World Health Organization

General considerations for CORE protocols for vaccine trials in the context of outbreaks

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WHO R&D Blueprint

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Powering research to prevent epidemics

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Guiding principles

A successful vaccine trial needs to **randomly** put the vaccine(s) and comparator were **transmission of the infectious agent** of interest is occurring

- **Randomized** evidence
- **Sufficient number** of endpoints

This requires a core protocol that provides reliable randomized evidence over one or more outbreaks over time and space

Group sequential methods are used until pre-determined endpoints are met

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Trial design choices to **demonstrate VACCINE efficacy** include:

- **Randomized clinical endpoint trials**
  - Individually randomized
    - Large scale (many locations and/or countries), and/or
    - Randomization within clusters
  - Cluster randomized
  - Pragmatic trials (including randomization during deployment)
- **Randomized trials, both individual and cluster, should provide immunological evidence for**
  - Correlates of protection/risk
  - Immunobridging

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Some disease factors that can influence **trial design choice**

- Incidence and distribution (including higher risk groups)
- Transmission, outbreaks, and seasonality (R_0, mode of spread, can clusters be identified?)
- Natural history (incubation period, severity, rapidity of onset)
- Immune response (pre-existing immunity, correlates of protection)
- Severity and public health urgency

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Core protocols

- Primary outcome is laboratory confirmed clinical illness
- Vaccine safety
- Secondary outcomes
  - Severe disease
  - Disease outcome in specific subgroups
  - Viral load
  - Viral shedding
  - Infection
  - Asymptomatic infection

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Core protocols

- Secondary outcomes for immunogenicity data endpoints
  - Neutralizing antibody responses
  - Cellular immune responses
  - Duration of immunity
- Exploratory outcomes

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Trial governance

- Trial oversight Trial oversight will be provided by a **single Steering Committee** (SC) and a **single data monitoring committee** (DMC).
- Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data.
- The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues.
- Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.

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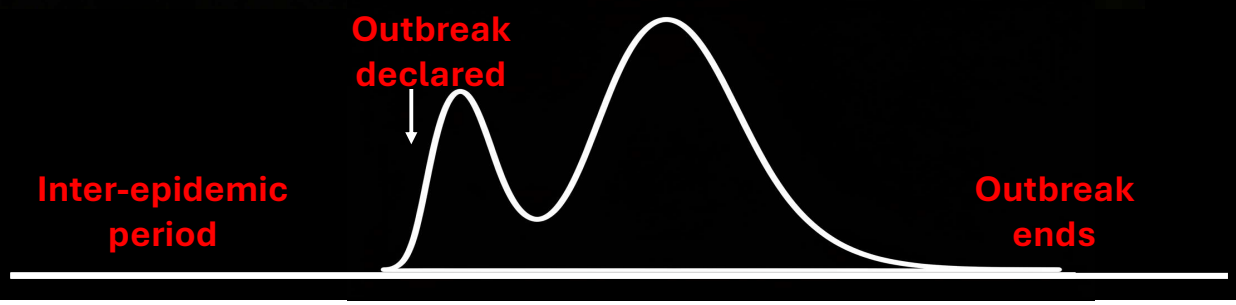
CORCs supporting development of research priorities and rapid assessment of candidate MCMs during outbreaks

1. Prioritization of candidate MCMs
2. Availability of candidate doses
3. CORE protocols ("pre-approved")
4. Agreements with developers
5. Funding for trials initiation
6. COLLABORATION
7. Research priorities outbreak
8. Prompt initiation of RCTs (within a week)
9. Encourage high-quality collaborative research
10. Review Outcomes/ Impact of research



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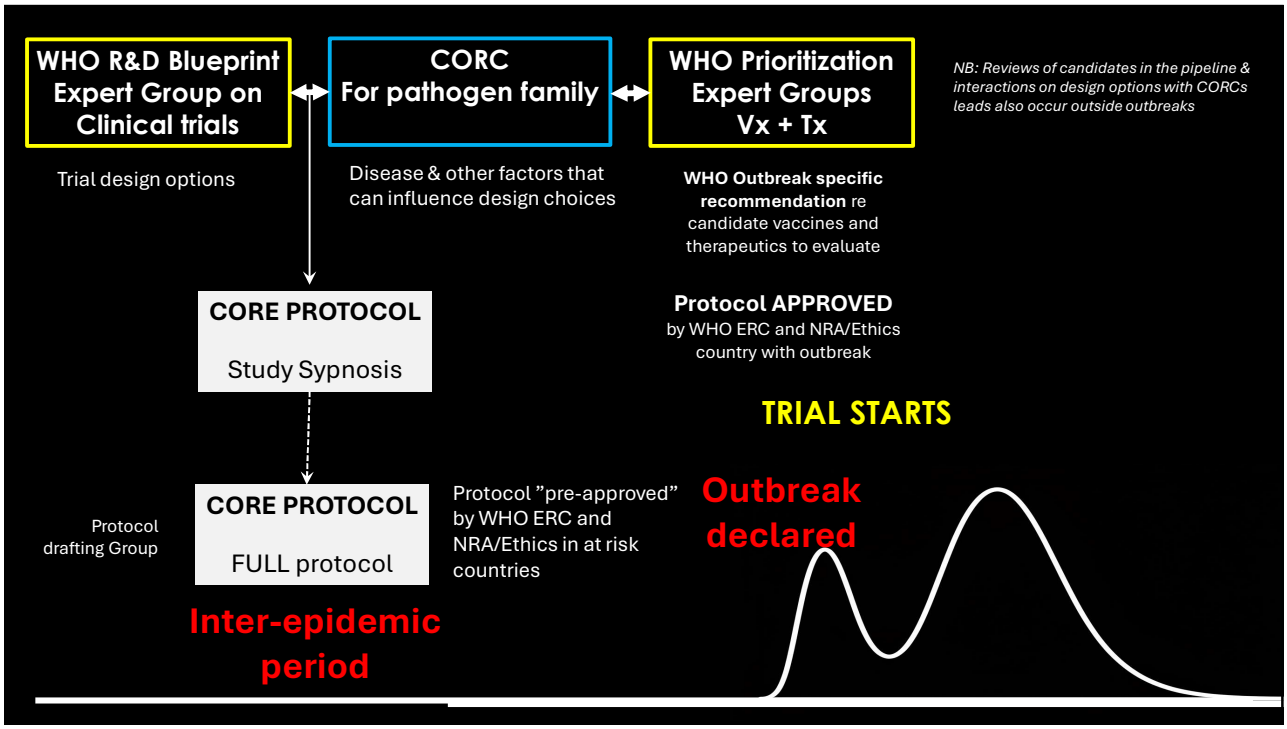

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Way Forward

WHO R&D Vaccine Trials Working Group

- Agreement on trial design synopses
- Match designs to the families and or priority and prototype pathogens
- Produce fully written CORE protocols
- Monthly meetings of the group
- Ad-hoc regular meetings of the subgroups

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Thank you

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