Clinical Trial Designs in HIV Prevention

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2024

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Presentation Outline

- Clinical Trials - Definitions, Importance of Trials
- Role of Clinical trials in Clinical Product Development
- Different types of Clinical trials and their phases
- Important Regulations and Guidelines - ICH & GP
- Clinical Trials Design
- Randomization and Blinding
- Data Management in Clinical Trials - Standards (DISC, STM)
- Overview of Analysis of Clinical Trials

The brief history of HIV prevention

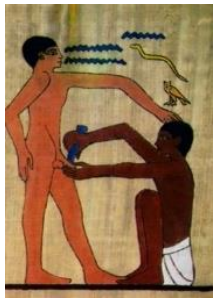
We have come a long way….

Risk reduction counseling

Condoms (both M and F)

STI testing and treatment

Injection harm reduction



VMMC

PEP

Partner testing / couples counseling

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And then …

Science, research & clinical trials got us here!

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What is a Clinical Trial

Definitions

- Clinical trials are scientific investigations that examine and evaluate safety efficacy of different therapies in human subjects.
  - A research study with human volunteers
- Designed to answer specific health questions
- **Interventional trials** test if a new intervention is safe and effective for people to use
  - Interventions can be drugs, devices, techniques, behavioral, or social
- **Observational trials** gather information about health issues from groups of people without any intervention

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What Is a Clinical Trial?

Importance

- Effectiveness of intervention to treat or prevent a disease
- Safety of a new drug
- Defining dose administration
- Testing drug formulation
- Exploring combination therapies
- Evaluating effect of therapies on quality of life

Clinical Trials

Basic Concepts

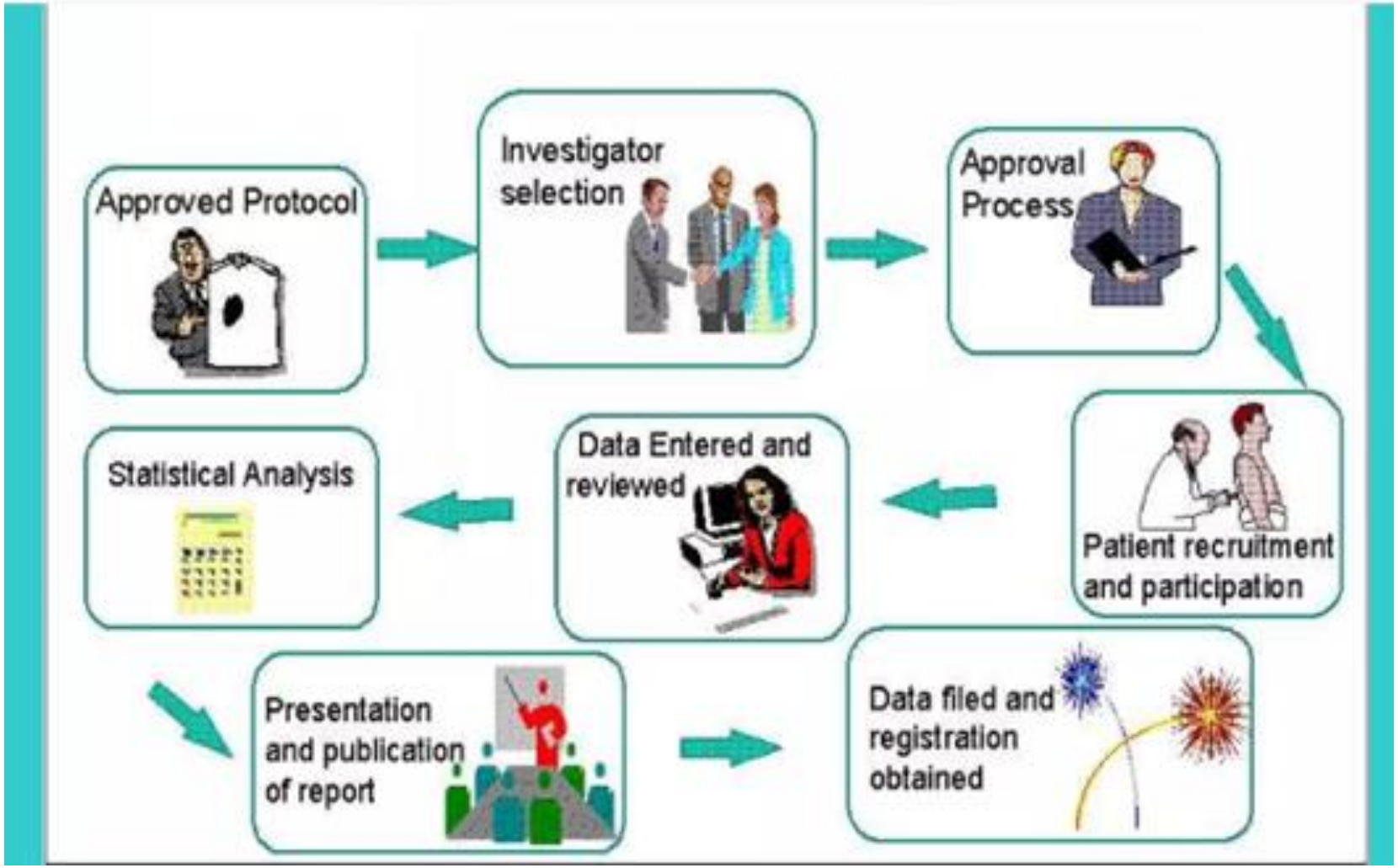
- **The protocol**. Establishes the question – ideally has just one and this is the **primary end point**. Common failing is too many end points. The best designed trials keep it simple as this make a clear answer more likely and easier to achieve
- **Secondary objectives**; a few related, appropriate secondary questions are normal as long as they do not distract from the primary. Some might be exploratory.
- Trial is then designed around these. The protocol sets out how the question will be answered

Clinical Trials

What information is in the study protocol

- Single centre, placebo controlled etc etc
- Who is conducting the trial, who is sponsoring it, where is it to be conducted and on whom will you be conducting the research
- What are you testing? Is it safe, have the tests been validated? Why is this research needed.
- What are the risks, what are the procedures, how will data be collected. How did you calculate how many patients you will need.

What is a clinical trial- in a nutshell



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Different types of Clinical trials and their phases

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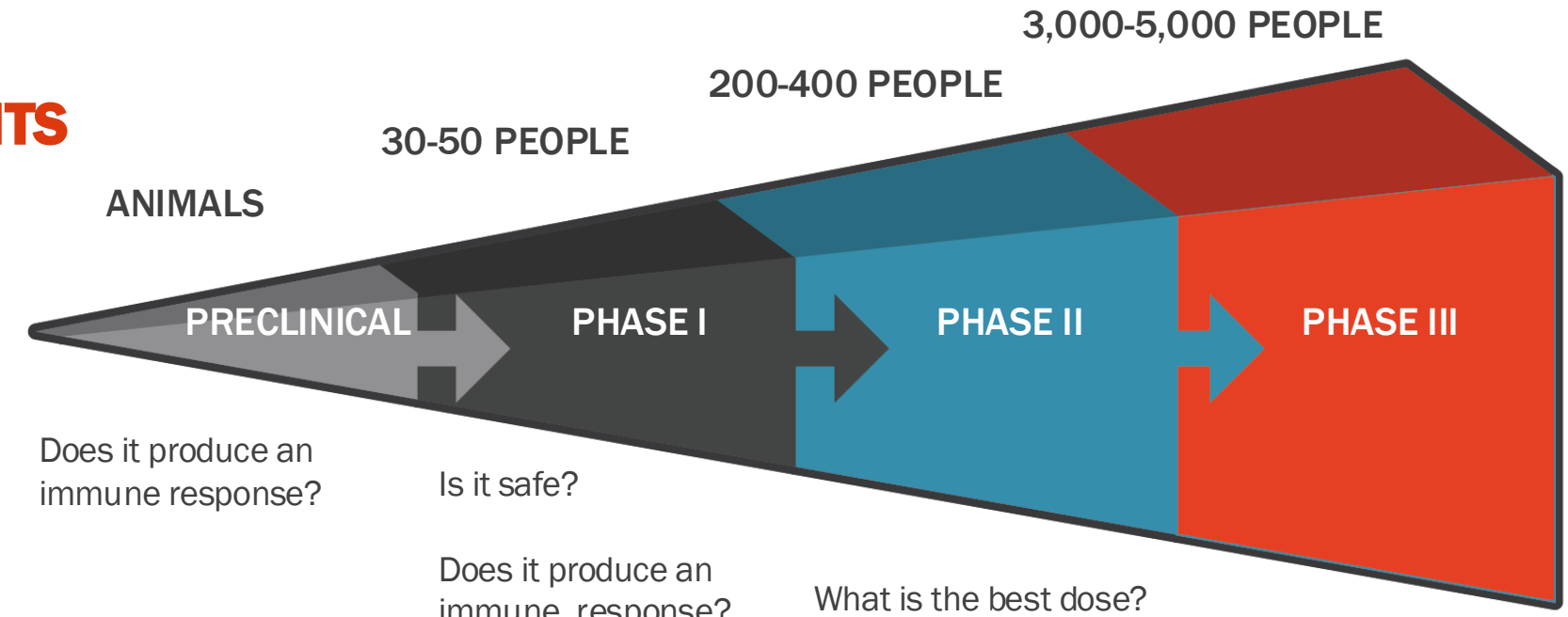
The Product Development Process



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Phase 1 clinical trials for drugs

- Also called “first in humans”
- Aim to establish safety, dose and side effect information
- Small number of participants

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Phase 2 clinical trials for drugs

- Aim to establish efficacy, learn more about dose and side effect information
- For a larger number of participants

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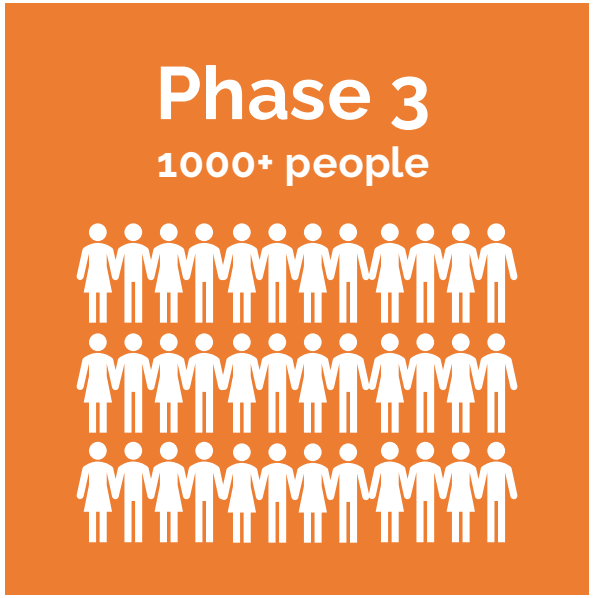
Phase 3 clinical trials for drugs



- Aim to see how long effects last, learn more about dose and side effect information
- For a large number of participants
- A randomized clinical trial is when two or more interventions or treatment arms are compared to each other.
- Participants are assigned by chance to one of the interventions to reduce bias.

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Phase 4 clinical trials for drugs

- Also called post-marketing surveillance
- Study long term side effects
- For a very large number of participants

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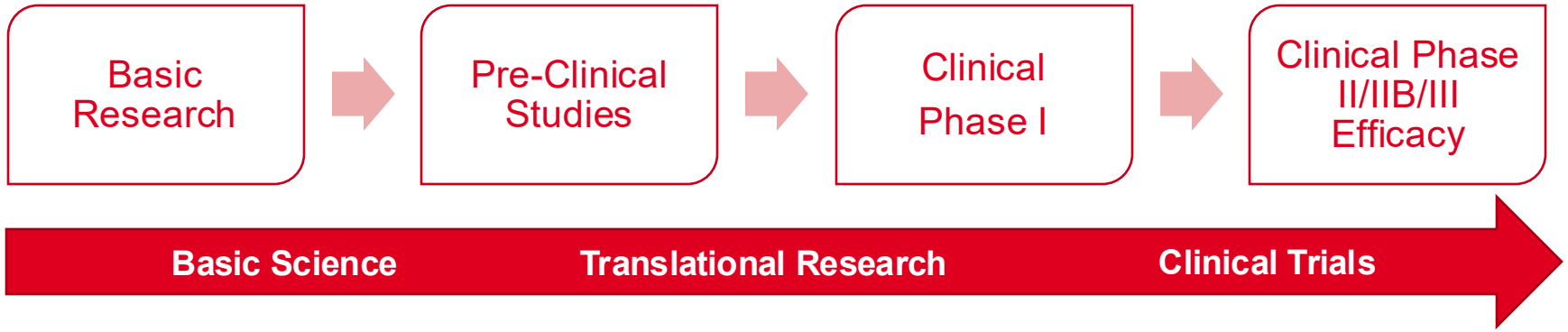
The Research Process: In summary

From the lab to you

- Preclinical research (concept, lab, animal studies)
- Clinical (human) research
  - Phase 1: small safety studies
  - Phase 2: larger, longer, look at safety and immunogenicity
  - Phase 2b/3: even larger, look at safety and efficacy
- After effectiveness results
  - Open-label, 3b, post-licensure Phase 4 marketing studies



Gold Standard of Clinical Research: Randomized Control Trial (RCT)

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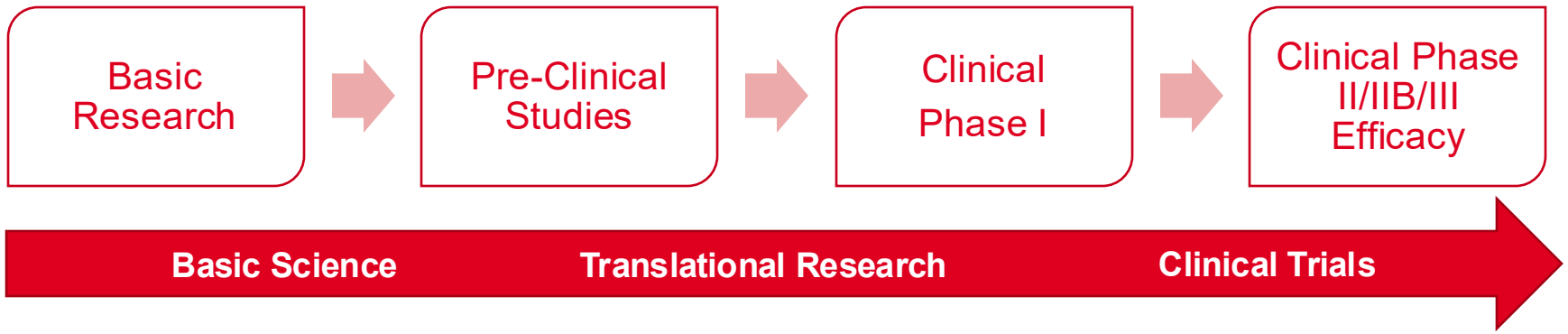
Randomized Control Trials

Concept you need to understand:

- "Gold standard" in research is a randomized and controlled study (RCT)
- Three key concepts:
  - Controlled
  - Randomized
  - Double-blind



Gold Standard of Clinical Research: Randomized Control Trial (RCT)

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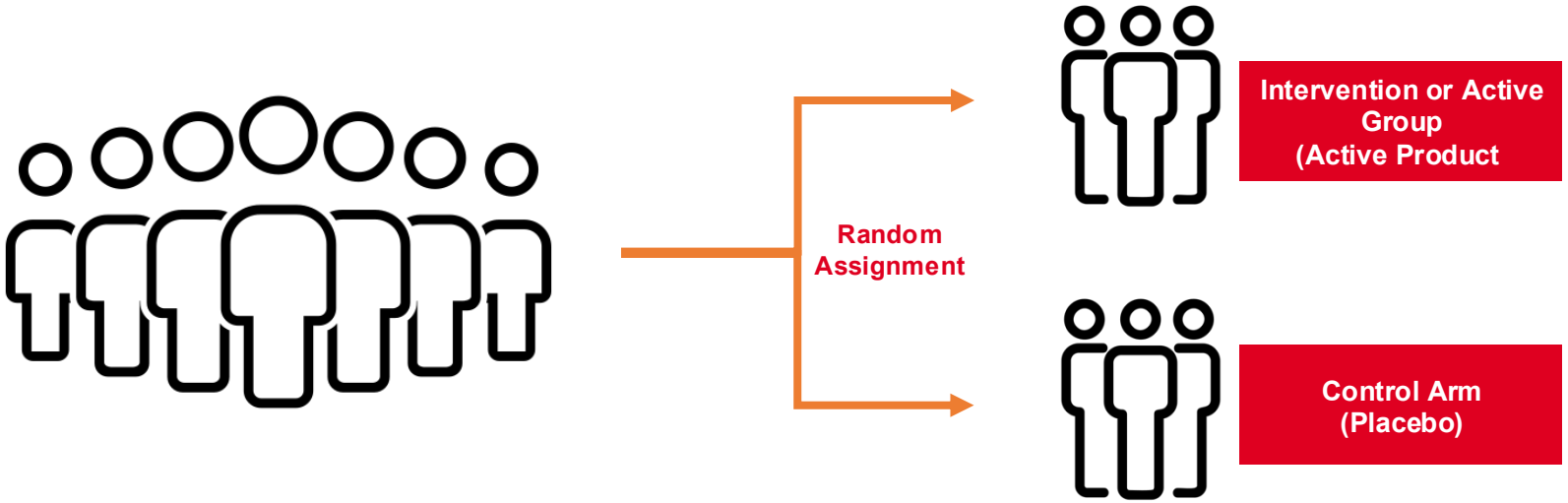
Randomized Controlled Trials

- Looks at the effect of an intervention/product in a trial setting – factors are more controlled than in a real-world setting
  - Involves a minimum of two arms (study groups):
  - Intervention or active arm
  - Control arm



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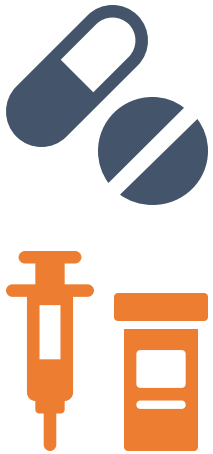
Placebo

Concept you need to understand:



- An inactive therapy (such as a drug, natural health product, or device) that looks like an active therapy
- Not intended to have any effect on the condition being studied
- Is used to make the results of the study more reliable
- Used if there is no ‘standard of care’ for a condition or disease

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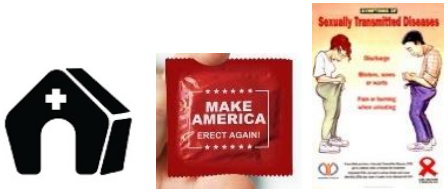
Standard of prevention pre-PrEP

VS.



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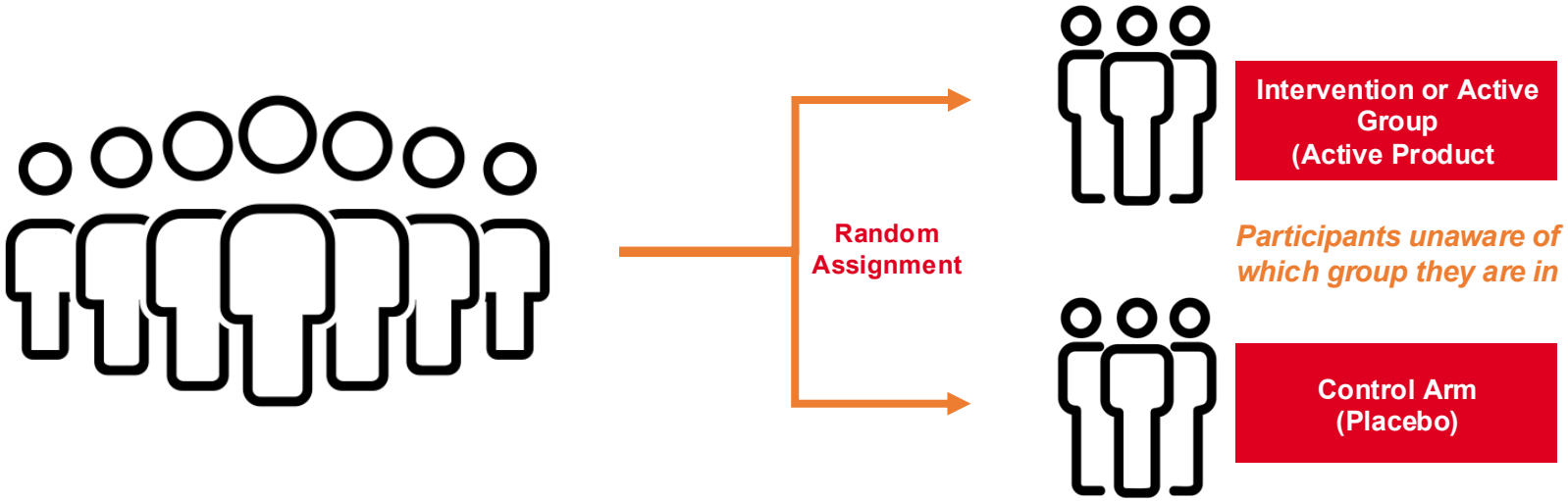
Double Blinded RCT

- Neither participants nor researchers know whether a participant is in the active arm or control arm(s)
- Less potential for bias
- Data unblinded at the end of the study to compare between groups



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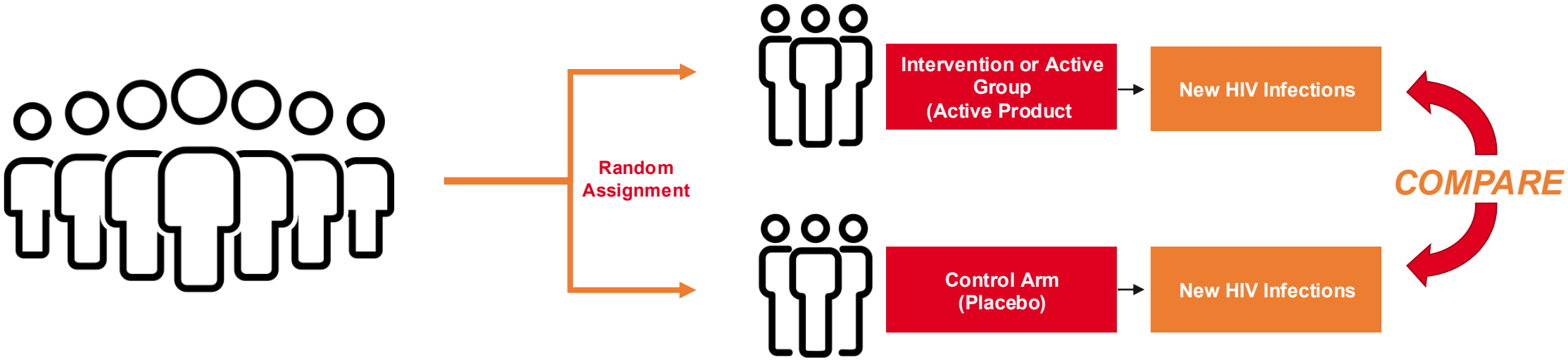
Goal of RCTs

- Goal is to assess if the active study product really works by comparing to the control
- HIV prevention research compare new HIV infections in the study arms to determine if the intervention prevented infection and/or progression to disease



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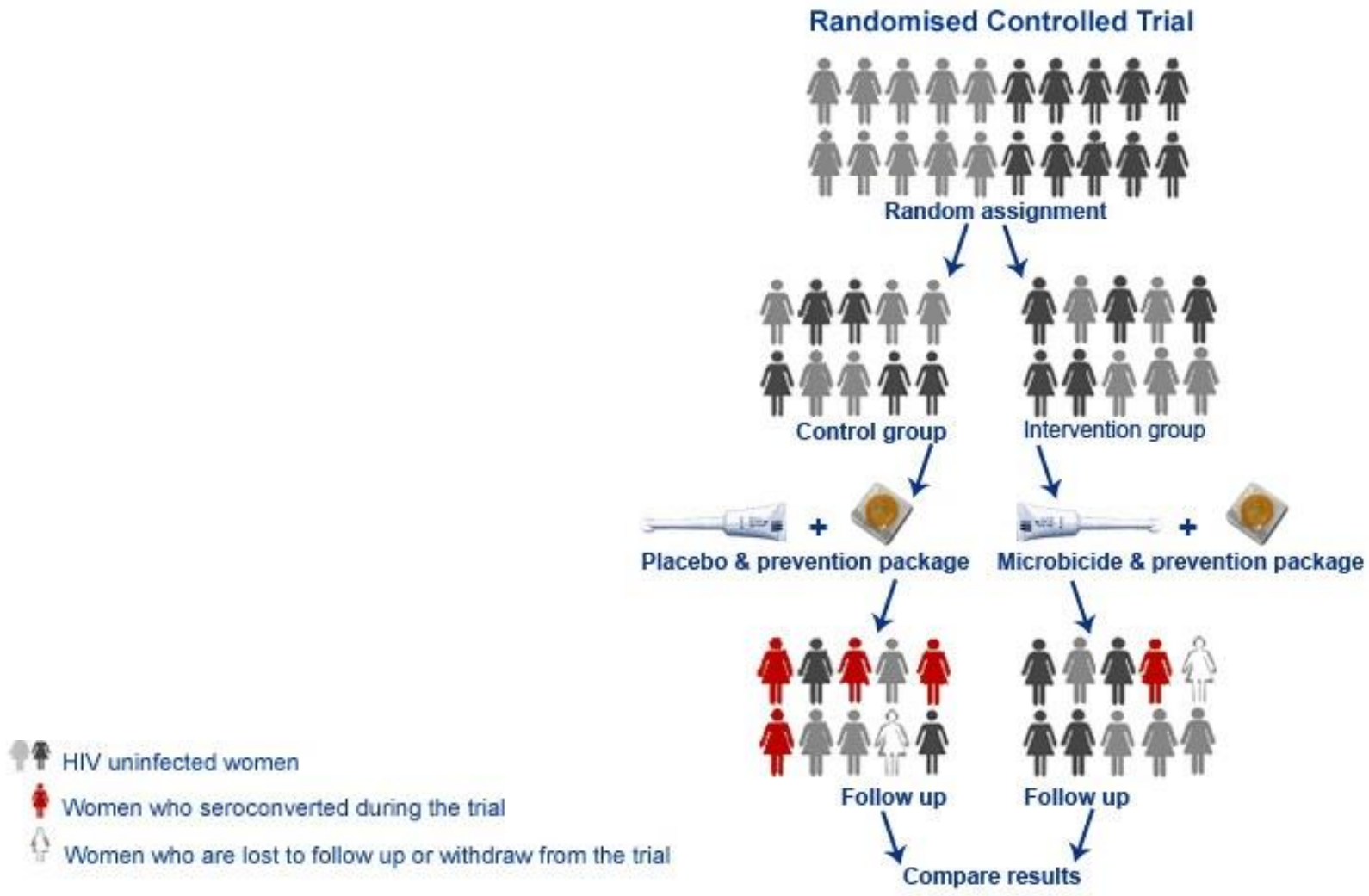
Measuring Effectiveness



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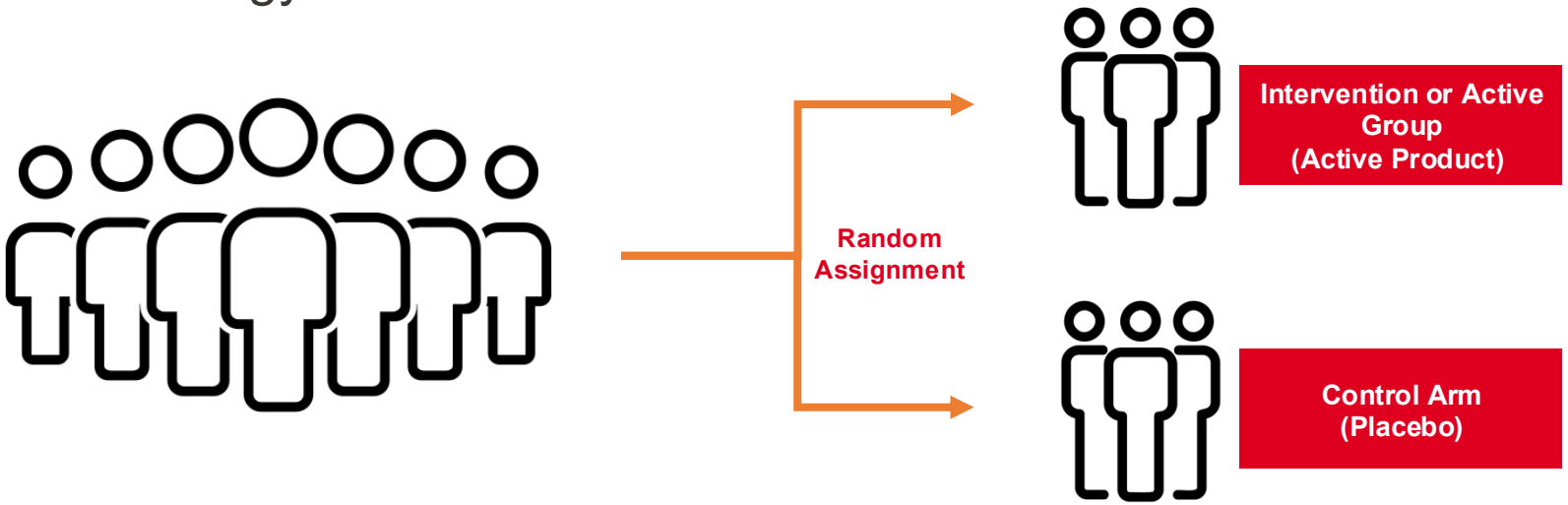
RCT Summary

- One group of participants uses the test product or strategy (active arm)
- Other group does not use the rest product or strategy at all (control arm)
- All participants get standard prevention tools
- At the end, researchers compare outcomes (e.g., # new HIV infections) in each group
- If fewer people got HIV in the active arm than in the control arm, that would suggest that the test strategy reduced HIV risk



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Safeguards in Clinical Trials

- International Ethical Standards
- National Regulatory Bodies
- Institutional Review Boards (IRBs) / Ethics Review Committees
- Community/stakeholder input – governed by Good Participatory Practices (GPP) guidelines
- Good Clinical Practice
- Informed Consent
- Adverse event monitoring
- Data Safety and Monitoring Boards (DSMBs/IDMC)
- Community involvement

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Potential Outcomes of Clinical Trials

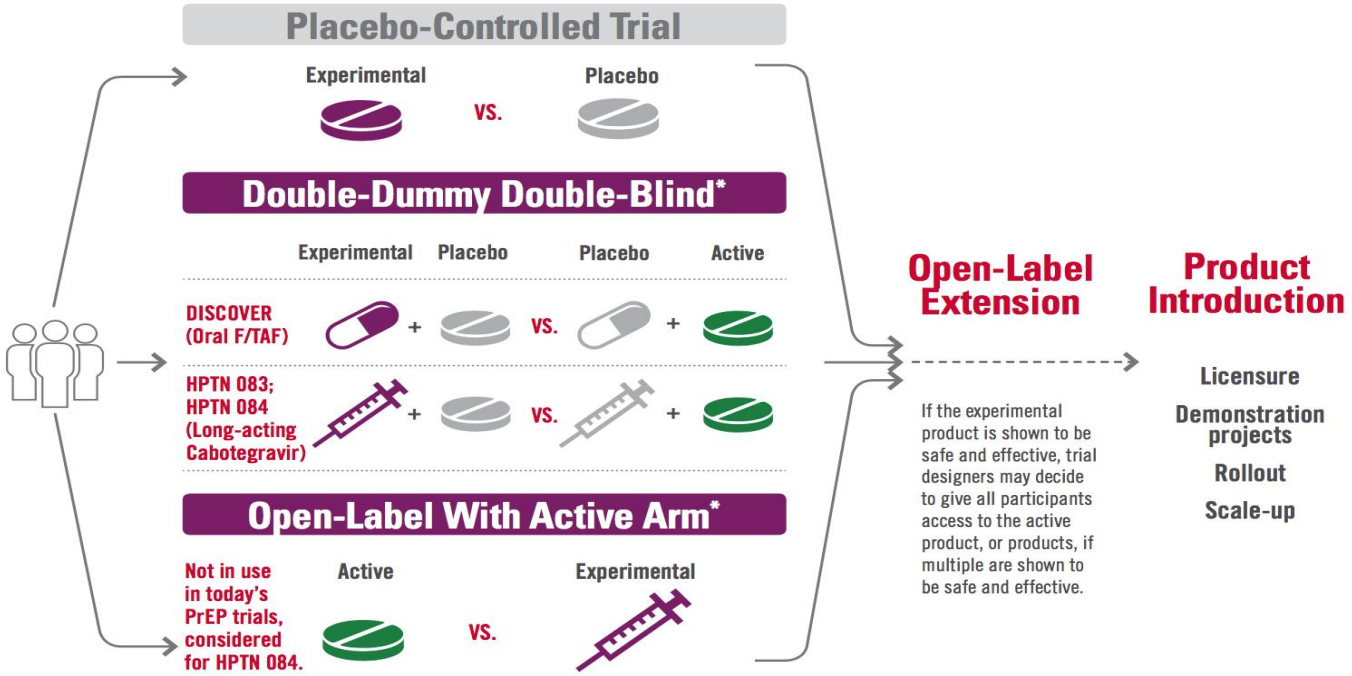
There are four possible outcomes from a clinical trial

- **Positive trial:** The clinical trial shows that the new treatment/prevention product has a large beneficial effect and is superior to standard treatment.
- **Non-inferior trial:** The clinical trial shows that that the new treatment/prevention product is equivalent to standard treatment. Also called a non-inferiority trial.
- **Inconclusive trial:** The clinical trial shows that the new treatment/prevention product is neither clearly superior nor clearly inferior to standard treatment.
- **Negative trial:** The clinical trial shows that a new treatment/prevention product is inferior to standard treatment

The Research Process

Research Complexity in Post-Placebo Era

- Active control (instead of placebo control)
- Double-dummy double-blind trials
- Open-label trials
- Non-inferiority trials
- Superiority trials



All of these designs are randomized, meaning that participants are assigned to a study arm by chance. This protects against bias, whether the particpant knows what he or she is receiving or not.

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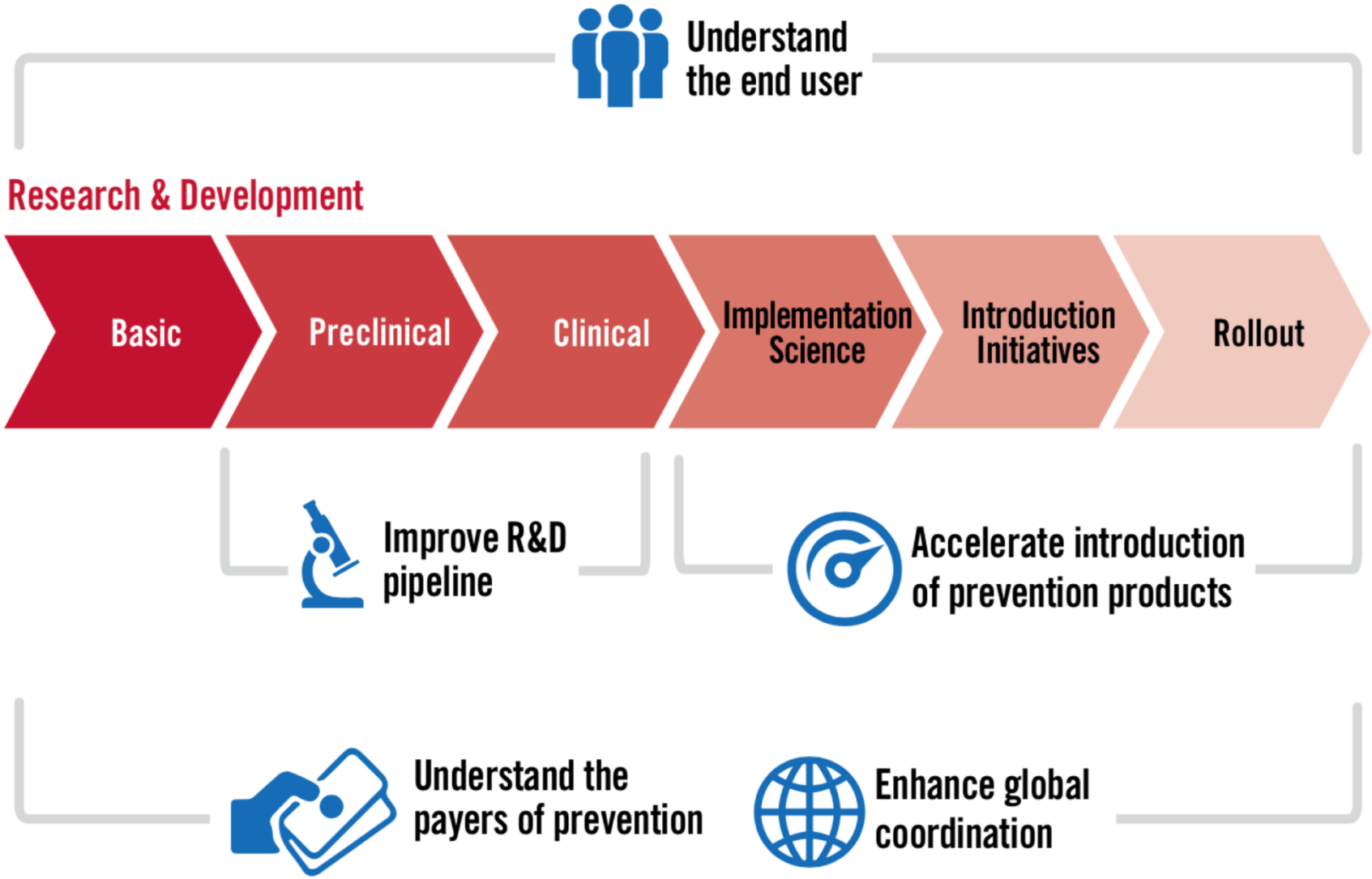
The New Era of Trial Designs

- Active-controlled HIV prevention trials
- Registrational cohort
- Recency assays
- External trial placebo arm
- Biomarker of HIV incidence/exposure
- Clinical trials using innovative designs

Research to Roll Out



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