**IP22 ARE SINGLE-ARM CLINICAL TRIALS SUFFICIENT TO ASSESS VALUE IN ONCOLOGY AND RARE DISEASES?**

**Perspective of Society and Payers**

Barcelona 14th November 2018

Pr. Mondher Toumi

---

**Why do we do trials?**

- We do clinical trials to test the incremental benefit (Efficacy and/or safety) of an intervention vs another.
  - The alternative intervention may be doing nothing, palliative therapy, just standard of care
  - The objective is to test an hypothesis \( (H_0) \)
- Why double blind comparative randomized trials are the norm?
  - This will avoid selection bias the most critical one when doing comparison and avoid channeling per indication.
Risk associated to Single Arm Trial (SAT)

- Without reliable evidence there is a risk to accept product that may later prove to harm patient or not bring expected benefit
  - Unethical from the society perspective
- EUnetHTA concluded in it’s guidelines that adding non randomized studies requested substantial assessment efforts and failed to impact the conclusion effort
  - Not valuable for gaining patients access

“Dramatic effect” (ICH E10)

- Use of the external control design is restricted to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable;
- Start with externally controlled trial and switch to RCT (or stop) if effect not dramatic;
  - What is the threshold for “dramatic”?
  - Based on what outcome?
  - Can we operationalise the concept?
Is Rarity an obstacle to Running RCT?

• Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011 Nov;47(17):2493-511
  - Centers of excellence for rare cancers or groups of rare cancers could provide the necessary organizational structure and critical mass for carrying out clinical trials and developing alternative approaches to clinical experimentation for these cancers.

• No clear operational rules for designing and accepting SAT at regulatory
  - To be acceptable manufacturers should prove that randomized control trial was not feasible
  - A check list for feasibility assessment should be developed by stakeholders

• US oncologists call for government regulation to curb drug price rises
  - BMJ 2015; 351 Michael MacCarthy
  - Out of 36 drugs approved by FDA for cancer ../... 19 were approved on response and 17 PFS../... Ultimately 4 years later only 5 happen to improve survival, 18 failed and for 13 it was unknown

Single Arm Study Acceptability

Evidence support and RCT is not feasible, historical cohorts may be accepted in some circumstances

- A reasonably robust historical control do exist

1. Method control for matching of confounding e.g. propensity score matching
2. Population is relatively homogeneous: Studying heterogeneity in the patient population and impact on outcome
3. Confounding factors affecting the outcome are well known and control
4. Patients management is well established and reasonably standardized
5. Primary end point is objective and robust
6. Effect size of the new therapy is outstanding vs the historical cohort
7. Proactively assess the generalizability and transferability of the clinical data
8. Risk of irreversible damage

If these factors are considered, the historical cohort may be accepted
If these factors are not considered, the historical cohort may not be accepted
Conclusion

- Do not claim too fast RCT is not feasible
  - Need a check list for non feasibility of RCT
- Feasibility is not only a matter of statistics
  - It is first a matter of common sense as it is a complex decision
- Need an investment from multi-stakeholders to develop operationalizable guidelines for SAT
- Consider SLR and defining a reference value for comparison of primary and key secondary outcome
- Avoid surrogate end points in SAT go for a patient relevant end points