GLOSSARY OF TERMS

Key Terms, Concepts, & Components in Clinical Trial

Term	**Definition**	**With respect to new clinical trial design**
Active Control	The subjects are randomly assigned to the test treatment or to an active control treatment. Active control trials can have two distinct objectives with respect to showing efficacy: (1) to show efficacy of the test treatment by showing it is as good as a known effective treatment or (2) to show efficacy by showing the test treatment is better than the active control. (See also ***non-inferiority*** and ***superiority***.)	Studies of this size are infeasible because they exhaust the precious resources of time, participants, and resource dollars while the prevention pipeline is increasing.
Counterfactual	The **counterfactual** intends to measure what would have happened without the intervention of interest – as if looking into a crystal ball. It is an ideal that can never be observed or achieved. It is counter to fact. The best we can do is to estimate it. *Suppose a patient may receive one of two treatments: an experimental drug E or a control C. Then this patient has two potential outcomes: their response if they receive treatment E, and their response if they receive treatment C. If only treatment E was actually given (i.e. no one received the control treatment C) than the only the outcome corresponding to the treatment E will be observed and thus be factual, the other control C will remain counterfactual.*	Counterfactual estimate is a valid, logical estimate based on scientific data. Not all data sources equally valid. For example, in PrEp studies contemporaneous and population appropriate data source would be more valid than a historic control. Once the counterfactual has been estimated, a ***threshold*** value is determined based on the data and agreed with regulators and other decision-makers.
Endpoint	The **endpoints** (or outcomes), determined for each study participant. These are the quantitative measurements required by the study objectives.	For PrEP trials the endpoint is HIV infection (HIV incidence) and the sample size calculation is dependent on the incidence rate.
External control	An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal control group consisting of patients from the same population randomized to a different treatment group. The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time but in another setting. In PrEP studies the latter is the case. *An external control could be restricted to a specific population. When we are estimating the counterfactual, many other ways to obtain evidence could be useful, such as surveillance data, registry (for rare diseases), cross-sectional recency assay, natural history cohort, etc.*	External control is one way of estimating counterfactual by getting closer to what would have been a placebo, which is not a counterfactual but is an estimate of a counterfactual. Data would be used to infer the background HIV incidence rate among the local population not currently on PrEP. This incidence would then be compared to the HIV incidence in trial

GLOSSARY OF TERMS

Key Terms, Concepts, & Components in Clinical Trial

Historical Control	The type of external control (**See also External Control**). The comparator to the treated group is not a concurrent a separate group of patients. The comparison is between two different times.	Requires believing there are no meaningful differences in prognostic factors, known or unknown. No randomization step to support that belief
Non-Inferiority Trials	The aim is to test whether a new intervention is as good or not unacceptably worse than the current intervention *New intervention may provide more advantages than existing interventions (e.g. high adherence, better distribution of the intervention, higher safety profile)*	Specific challenges in design and analysis include the difficulty of demonstrating statistical superiority or non-inferiority due to the low number of events and identifying appropriate control populations against which to measure efficacy.
Placebo control	A term used to describe a method of research in which an inactive substance (a placebo) is given to one group of participants, while the treatment (usually a drug or vaccine) being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective than the placebo.	Placebos have been the gold standard and serves as an internal control to represent the counterfactual experience but is no longer ethical in PrEP studies
Randomization	Randomization is a process of assigning each participant to a group in a trial by chance. It creates groups that have similar characteristics such as age, sex, race, etc.	**Estimates** the counterfactual
Randomized Controlled Trials (RCT)	Trials where participants are assigned by chance, through randomization, to one of two or more groups to receive different interventions	One question remains: what is the counterfactual group that we compare the active intervention group to? What is an appropriate comparison group that would create the counterfactual experience against the intervention of interest?
Recency Assay	Method to assess the rate of "recent infections". It is one of the relatively simple, practical, and straightforward methods to assess the rate of "recent infections".	The method could potentially contribute to accurately estimate HIV incidence. With uncontrolled trials, background knowledge is deemed sufficiently clear to allow assumptions about new treatments in the absence of any defined control group
Superiority Trials	The aim is to show that new intervention is better (superior) than existing interventions	The number of participants needed to demonstrate superiority or non-inferiority may be too

GLOSSARY OF TERMS

Key Terms, Concepts, & Components in Clinical Trial

	New intervention is expected to reduce HIV incidence compared to existing intervention	large and cost-intensive to be feasible.
Trial	To test the functioning, value, or usefulness of (something) *Clinical trials are vital to determining the impact of a new potential treatment. With strict oversight by Institutional Review Boards, clinical trials provide the U.S. Food and Drug Administration with the scientific information needed to weigh the benefits and risks of a new medication and decide whether it is safe for patients.*	

REFERENCES & SOURCES:

https://www.phrma.org/en/Advocacy/Research-Development/Clinical-Trials

https://www.medicinenet.com/script/main/art.asp?articlekey=38699

https://pubmed.ncbi.nlm.nih.gov/31567437/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5114686/

https://www.avac.org/

https://events-support.com/Documents/Walton_Marc.pdf

https://www.fda.gov/media/71349/download

https://online.stat.psu.edu/stat509/node/31/