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How will new guidance impact the statistical analyses and interpretation for Patient-Reported outcomes (PRO) in the context of HA and HTA submissions

A clinician / external expert perspective

Prof Olivier Chassany
Health Economics Clinical Trial Unit (URC-ECO, Pr Isabelle Durand-Zaleski), Hôpital Hôtel-Dieu, AP-HP
Patient-Centered Outcomes Research (Dr Martin Duracinsky), Université Paris-Diderot, UMR 1123 Inserm
chassany.o@gmail.com

PRO are part of evaluation of drugs

Improvement in the measurement of PRO in clinical trials

- Validated/relevant questionnaires
- Justification of the choice
- Endpoint model / hierarchy (place of PRO among other endpoints and between different PRO)
- Hypotheses of change/differences
- Sample size
- Better analysis:
  - ITT / mITT

→ PRO Label claims granted by EMA & FDA (less prone)

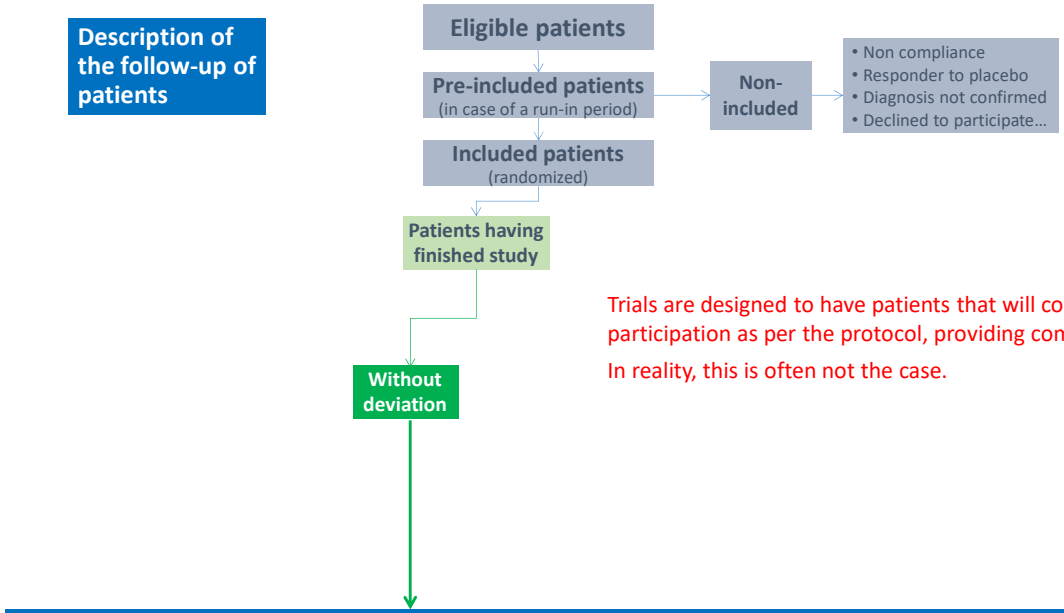
However, issues remain with PRO analysis and interpretation

- Especially since many PRO results within a trial:
  - Multidimensional questionnaires
  - Several questionnaires used
  - Repeated over time
- PRO still seen by some MA regulators/HTA assessors as a subjective endpoint (i.e. biased)
- Double-blind lacking
- Missing data
- PROs presented as exploratory endpoint

→Misalignment between sponsor/regulator expectations
→In many dossiers, PRO data are not considered especially for HTA

DeMuro C, Clark M, Doward L, Evans E, Mordin M, Gnanasakthy A. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). Value Health. 2013;16(8):1150-1155.

Description of the follow-up of patients



Trials are designed to have patients that will complete their participation as per the protocol, providing complete data.

In reality, this is often not the case.

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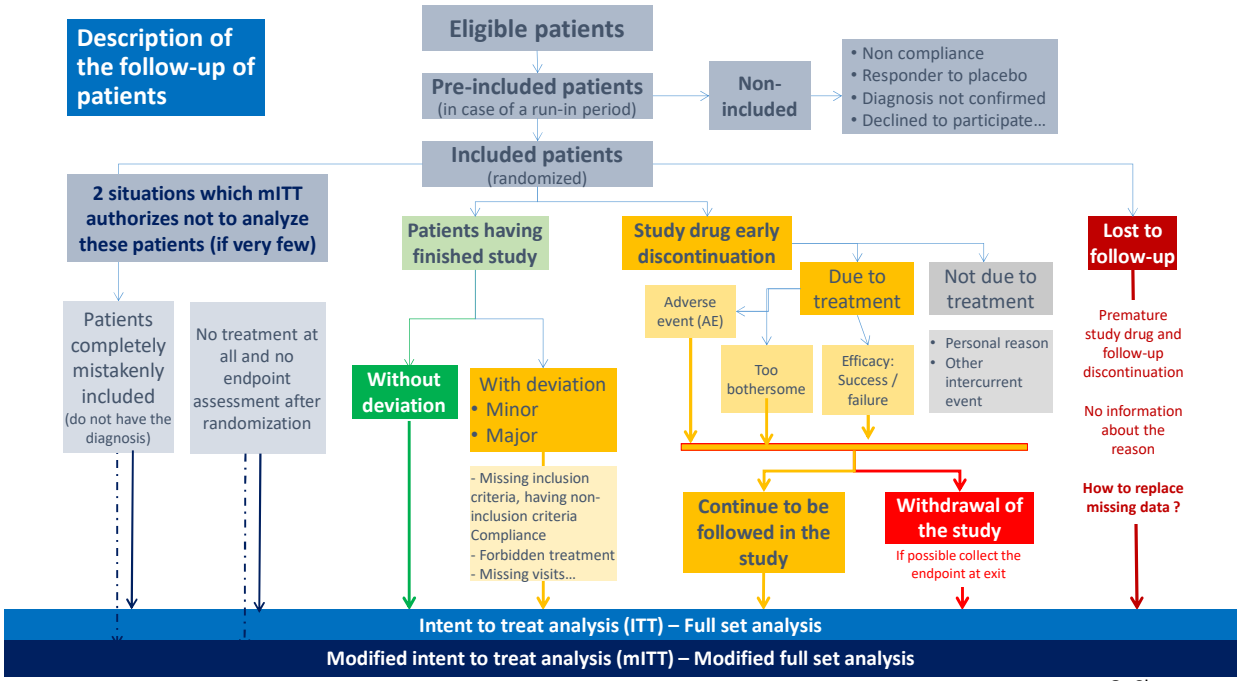

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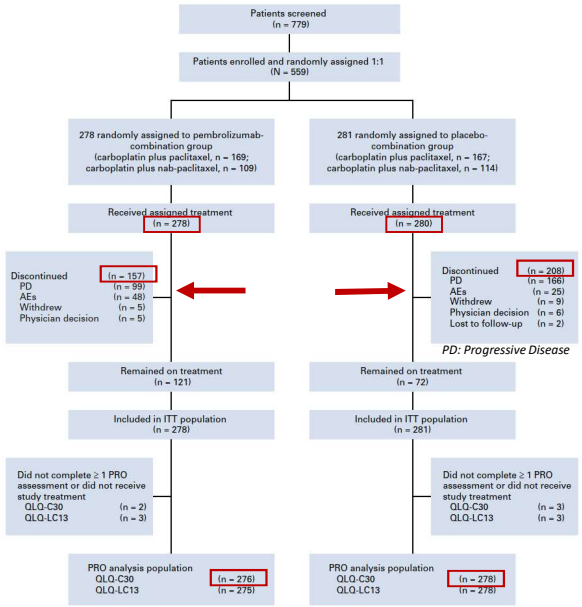
When reviewing the results of a dossier

- 1st instinct: to check that the number of patients analyzed in each group corresponds to the one randomized (to comply with ITT)
- 2nd: to look at the number of patients who did not complete their participation and to check whether the reasons seem to differ between the 2 groups
- 3rd: to understand if and how were imputed data not collected / missing data according to the different events

Generally laconic explanation if any: *multiple imputation for missing data with **missing at random (MAR) assumption** and then synthesized based on Rubin's rule (primary endpoint: QLQ-C30 global health status)*



Mazieres J, Kowalski D, Luft A, et al. Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020;38(3):271-280.

How are currently handled Intercurrent Events (IE) and missing data (MD)
Particularly important for PRO repeated measures over time

- To respect the strict ITT principle, most analyses are made with the strong assumption that data are **MAR/MCAR**
- With simple imputation approach:
  - Baseline value
  - Last observation carried forward (LOCF)
  - Mean of the subject's arm
- Easy to understand but may not be the truth

Example of MD handling in a longitudinal PRO assessment over 48 wk:

- Non-exploratory PROs*: imputed using a **LOCF** approach including **measures assessed at time of withdrawal**
- Exploratory endpoints: **observed cases without imputation, statistical modeling, or testing**.

* Some were key secondary endpoints and using an adaquate hierarchical testing strategy.

Question: Whether estimating an effect with ITT always represent the treatment effect of greatest relevance to regulatory and clinical decision making

Bell ML, Floden L, Rabe BA, et al. Analytical approaches and estimands to take account of missing patient-reported data in longitudinal studies. Patient Relat Outcome Meas. 2019;10:129-140.
Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. N Engl J Med. 2020;382(12):1124-1135. doi:10.1056/NEJMoa1909512. Supplementary material, protocol.

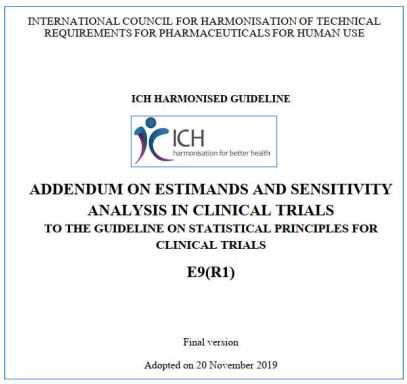
Intercurrent events → Estimand framework

Intercurrent events (IE): occurs after treatment initiation / randomization and either prevents the observation of the variable, or affects its interpretation.

Estimand: defines how IE will be dealt with and ensures the objective of the trial, the design, data collection, and analyses are consistent with this approach.

Estimand framework wants to revisit the strict ITT principle with a more explicit decision strategy about the interaction of IE on the variable observed.

5 strategies for addressing IE **(integrating some IE in the interpretation of the endpoint: e.g. a responder on the primary endpoint will be considered non responder if had rescue medication)**


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ICH harmonisation for better health

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

ICH E9 (R1) addendum - Estimands and sensitivity analysis in clinical trials
Estimands – What you need to know. Statistical Consultancy Team, Quanticate CRO Blog, Sep 08, 2019. https://www.quanticate.com/blog/estimands-clinical-trials

Integrating IE in the endpoint is already done

FDA virological failure snapshot (e.g. wk-48 time window)

- Success: HIV1-RNA < 50 copies/mL threshold
- Failure:
  - HIV1-RNA ≥ 50 copies/mL
  - Data in window not below 50
  - **Discontinued for lack of efficacy**
  - Discontinued for other reason while not below 50
  - **Change in background therapy**
- No Virologic Data at Week 48 Window
  - Discontinued study due to AE or death
  - Discontinued study for other reasons
  - On study but missing data in window

PRO - Oncology

QLQ-C30 global health score at 9 months (secondary endpoint)

- *"We assessed the potential effect of missing data using imputation to model the following scenarios:*
  - **Scenario 1, a global score of 0 was imputed for patients who died within 9 months of enrolment**
  - Scenarios 2–4, all patients alive and without progression at 9 months but missing QoL data were assigned a score, starting …
  - Scenario 5, …
- **Rationale for scenarios 2–4 was that patients might have missed submitting their questionnaires due to illness, in which case a lower quality of life would be expected.**

Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry. FDA November 2015.
https://www.fda.gov/media/86284/download
Blagden SP, Cook AD, Poole C, et al. Weekly platinum-based chemotherapy versus 3-weekly platinum-based chemotherapy for newly diagnosed ovarian cancer (ICON8): quality-of-life results of a phase 3, randomised, controlled trial. Lancet Oncol. 2020;21(7):969-977.

The best way to handle intercurrent events? ignore them during COVID epidemic

- Cohort
- 26 subjects treated with HQ in a center vs 16 controls enrolled in other centers
- Surrogate marker (SARS-CoV-2 PCR) : **clinical question of interest?**
- Analysis: **6 missing patients among the 26 HQ treated patients**
  - **3 transferred to ICU**
  - **1 died**
  - 2 discontinued the treatment (**1 nauseous (AE?)** and 1 went home)

Conclusion: *"Despite its small sample size, our survey shows that hydroxychloroquine (HQ) treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin."*

Based on this study and a few other biased reports, health policy on therapeutic recommendations for COVID has changed worldwide for a moment until RCT confirmed the inefficacy of HQ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Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

ARTICLE INFO

ABSTRACT

1. Introduction

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949.
Rosendaal FR. Review of: "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul;56(1):106063.

Conclusion

- This guideline is useful for increasing quality of trials for a better informed decision making by regulators and HTA assessors
- However, be careful that its implementation does not result in such a complexity that none will understand what has been done except statisticians

Contact information

Olivier Chassany

E-mail: chassany.o@gmail.com