Evidence Requirements Supporting Critical Decisions in Pharmacotherapeutics:

Proof of Concept

Vs

Proof of Value

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Proof of Concept

- The fundamental regulatory requirement for market authorization
  - High quality RCT new drug vs placebo
    - RCT's limit bias and minimize random chance
      - Extrapolation to large populations may be limited
      - Safety information may be limited
- POC drives design of Phase 2 and Phase 3 RCTs
  - High failure rate for new drugs in Phase 2
    - High percentage of kill decisions are strategic

Limitations of RCT's in POC

- Typically 2-arm, new drug vs placebo
- Only a few questions can be addresses in a single RCT
- RCT's powered for efficacy outcome have limited safety data
- RCT's powered for safety have a narrow focus
- Limited extrapolation to populations not specifically included in RCT for subset analysis

Limitations of POC Studies

- *Little information* on long term use
- *Little information* on any but the most frequent safety issues
- *Little information* on drug interactions
- *Little information* in full target population for the marketed product
- *Little information* comparing to existing drugs
- *Little information* regarding appropriate utilization

Limitations of POC Requirements

At the time of Market Authorization, we really do not know a lot about a new drug.

Evidence Required for Health Technology Assessment

- Information on long term use
- Information on population safety issues and their costs
- Information on drug interactions
- Information in full target population for the marketed product
- Information comparing to existing drugs
- Information informing appropriate utilization
- Cost effectiveness estimates

Economic Models

- Based upon direct comparison
  - Preferred, vary based upon assumption of equal efficacy (cost minimization) or superior efficacy (incremental cost effectiveness ratio)
- Based upon indirect comparison
  - Require stricter rules than simple meta-analysis
  - Difficult to agree upon appropriate assumptions
    - Wide variations within sensitivity analysis
- *Low quality evidence input yields low quality estimations in cost-effectiveness*

Non-inferiority Margins

- Basis of claim “Proven equivalent by non-inferiority....”
- Stipulation of quantum in statistical test of “not much worse than...”
- Requires both statistical and clinical basis for the margin
- POC may be more lenient than POV
  - When the NI is “generous”, is the payer willing to give away benefit of the older drug? (e.g., 20%, 1 in 5)

Post Hoc Data Analysis

- May be basis for sub-population efficacy claims
- Increasingly depended upon in economic models
- Frequently the basis for requesting payment decisions as second or third line therapy
- Perversion of RCT design strengths
  - Expect that an arrow is shot at a target, not that an arrow is shot, then the target painted around it
- “Data Mining” in Observational Studies

Open label extensions

- Often cited in clinical practice guidelines for efficacy as well as safety
- Magnifies bias issues from unblinding
- Removes concurrent assessment of “best practice”
- Often outcome measures are relaxed, incompletely reported, or inconsistently assessed.
- Need for objective patient level reporting

Methodology Issues

- Appropriate surrogate outcome measures, exclusion criteria, length of trials in POC vs placebo
- Appropriate active comparators
- Trial design for non-inferiority studies
- Pre-declared subpopulation analyses
- Open label extensions
  - Strengthen data requirements, build in comparisons
- Confidence on reliability of Observational Data