APPLY REAL-WORLD TRIALS TO ENHANCE EVIDENCE CAPABILITIES

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DISCLAIMER

• I’m a Novartis Pharmaceuticals Employee
• The opinions expressed herein are my own, based on my personal experience and do not necessarily represent those of Novartis Pharmaceuticals
A BIT ABOUT THE PERSPECTIVE

• I’m coming from the sponsor perspective
• Projects range from small to large size
• Always multinational, most of them prospective
• Always projects within Canada & Latin America, but on occasion countries outside those borders are included
• And always working with very limited resources
WHY ARE WE HERE?

- I’m I preaching to the Choir?
- Any Skeptics in the room?
BACKGROUND

• Patients and Clinicians live in the Real World
• Alternative sources of RWD and RWE are increasing
• The demand of RWE by stakeholders is increasing and the timeline for data needs has shorten
• Some “barriers” based on preconceptions need to be jumped.
  • The Randomized Clinical Trial paradigm
BACKGROUND

CT. Gov search Observational Trials

- NIH+: 6333
- Industry: 21625
- All Others: 9237
BACKGROUND

Observational Trials Posting


Number of Observational Trials Posting: 0, 1000, 2000, 3000, 4000, 5000
KEY CONCEPTS

• RWD\(^1\): as data collected from sources outside of traditional clinical trials, including registry studies, retrospective database studies, case reports, and routine public health surveillance

• RWE\(^1\): Defined as the evidence derived from aggregation and analysis of RWD

• Observational Study\(^2\): Study that provides estimates and examines associations of events in their natural settings without recourse to experimental intervention

\(^1\)FDA draft guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. July 2016

THE “EVIDENCE HERIARCHY”

ATTITUDES TOWARD OBSERVATIONAL STUDIES

• The “RCT Paradigm”
• It is clear that RCTs are gold standard for Efficacy and Safety evidence
• That determines players perspective, when presented with different models of evidence, like Observational Trials
• Truth is: “Reality surpass fiction” => RCT model has its own limitations and could be challenged
• Remember RCTs are an “experiment” (idealized environment/limited population)
EVOLVING ATTITUDES

• Acceptance and Relevance are increasing
• Better “Observational Study methods, more sophisticated use of data sets, improved trial design and more robust statistical method” is the stepping stone for this new attitude
• Britton (1998); Concato (2000); Ligthelm (2007) provide grounds for the use of Observational Studies as complement to RCTs
  • Britton goes even further and states: “a well-designed nonrandomized study is preferable to a small, poorly designed and exclusive RCT.”

1Lighthelm. Importance of Observational Studies in Clinical Practice. Clinical Therapeutics. 2007;1284-1292
EVOLVING ATTITUDES\textsuperscript{1}

• Guidelines have been developed in recent years, providing a more robust system for design, conduction, analysis, reporting and even review:
  
  • Safety Assessment of Marketed Medicines guidelines (UK, 1994)
  • European Post-Authorization Study Guidelines (EU, 2006)
  • Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices-Draft-. (FDA, 2016)

\textsuperscript{1}Lighthelm. Importance of Observational Studies in Clinical Practice. \textit{Clinical Therapeutics}. 2007;1284-1292
WHEN IMPLEMENTING REAL-WORLD RESEARCH

Challenges
- The “RCT Paradigm”
- Preconceptions
- Broad targeting: trying to do too much with it
- Heterogeneous data collection, makes harder data aggregation

Opportunities
- Evolving methodology and change in attitude favors RWD use
- Needs from stakeholders are increasing the demand for RWD/RWE
- Technological advances, ease collection of reported outcomes
- Global trend for EHR
HOW RWD FIT?

• Key word is “Complement”
• Sometimes RCT’s nature very well could leave gaps: Treatment Compliance, Resource Utilization, QoL, etc
• This is where RWD comes to play a gap filling role
• By implementing a well designed “Real Life” study, rich data could be obtained, that would complement/show/support the added value of a treatment and/or procedure
• Some examples next:

1. Lighthelm. Importance of Observational Studies in Clinical Practice. Clinical Therapeutics. 2007;1284-1292
ROUTINE USES OF REAL LIFE DATA

• Patient Profiling and prevalence
  • case drawn from the IMS disease analyzer dataset compared to a large, classic epidemiology type study in gout

Lleven et al. Real Life Data a growing need. ISPOR Connections. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp
ROUTINE USES OF REAL LIFE DATA¹

• Treatment flows - Patient Journeys:
  • anonymized example for a cardiovascular indication, showing the ability to map and better understand the pathway of treatment and patterns of care

¹Lleven et al. Real Life Data a growing need. ISPOR Connections. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp
• Compliance and Persistence:
  • ARBs and diuretics were associated with better persistence, use of better BioStat Model and analysis allowed to determine factors favoring persistence (fear, time from Dx, etc)

1Lleven et al. Real Life Data a growing need. ISPOR Connections. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp
ROUTINE USES OF REAL LIFE DATA

• Treatment costs and costs in disease stages:
  • Cost of treatment in Parkinson’s disease, differences across age and between countries. Data collected from IMS

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1 Lleven et al. Real Life Data a growing need. ISPOR Connections. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp
ROUTINE USES OF REAL LIFE DATA¹

• Health Outcomes and disease sequelae:
  • Usually long term chronic conditions
  • For RCTs would be impossible
  • Prospective long term observation is a viable solution

¹Lleven et al. Real Life Data a growing need. ISPOR Connections. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp
SOME EXAMPLES OF REAL LIFE DESIGNS AND THEIR INFLUENCE

• RWD can very well support key results from Phase III RCTs\(^1\)
  • Wirth’s PMS with Orlistat where a 10 times larger population, supported previous RCT findings\(^2,3\)

• How treatment outcomes with a particular drug compare with those from a number of alternative therapies.
  • PURE Study (NVS Sponsored) Psoriasis registry Canada and Latin America, treat with secukinumab, or one of the other indicated therapies regimens approved for the management of moderate to severe chronic plaque psoriasis\(^4\)

• Head to head comparisons particular clinical endpoint. Ttx outcomes in heterogenuos population with complex chronic diseases

\(^1\)Lighthelm. Importance of Observational Studies in Clinical Practice. *Clinical Therapeutics*. 2007;1284-1292
\(^4\)Data on file. ClinicalTrials.gov
SOME EXAMPLES OF REAL LIFE DESIGNS AND THEIR INFLUENCE

• Head to head comparisons of treatment on the basis of particular clinical endpoint.
  • In Osteoporosis large (n=33K) comparative retrospective analyses, such as the REAL study, are an important means of filling gaps in the evidence base. It is unlikely H2H comparative clinical fracture trials would be done

• Treatment outcomes in heterogonous population with complex chronic diseases
  • In diabetes the PREDICTIVE(2007), EDGE (2013) are examples of large (n>30K) prospective global observational studies

1 Lighthelm. Importance of Observational Studies in Clinical Practice. Clinical Therapeutics. 2007;1284-1292
3 Dornhorst et al. Safe W and efficacy of insulin detemir in clinical practice: 14-Week Follow-up data From type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. Int J Clin Pract.2007;61:523-528
KEY MESSAGES

• RWD/RWE fill the gaps left by classical CRTs
• Acceptance of RWE is growing, but some additional work needs to be done.
• Policy makers are considering and learning the value of real world generated data
• Exciting times we are living, as new technological advances allow for better and reliable data collection in the Real World/Real Life Setting
• Every tool has its limits, pros & cons must always be considered when trying to design a solution to a problem
• Real-world research can be applied throughout a product’s lifecycle, as shown on examples above
THANK YOU

What is the answer to the ultimate question about life, the universe and everything else?

Deep Thought answers: “42”

If you don't understand the answer, is because you didn't understand the question in the first place

From: Hitchhiker's Guide to the Galaxy by Douglas Adams

- “All you really need to know for the moment is that the universe is a lot more complicated than you might think, even if you start from a position of thinking it’s pretty damn complicated in the first place”

-Douglas Adams