Facts

Summary of the global HIV epidemic (2018)

	People living with HIV in 2018	People newly infected with HIV in 2018	HIV-related deaths 2018
Total	37.9 million [32.7 million – 44.0 million]	1.7 million [1.4 million – 2.3 million]	770 000 [570 000 – 1.1 million]
Adults	36.2 million [31.3 million – 42.0 million]	1.6 million [1.2 million – 2.1 million]	670 000 [500 000 – 920 000]
Women	18.8 million [16.4 million – 21.7 million]	–	–
Men	17.4 million [14.8 million – 20.5 million]	–	–
Children (<15 years)	1.7 million [1.3 million – 2.2 million]	160 000 [110 000 – 260 000]	100 000 [64 000 – 160 000]

Source: UNAIDS/WHO estimates

World Health Organization

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Global efforts towards prevention & cure

TAG Treatment Action Group

Research Toward a Cure January 17, 2020

Table 1. Current Clinical Trials

Trial	Trial Registry Identifier(s)	Sponsor(s)	Phase	Estimated End Date/Interim Results
ADOPTIVE IMMUNOTHERAPY				
HST-NEETs: HIV-1 specific T-cells for HIV-infected individuals	NCT03485963	Children's Research Institute	Phase I	December 2021
ANTIBODIES				
UB-421 (antibody inhibitor of HIV binding to CD4 receptors)	NCT03743376	United BioPharma	Phase II	December 2020
UB-421	NCT04041362 (not yet open for enrollment)	United BioPharma	Phase II	March 2021
vedolizumab (anti-$\alpha_4\beta_7$ integrin antibody)	NCT03577782	Hospitales Universitarios Virgen del Rocío	Phase II	May 2020
vedolizumab	NCT03147859	Ottawa Hospital Research Institute	Phase II	December 2018 CROI 2019, Abstract 393, Webcast
PGT121 + VRC07-523LS +/- PGDM1400	NCT03721510	International AIDS Vaccine Initiative	Phase I/IIa	November 2020
VRC01 (broadly neutralizing antibody) in infants	NCT03208231	NIAID	Phase I/II	July 2021
VRC01LS + 10-1074 (broadly neutralizing antibodies) in early-treated children	NCT03707977	NIAID	Phase I/II	October 2021
10-1074-LS + 3BNC117-LS (long-acting broadly neutralizing antibodies)	NCT03554408	Rockefeller University	Phase I	June 2021
3BNC117 + 10-1074 (broadly neutralizing antibodies)	NCT03571204	NIAID	Phase I	June 2021
3BNC117 + 10-1074	NCT03526848	Rockefeller University	Phase I	May 2020
3BNC117-LS	NCT03254277	Rockefeller University	Phase I	August 2020
AAV8-VRC07 (broadly neutralizing antibody delivered by AAV vector)	NCT03374202	NIAID	Phase I	March 2020
Elipovimab (formerly GS-9722; PGT121-derived broadly neutralizing antibody)	GS-US-420-3902 Adisinsight entry (not listed in clinicaltrials.gov)	Gilead Sciences	Phase I	N/A

Entries shaded in light grey include analytical treatment interruptions (ATIs); in some cases ATIs are only initiated if certain outcomes are achieved.
For the most up-to-date version, visit: http://www.treatmentactiongroup.org/cure/trials. Please send updates, corrections, or suggestions to Richard Jefferys at richard.jefferys@treatmentactiongroup.org

Ref: https://www.treatmentactiongroup.org/wp-content/uploads/2020/01/research_toward_a_cure_trials_1_17_2020_final.pdf

Clinical Trials: Intention-To-Treat (ITT) vs. Per-Protocol (PP) analysis population

Samuel Bosomprah, PhD, CStat

Senior Technical Advisor & Head of Analysis, CIDRZ

Former Head of Biostatistics Department, University of Ghana

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The context: Hypothesis Test!

- ✓ Often, statistical inquiries involve having to test a hypothesis

- ✓ For example, a researcher might assert that an investigational treatment is superior to or better than a placebo in terms of improving a certain primary outcome of interest (i.e. **research hypothesis**).

What is worse?

1. to **claim that a treatment worked when in fact it does not**, and thus, to potentially harm patients with an inefficacious therapy, or

2. to conclude that the **efficacy of an actual efficacious treatment cannot be proven** and, as a consequence, to potentially refuse patients an efficacious therapy.

The answer might not be straightforward, from patient's perspective

However, from clinical research perspective - situation 1 is worse!).

Type 1 and Type 2 errors

To answer this, consider the essential difference between the two cases

- ✓ Scenario 1 means that **a statistically proven result is actually wrong (i.e. Type 1 error)** – a result that might cause harmful effects. Based on such a proof, an inefficacious treatment might be approved, and may harm patients.

- ✓ Scenario 2 on the other hand means that **efficacy was not proven but also not refused (i.e. Type 2 error)**. However, the non-proven efficacy does not equal a proven inefficacy!
  - o From a scientific perspective, such a nondecision has less implications than a wrong proof.

Controlling Type 1 and Type 2 errors

In clinical trials,

- ✓ Scenario 1 is strictly controlled via a low pre-defined level of significance: a level of 5% e.g. says that (if there is actually no effect) the probability of Scenario 1 is only 5% or less.

- ✓ Scenario 2 on the other hand, is controlled via a meaningful sample size calculation, but usually with a less strict criterion (e.g. 20%).

The common rule for clinical trial analyses

- ✓ Rule is: **Be conservative!,** which means - **do not increase the probability of a type I error!**

Answer to our question "What is worse?": It is more essential to avoid a wrong proof than to avoid a wrong nondecision (which is also bad, **but 1 is worse**…).

It is essential to keep the probability of Scenario 1 below the level of significance (e.g. 5%).

Learning objectives

By the end of this session, participants should be able to:

- ✓ Demonstrate understanding of ITT and PP analysis set
- ✓ Understand the consequences for the choice of ITT and PP analysis set

The Intention-To-Treat (ITT) principle

- ✓ The ITT principle defines that **every patient randomized** to the clinical study should enter the primary analysis.
  - o This means that, patients who drop out prematurely, or are non-compliant to the study treatment, or even take the wrong study treatment, are included in the primary analysis within the respective treatment group they have been assigned to at randomization (“as randomized”).
- ✓ In an analysis according to the ITT principle, the original randomization and the number of patients in the treatment groups remain unchanged, the analysis population is as complete as possible, and a potential bias due to exclusion of patients is avoided.
  - o Thus, the patient set used for the primary analysis according to the ITT principle is called “**full analysis set**”.

Circumstances for exclusion of a patient from ITT

- ✓ **No treatment** was applied at all
- ✓ There are **no data** available after randomization
- ✓ In addition, the ICH E9 guideline mentions "**failure of major entry criteria**" as a reason for exclusion.
  - o However, as these major entry criteria are quite specific and only valid under certain circumstances, they are not commonly used for the definition of a full analysis set.

The Per-Protocol (PP) principle

- ✓ The PP principle defines that only patients who are **fully compliant** to the clinical trial protocol should enter the primary analysis.

- ✓ The aim of a PP analysis is to identify a **treatment effect which would occur under optimal conditions**; i.e. to answer the question: what is the effect if patients are fully compliant?

- ✓ Therefore, some patients (from the ITT set) need to be excluded from the population used for the PP analysis (**PP population**).

Criteria for exclusion: PP population

- ✓ any major **protocol deviations** (e.g. intake of a concomitant medication affecting the primary endpoint)
- ✓ non-availability of measurements of the **primary endpoint**
- ✓ non-sufficient exposure to **study treatment**

Further consideration: PP population

- ✓ The assignment to the PP analysis set needs to take place **prior to the analysis** (in a **blinded** manner (if possible)).

- ✓ Deviations that might be **affected by the actual treatment** should not be used as exclusion criteria: e.g., “premature discontinuation from the study” might not be a good choice of criterion for exclusion from the PP analysis, if this discontinuation was due to lack of efficacy (and therefore associated with the treatment received).

What is the consequence for the choice of a patient analysis set? ITT vs PP?

Recall the common rule: **Be conservative!**

- ✓ A high treatment effect leads to a successful trial (i.e. to proven efficacy). However, if you choose a too optimistic method of analysis, i.e. if you over-estimate the effect, you receive more likely a positive result. Or in other words: you **increase the probability of a type I error**.

- ✓ Therefore, in clinical trials any over-estimation of the effect needs to be avoided. With respect to prevention of type I error it is still **better to choose a method which under-estimates the effect (conservative approach)** than a method which might over-estimate it.

- ✓ What does this general rule mean for the choice of ITT vs. PP? What is the more conservative approach in this context? The simple answer is: it's the analysis according to the **ITT principle**.

Let's illustrate with superiority trials (as the situation is different for noninferiority trials).

Example

Consider a superiority trial with two treatment arms (treatment vs. placebo), with a dichotomous outcome (yes =1, no=0). Now assume that 10% of the patients in both study arms previously drop out from the study due to missing follow-up (i.e., 10% dropouts, 90% completers). Due to their shortened observation period, none of the dropouts achieved response (a reasonable assumption).

Groups			% Response (ITT)	% Response (Actual)
Treatment (n=100)	Completers=90	Responders =54 (i.e. 60%)	54%(=54/100)	60%(54/90)
	Dropouts=10	Responders =0 (i.e. 0%)		
Placebo (n=100)	Completers=90	Responders =36 (i.e. 40%)	36%(36/100)	40%(36/90)
	Dropouts=10	Responders =0 (i.e. 0%)		
Effect (risk difference)			18%	20%

- ✓ The real response rates, i.e. the response rates that are expected (actual), are 60% under treatment and 40% under placebo; thus, there is a real treatment effect of 20% points (risk difference scale).
- ✓ According to the ITT principle, all patients (including dropouts) are included in the full analysis set. The estimated treatment effect in this analysis is 18%, i.e. the actual treatment difference of 20% is under-estimated (making the ITT conservative)

…further

- ✓ With respect to the aim to not increase the probability of a type I error, this “wrong” (or conservative) estimation is still better than an over-estimation of the effect.

- ✓ How about the PP analysis in this context? Exclusion of patients from the analysis due to major protocol deviations can of course also cause a tendency to wrong estimations of a treatment effect.
  - o This is particularly the case, if the frequency of and the reasons for exclusion **vary between the study groups**.

- ✓ However, for a PP analysis it is not straightforward to pre-guess the direction of a wrong estimation (i.e. over or under-estimation).
  - o Some authors and guidelines claim a tendency of PP analyses to over-estimate an effect (e.g. ICH E9 guideline) although this cannot be derived mathematically.

Conclusion

- ✓ In summary, the ITT approach that tends to under-estimate an effect is the more conservative approach in a clinical (superiority) trial. Following the general analysis rule above (stay conservative!), **the ITT population is the method of choice for the primary analysis**.

- ✓ Nevertheless, a PP approach is of course a reasonable analysis strategy for sensitivity analyses.

- ✓ In any case, if within a trial the results of the ITT and the PP analysis differ considerably, this is always a reason to start asking unpleasant questions.