R&DBlueprint
Powering research to prevent epidemics

22 April 2026
13:00 – 18:15 Central European Time

# Trial Designs to Evaluate Pre-Exposure Prophylaxis

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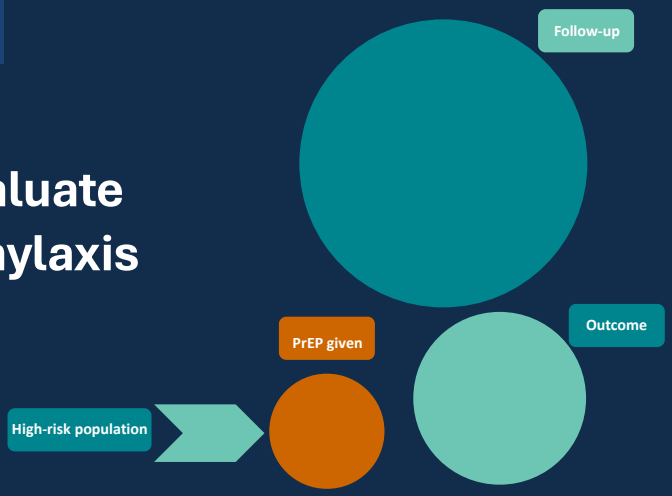


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## Why PrEP Trials Matter in Outbreaks

- ✓ Preventive countermeasures given before exposure can protect identifiable high-risk groups during outbreaks.
- ✓ The trial design challenge is to generate credible efficacy and safety evidence despite shifting incidence and operational constraints.
- ✓ PrEP is most relevant when transmission risk is concentrated in identifiable groups before exposure occurs.
- ✓ Examples include healthcare workers, household contacts, burial teams, laboratory staff, and hotspot communities.
- ✓ Prepared designs can accelerate evidence generation for emergency use, policy, and future licensure within a pathogen family.


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## The Core Design Question

**Who to enroll**
Prospectively identifiable high-risk groups

**What comparator**
Placebo, optimized standard prevention, or active control

**What endpoint**
Incident infection, severe disease, safety, adherence

**When to adapt**
Activation, stopping, sample-size re-estimation, site shifts

References: Delany-Moretlwe S, et al. HIV Clin Trials. 2017;18(5-6):177-188. PMID: 29039265. Study Design Considerations for Evaluating Efficacy of Systemic PrEP Interventions.

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## Candidate Trial Designs

| Design | Best use case | Main strength | Main limitation |
|---|---|---|---|
| **Individually randomized** | Person-level risk; limited contamination | Strongest causal inference | Sensitive to falling incidence |
| **Cluster randomized** | Group-based delivery or spillover | Operational realism | Larger sample size needed |
| **Pragmatic rollout** | Program deployment during emergency | Integrates research and response | Confounding if poorly controlled |
| **Adaptive platform** | Multiple candidates/shared infrastructure | Efficiency and flexibility | Needs strong advance planning |

References: WHO workshop agenda, 22 Apr 2026. Delany-Moretlwe S, et al. HIV Clin Trials. 2017;18(5-6):177-188. PMID: 29039265.

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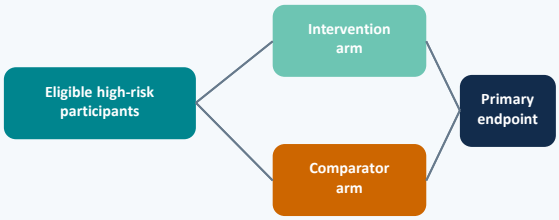
## Individually Randomized PrEP Trials

Preferred when the goal is a fast and unbiased efficacy estimate and contamination is manageable.

Works best when high-risk participants can be identified prospectively and followed with standardized surveillance.

Main threats are rapidly changing incidence, event shortfalls, and ethical change once effective prevention exists.




References: Rajasingham R, et al. Clin Infect Dis. 2021;72(11):e835-e843. PMID: 32995820. Abella BS, et al. JAMA Intern Med. 2021;181(2):195-202. PMID: 33001138.

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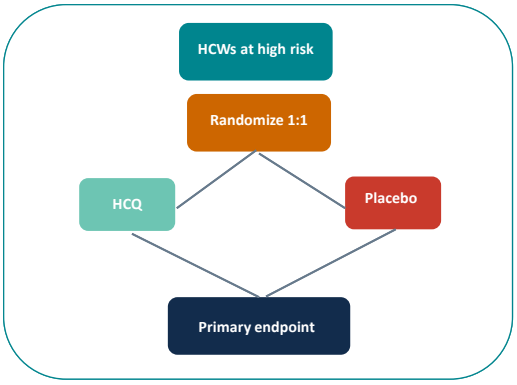
## Practical Example: Individually Randomized Design

COVID-19 PrEP in healthcare workers

Example from the literature: double-blind placebo-controlled hydroxychloroquine PrEP trials among healthcare workers with ongoing exposure to COVID-19.

Typical structure: 1:1 individual randomization, person-level eligibility, and a primary endpoint of confirmed or probable COVID-19-compatible illness.

Methodological lesson: this design is strongest when high-risk persons can be identified prospectively and contamination between arms is limited.

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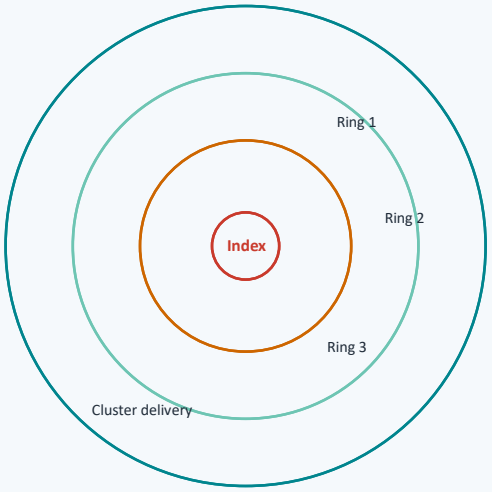
## Cluster and Ring-Based Designs

Useful when exposure or delivery is organized by facility, district, contact network, or deployment unit.

Can better capture indirect protection and match how the countermeasure is deployed in practice.

Trade-offs include more participants, intracluster correlation, and greater risk of cluster-level bias.




References: Henao-Restrepo AM, et al. Lancet. 2015;386(9996):857-866. PMID: 26215666. Henao-Restrepo AM, et al. Lancet. 2017;389(10068):505-518. PMID: 28017403.

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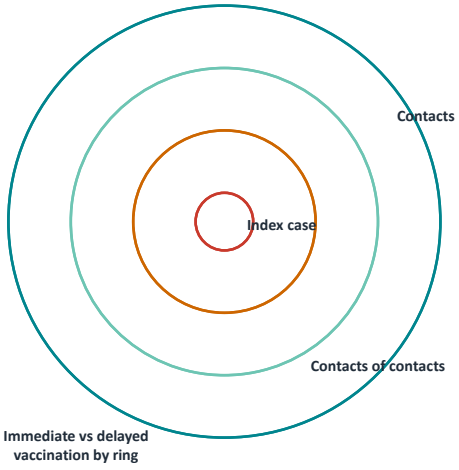
## Practical Example: Cluster-Randomized Ring Design

Ebola ça Suffit! ring vaccination trial in Guinea

Contacts and contacts of contacts around a confirmed Ebola case were assembled into rings and randomized to immediate versus delayed vaccination.

This aligned trial recruitment with transmission chains and allowed evaluation during a rapidly evolving epidemic.

Methodological lesson: when exposure is structured around networks or rings, cluster randomization can be both rigorous and operationally realistic.

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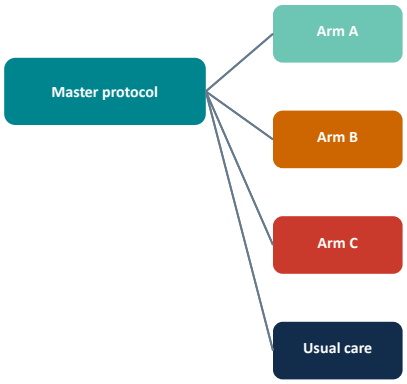
## Practical Example: Adaptive Platform Design

PANORAMIC community trial during COVID-19

PANORAMIC used a master protocol to add or stop antiviral arms as evidence evolved during the pandemic.

The platform allowed shared infrastructure, interim analyses, and rapid assessment of multiple candidate interventions in high-risk outpatients.

Methodological lesson: platform methods can preserve speed and comparability when several candidate products emerge sequentially.




References: Butler CC, et al. Lancet. 2023;401(10373):281-293. PMID: 36566761. Platform-adaptive master-protocol methods as implemented in PANORAMIC.

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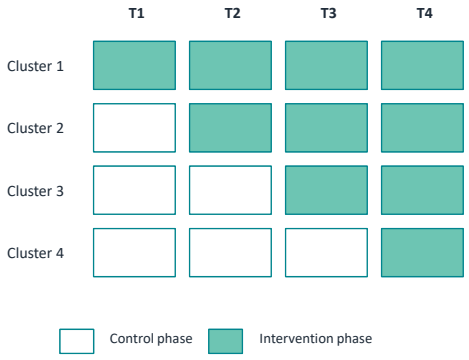
## Practical Example: Stepped Rollout / Stepped-Wedge Design

Phased implementation when simultaneous rollout is not feasible

In stepped-wedge cluster randomized trials, clusters cross from control to intervention in a randomized sequence over time.

This is useful when logistics or ethics favor phased rollout rather than permanent withholding of the intervention.

The prevention literature includes phased malaria-control implementation studies that illustrate how rollout designs can be embedded in real-world programs.




References: Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. BMJ. 2015;350:h391. Palmer JJ, et al. Lancet Glob Health. 2019 stepped implementation example.

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## Can MEURI be used for prevention with pre-exposure prophylaxis?

Yes, potentially. WHO guidance frames MEURI as emergency use of unproven clinical interventions outside trials during public health emergencies, and related ethics commentary notes that unproven *prophylaxis* may also be considered when no proven options exist and trial access is not immediately feasible.

### Practical reading for outbreak PrEP

**Target population:** persons at very high exposure risk before infection, for example frontline workers or close contacts in sustained transmission settings.

**Intervention type:** investigational vaccine, monoclonal antibody, or drug intended to prevent infection or severe disease.

**Ethical tension:** offering access quickly while still collecting interpretable safety and outcome data and not displacing proper trials.

https://www.who.int/publications/i/item/9789240041745

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## When outbreak PrEP under MEURI is ethically strongest

**Justification:** the outbreak creates serious risk, standard prevention is absent or inadequate, and waiting for a trial would expose a clearly identifiable high-risk group.

**Evidence threshold:** there is preliminary evidence of safety and biologic plausibility or early efficacy signal for the preventive use, but not enough evidence for routine deployment.

**Oversight:** a protocol defines eligibility, dosing schedule, follow-up, adverse-event reporting, consent, and rules for stopping or transition to research.

**Trial protection:** MEURI use should complement, not delay, rapid randomized or other rigorous studies whenever these become feasible.

### Decision balance for preventive use


**Key nuance:** because pre-exposure prophylaxis is given to people who are not yet ill, the acceptable harm threshold is generally tighter than for emergency treatment; that makes safety monitoring, consent, and fair selection especially important.

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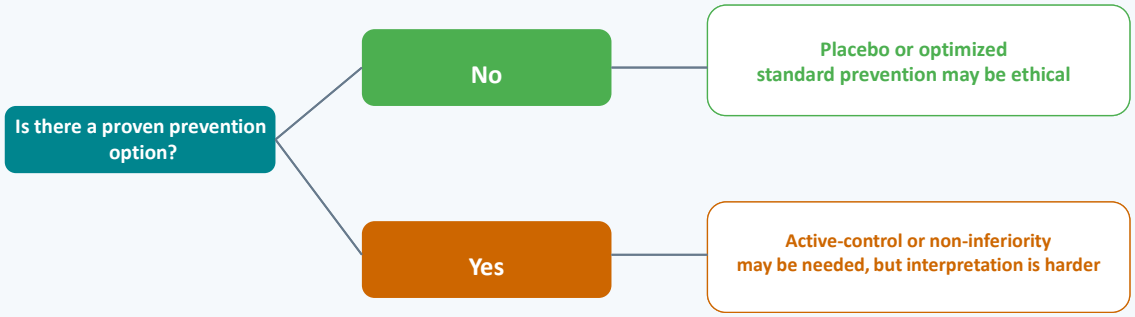
## Comparator Choice Is Decisive




References: Delany-Moretlwe S, et al. HIV Clin Trials. 2017;18(5-6):177-188. PMID: 29039265. WHO workshop agenda, comparator discussion.

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Example 1

## PrEP analogue: active-control non-inferiority when placebo is unethical

**Scenario.** A next-generation preventive product is compared with a standard effective option because withholding prevention is unacceptable.

- Primary question becomes non-inferiority or inferiority or superiority versus active control, control, not product-versus-nothing.
- Credible interpretation requires adherence measures, exposure assessment and a justified margin linked to preserved benefit.
- The same logic applies to outbreak vaccines when a first-wave product already exists but a second-wave candidate may be easier to deploy, broader, or more durable.

### Design transfer

PrEP trials teach that regulatory-grade evidence can still be generated without placebo if the comparator, margin, assay sensitivity and implementation context are explicit.

| Question | PrEP | Outbreak vaccine |
|---|---|---|
| Comparator | Standard oral PrEP | Authorized first-wave vaccine |
| Main endpoint | HIV incidence | Lab-confirmed disease |
| Critical bias | Adherence misclassification | Exposure and case ascertainment shifts |

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Example 2

## PrEP analogue: counterfactual incidence when events collapse

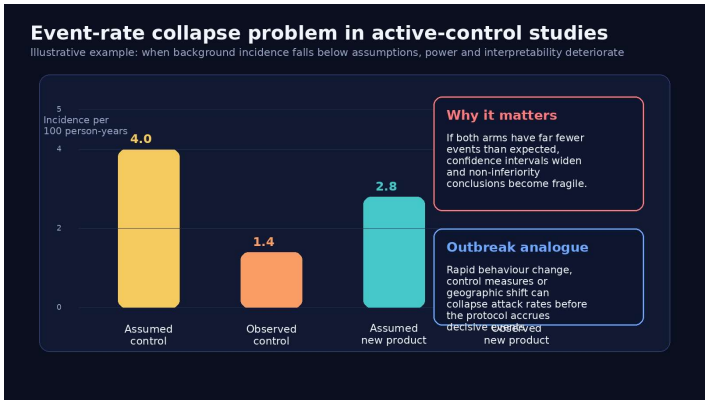


Figure: illustrative event-rate problem showing how lower-than-expected incidence undermines power and interpretability.

- In PrEP studies, falling HIV incidence can make direct efficacy estimation difficult even when prevention is working.
- Investigators then face the challenge of estimating a counterfactual placebo incidence from cohorts, registries or external controls.
- Outbreak trials face the same problem when transmission falls rapidly, hotspots move, or deployment changes risk during the trial itself.
- This strengthens the case for pre-positioned surveillance cohorts, harmonized background-incidence data and trigger-based trial activation rules.

**Without a reliable denominator and background risk estimate, even excellent fieldwork may not yield licensure-useful evidence.**

*Delany-Moretlwe S et al. HIV Clin Trials. 2017*

PrEPVacc methodological analysis on counterfactual placebo HIV incidence (2024/2025); WHO scientific framework (2024); WHO R&D Blueprint materials on prioritizing candidate vaccines during outbreaks.

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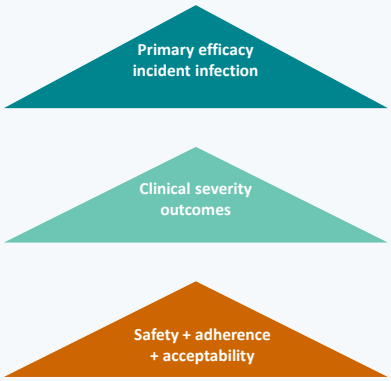
## Endpoints Must Match Biology and Use Case

The most persuasive primary endpoint is usually laboratory-confirmed incident infection when surveillance is feasible.

Secondary endpoints include severe disease, hospitalization, death, safety, adherence, and acceptability.

Standardized definitions, ascertainment windows, and specimen plans should be pre-specified in CORE protocols.




*References: WHO implementation tool for pre-exposure prophylaxis of HIV infection. 2024. WHO workshop agenda, CORE protocol discussion.*

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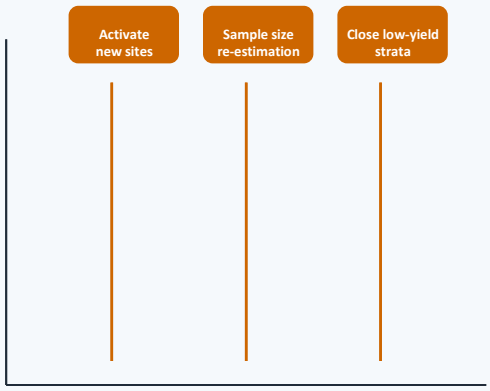
## Event-Driven and Adaptive Features Improve Resilience

Outbreak incidence can rise, fall, or move geographically faster than fixed sample-size assumptions can tolerate.

Event-driven accrual, flexible site activation, and modular annexes can preserve efficiency and interpretability.

Adaptations should be prospectively specified, simulation-tested, and acceptable to ethics committees and regulators.




References: Butler CC, et al. Lancet. 2023;401(10373):281-293. PMID: 36566761. PANORAMIC protocol. BMJ Open. 2023.

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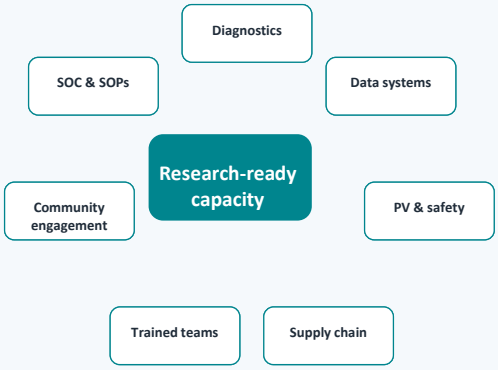
## Operational Readiness Can Make or Break the Trial

Valid trials need diagnostics, pharmacovigilance, data systems, supply chains, trained teams, and optimized supportive care.

Adherence and persistence must be measured because poor implementation can mimic poor biological efficacy.

Implementation outcomes improve explanation, interpretation, and future generalizability.




References: WHO workshop agenda, minimum research-ready capacities. WHO implementation tool for pre-exposure prophylaxis of HIV infection. 2024.

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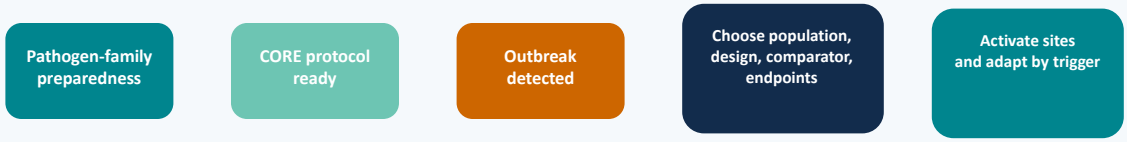
## A Practical Design Framework for Outbreak PrEP




Identify high-risk populations early and favor individual randomization when feasible.

Switch to cluster or rollout designs when countermeasures are delivered by group, place, or network.

Pre-agreed comparators, triggers, and data elements are what make speed and comparability possible.

*References: WHO workshop agenda, CORE protocol and pathogen-family preparedness discussion.*

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## Take-Home Messages

**Population**
Risk must be identifiable before exposure

**Comparator**
Ethics and interpretability must stay aligned

**Endpoints**
Use outcomes that are regulator-relevant

**Preparedness**
Ready protocols and sites are the real accelerator

**As for curative treatment, preparedness in prevention means not only candidate products, but also ready-to-activate protocols, sites, and partnerships able to generate licensure-grade evidence during emergencies.**

*References: WHO workshop agenda, 22 Apr 2026. WHO. Pre-exposure prophylaxis (PrEP). Delany-Moretlwe S, et al. HIV Clin Trials. 2017;18(5-6):177-188. PMID: 29039265.*

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## Selected References


WHO. Integration of Rigorous Research into Outbreak Response to Accelerate Medical Countermeasures Licensure. Workshop agenda, 22 Apr 2026.

Delany-Moretlwe S, et al. HIV prevention trial design in an era of effective pre-exposure prophylaxis. HIV Clin Trials. 2017;18(5-6):177-188. PMID: 29039265.

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Butler CC, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC). Lancet. 2023;401(10373):281-293. PMID: 36566761.

WHO. Implementation tool for pre-exposure prophylaxis of HIV infection. 2024.