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Standards of Prevention and Care in HIV Prevention Trials

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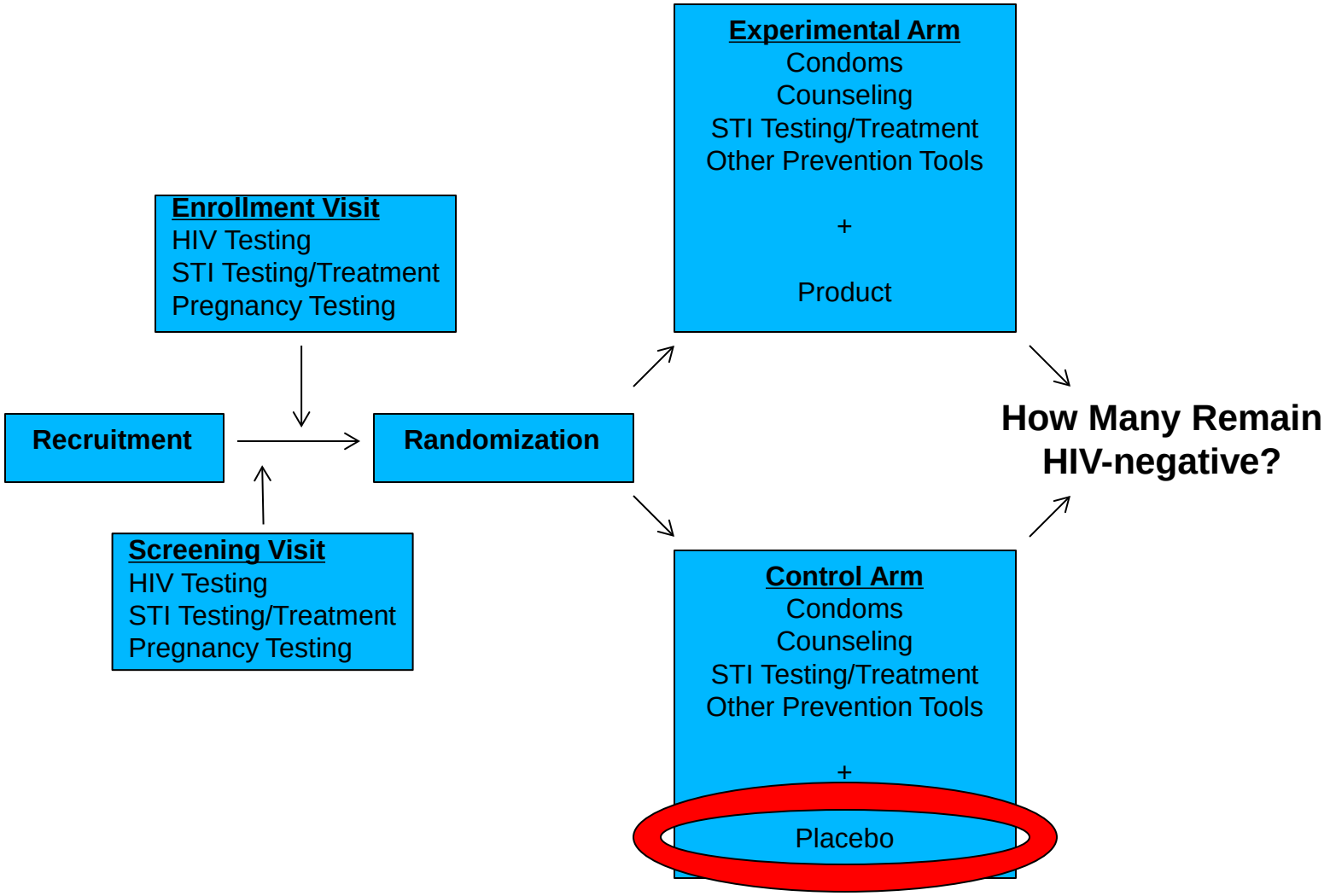
BASIC TRIAL DESIGN



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A BRIEF HISTORY OF PLACEBOS

Placebos control for the aspects of prescribing a new drug, experimental procedure or novel intervention that are not directly due to the intervention itself.

Types of placebos:

- Inactive placebos.
- Active placebos.
- Sham procedures.
- Sham interventions.

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ARE PLACEBOS ETHICAL?

It is generally ethical to randomize study participants to receive a placebo control when there is:

- No standard therapy;
- Standard therapy is no better than placebo;
- Standard treatment is placebo;
- There is doubt about the net therapeutic advantage of standard therapy;
- Standard treatment is unavailable (e.g. because of cost or supply);
- When the study enroll participants who refractory to standard treatment; or
- When the placebo is added on top of standard treatment (add-on studies).

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ETHICAL QUESTIONS

What is the obligation to provide new HIV prevention tools to participants enrolled in planned or on-going clinical trials?

Is it ever ethical to provide a less than “Cadillac” standard of prevention to participants in HIV prevention trials?

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CURRENT GUIDANCE

UNAIDS/WHO (2007) Ethical Considerations in Biomedical HIV Prevention Trials - Guidance Point 13:

- Researchers, research staff, and trial sponsors should ***ensure … that appropriate counseling and access to all state of the art HIV risk reduction methods are provided to participants***.

- New HIV risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are *scientifically validated* **or** as they are *approved by relevant authorities*.

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SCIENTIFIC CHALLENGES

'Cadillac' prevention packages make it difficult to assess experimental interventions.

- Social desirability bias.
- Complications of poor measurement.
- Attenuation of power.

Prevention packages don't address the needs of many participants, and may be unsustainable once a trial ends.

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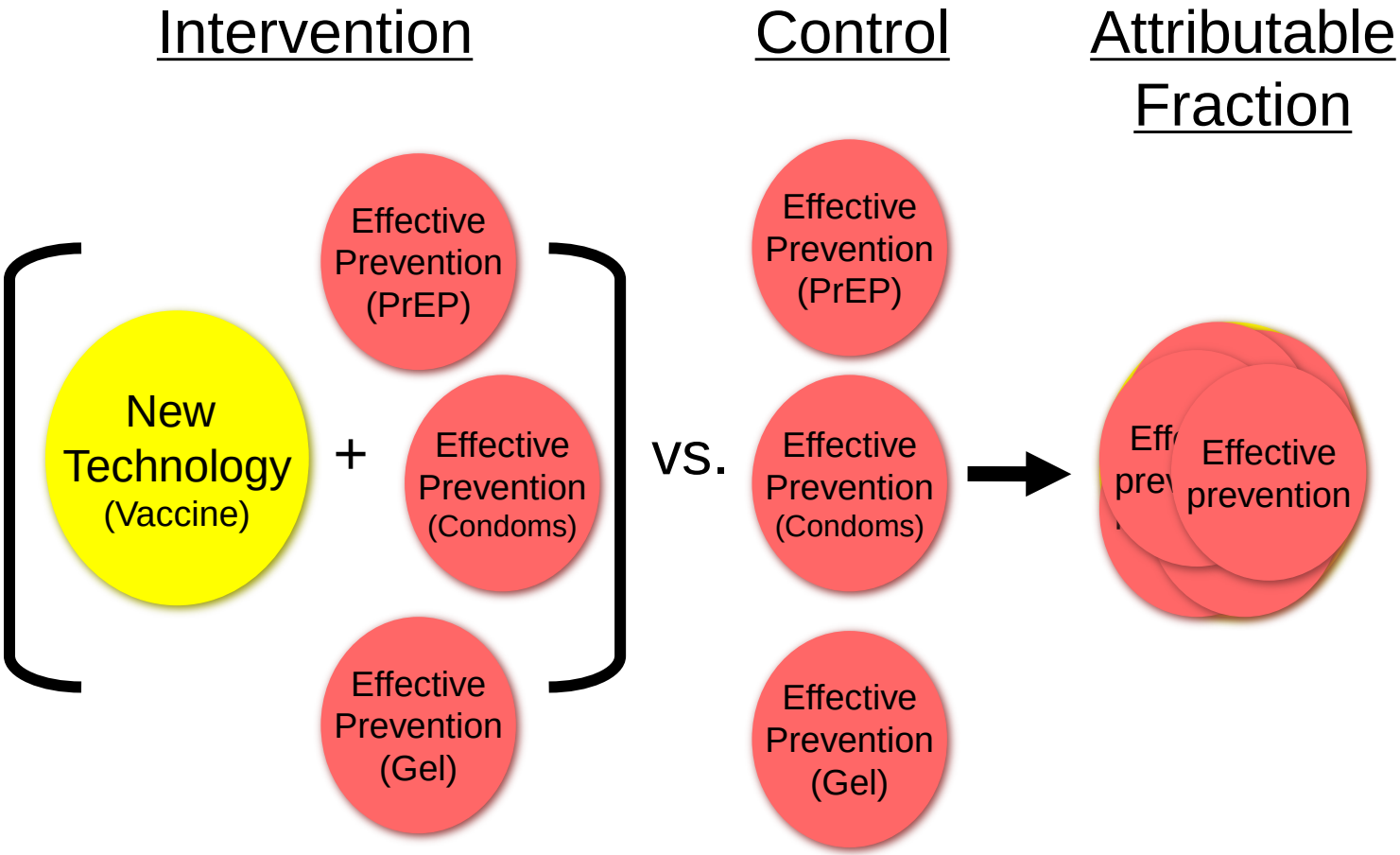
EVALUATING EFFECTIVENESS



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SAMPLE SIZE

Assumptions:

- Background HIV rate: 4.5%
- Effectiveness of standard package: 0%
- Effectiveness of new intervention: 55%
- 12 month follow-up with 10% attrition
- 300 HIV endpoints required

Number of Participants: 10,218

Estimated Cost of Trial: $71m US

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SAMPLE SIZE (2)

Assumptions:

- Background HIV rate: 4.5%
- Effectiveness of standard package: 50%
- Effectiveness of new intervention: 55%
- 12 month follow-up with 10% attrition
- 300 HIV endpoints required

Number of Participants: 20,435

Estimated Cost of Trial: $142m US

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SAMPLE SIZE (3)

Assumptions:

- Pre-Trial HIV rate: 4.5%
- HIV rate during trial: 2.0%
- Effectiveness of standard package: 50%
- Effectiveness of new intervention: 55%
- 12 month follow-up with 10% attrition
- 300 HIV endpoints required

Number of Participants: 50,731

Estimated Cost of Trial: $267m US

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ESTABLISHED AND PROVEN

If we accept the argument that researchers should provide all state-of-the-art interventions to study participants, we must ask:

- When is something “proven” to be effective?
- Once proven effective, when does it become an “established” intervention?

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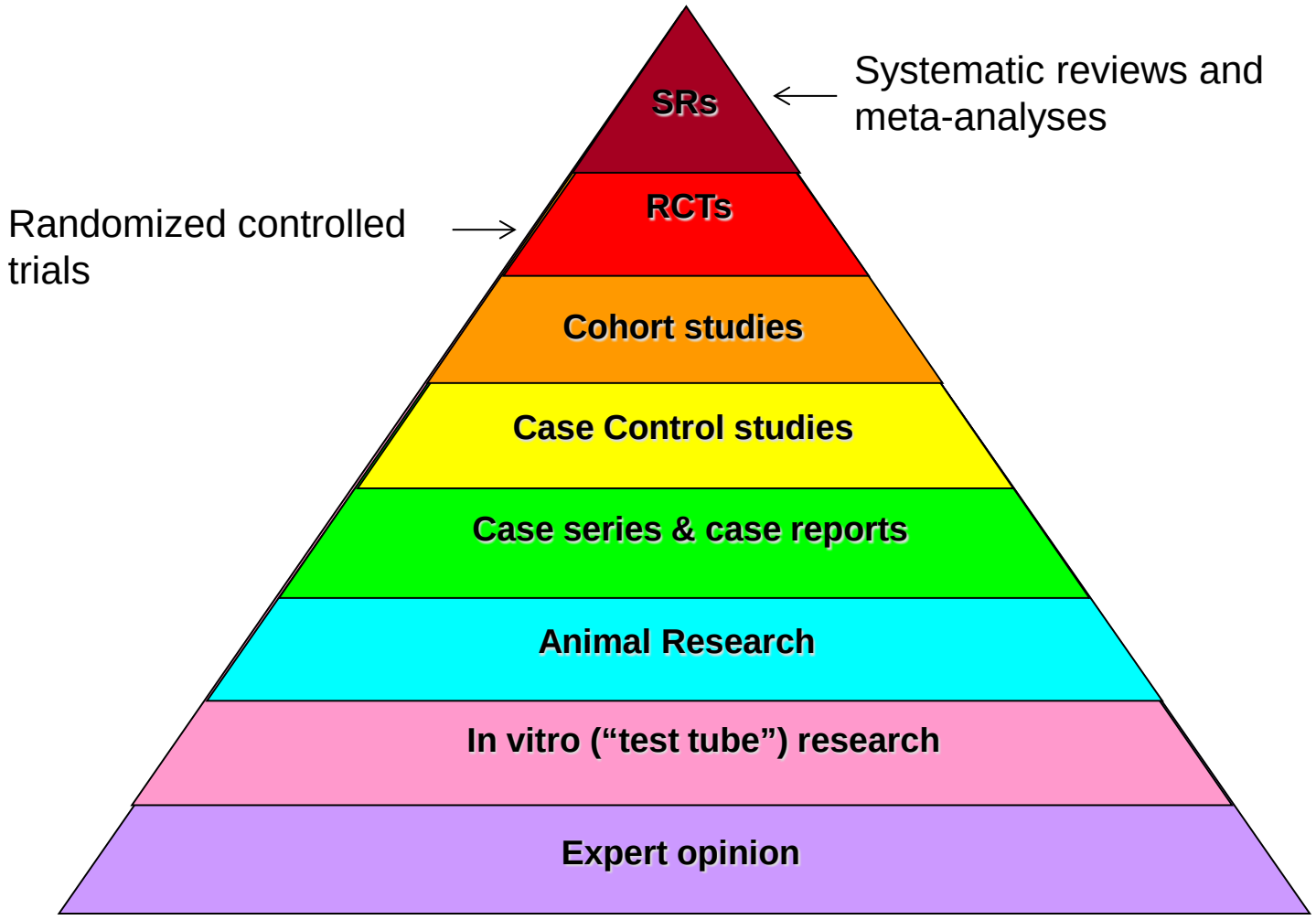
EVIDENCE PYRAMID



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PREVENTION SCORE CARD

Intervention	RCTs Completed	RCTs Showning Efficacy
Behavior change	10	0
Male circumcision	4	3
Diaphragm	1	0
Microbicides	11	1
STI treatment (including HSV2)	9	1
PrEP	6	4
Partner treatment	3	2
Vaccines	4	1
Total	47	12

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ESTABLISHED INTERVENTIONS

When does an intervention become an established?

- Recommendations from normative agencies?
- Added to national prevention strategy?
- Becomes common practice?

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UGANDA CONSULTATION

New prevention tools should be added on case-by-case basis according to the such objective criteria as:

- Data from comparable populations and routes of exposure;
- The weight of evidence for estimates of effect;
- Feasibility; and
- Impact of the new tool on the ability to isolate the efficacy of other prevention methods being tested.

- Philpott et al. The challenge of defining standards of prevention in HIV prevention trials. *J Med Ethics*. 2011; 37(4): 244-8.

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BELMONT PRINCIPLES

Respect for persons

- Voluntary informed consent.
- Protection of vulnerable persons.

Beneficence

- Maximize benefits and minimize harms.

Justice

- Non-exploitation.
- Individuals and groups that participate in trials should benefit from participation.

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BELMONT IN PRACTICE

When applied to HIV prevention trials, the three Belmont principles require that:

- Participants be informed of the risks and benefits of participation;
- Risks minimized and benefits maximized by providing an appropriate HIV prevention package and other services; and
- Trial participants and communities are not chosen solely for expedience or cost, and are not denied services to which they are normally entitled.

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A MODEST PROPOSAL

All trial participants should have information about proven and established HIV prevention services.

It is not obligatory, however, to always provide or ensure access to the full range of proven and established prevention tools.

The prevention package in a trial can vary in the type of services are provided so long as it:

1) Is developed in consultation with the community; and

2) Addresses the specific needs of the community.