validation of biomarker embedded in TNCC?