Systematically defining research objectives and framing questions using the estimand framework

Moderators: Bellinda King-Kallimanis & Laura Lee Johnson
Disclaimer

• We have no financial relationships to disclose

• Specific PRO instruments discussed in this talk are used as examples, not direct endorsements
Panelists

Jane Perlmutter, PhD, MBA – Patient advocate
Sigrid Klaar, MD, PhD – EMA/HTA
Jim Shaw, PhD, PharmD, MPH – Industry
Katherine Szarama, PhD – Domestic payer
Lori Minasian, MD – Oncologist/Researcher
14.2.5 Clinical Benefits Endpoints

- Quality of Life measured using the EORTC questionnaire.
- Tumor-Related Symptom Assessments measured by pain intensity (Visual Analog Scale), analgesic consumption, and ECOG performance status.

The primary health outcomes research goal is to assess if the combination therapy is able to impact the quality of life, as measured by the EORTC QLQ-C30 (Aaronson et al. 1993).

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>To evaluate patient reported outcomes for health-related quality of life in the two treatment arms</td>
<td>Time to 10% deterioration in the global health status/QoL scale score of the EORTC QLQ-C30</td>
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<tr>
<td></td>
<td>Change from baseline in the global health status/QoL scale score of the EORTC QLQ-C30</td>
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Secondary objectives of the study were to compare IDFS including second primary non-breast cancers (SPNBC), disease-free survival (DFS), overall survival (OS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI), cardiac safety, overall survival, and health related quality of life (HRQoL) in the two treatment arms.

6) **Objective**: To evaluate patient-reported treatment effects at pre-specified time points while on treatment and post-discontinuation as measured by changes from baseline in all domains and single items of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (C30) and Lung Cancer 13 (LC13), with particular emphasis on EORTC QLQ-C30 QoL domain, chest pain (LC13 question [Q] 10), cough (LC13 Q1), and dyspnea domain (LC13 Q5 to Q5) in previously untreated advanced NSCLC subjects receiving either [redacted] or comparator.

7) **Objective**: To summarize and compare by treatment arm, the number and proportion of subjects who improved, worsened, or remained stable for all domains and single items of the EORTC QLQ-C30 and LC13.
The Problem

Even if we specify that we want to know the difference on Physical Functioning between patients on treatment A versus treatment B at week 26 – there is still ambiguity about the scientific question of interest.

For example, there will be patients who cannot tolerate the therapy due to drug side effects.

Do I want to know about the subgroup of patients who can tolerate therapy, or all patients?
The estimate produced is not actually what we are interested in clinically/scientifically
Estimand Framework

BUT what is the definition?

It is what we actually want to estimate

Which we get to by describing key attributes

The estimand framework provides a structure so that all stakeholders are speaking in a common language

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Case Study Clinical Scenario

• Scenario
  • Metastatic ER/PR+ HER2- breast cancer after progression on 1st line therapy

• Epidemiology and Disease Information
  • Breast cancer has heterogeneous disease symptoms and many women will be asymptomatic at baseline, even in the 2nd line setting
  • 2nd line prior studies have shown a median OS of 2-2.5 years with 2nd line hormone therapy alone and a median PFS of approximately 10-12 months

• Treatment Goal
  • Addition of targeted therapy to hormonal agent will improve PFS by 6-8 months
  • Combination is expected to add symptomatic toxicity

source: https://www.uptodate.com/contents/treatment-approach-to-metastatic-hormone-receptor-positive-her2-negative-breast-cancer-endocrine-therapy-and-targeted-agents
Case Study Clinical Scenario Cont.

• **Study Design:** Randomized controlled trial
  - Treatment: SoC + oral targeted investigational agent
  - Control: SoC + placebo

• **Expected Outcomes**
  - **Expected Efficacy:** 6-8 month PFS benefit
    - OS may be impacted due to crossover
  - **Expected Safety:** Symptomatic toxicities including diarrhea, fatigue and rash greater on investigational arm

• **Population Assumptions**
  - Population is generally high functioning (ECOG 0 or 1)
  - A small percentage of the population is symptomatic (from disease) at baseline
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Primary Statistical Techniques in Peer Review Literature: Pe et al - SISAQOL

- (Generalized) linear models
- Wilcoxon ranks sums test/between subject t-test
- ANOVA/Linear regression
- Time to event
- Repeated measures ANOVA
- Responder analysis
- Other
- Not reported/unclear

Pe, Dorme, Coens et al. 2018. Lancet Oncology. 19:e459-69
Using our case study - If this trial had captured 12 months of physical function data (i.e., each cycle of therapy) and concluded:

There was no difference between the two treatment arms on physical function

What conclusion would each stakeholder draw?
Estimand Framework Attributes

Population: Which patients are the focus of the scientific question

Variable (or Endpoint) of Interest: What will be measured and how

Intercurrent Events: What events can distort interpretation

Population-Level Summary: What is the basis for comparison

Estimand: Target of estimation to address a trial’s scientific question of interest
Communication of Results

Analysis Plan: Exploratory or Confirmatory

- **Target Study Population**
  - Study population
  - Characterized via rules for inclusion (e.g., baseline assessment present)

- **Variable (or end-point) of Interest**
  - Tool total score
  - Individual or group level analysis
  - Threshold

- **Intercurrent Events**
  - Death
  - Progressive disease
  - Concurrent palliative interventions

- **Population-Level Summary**
  - Median time-to-event (Hazard ratio)
  - Proportion of patients with event at time \( t \)

**Estimand**

**PRO Research Objective**
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Conclusions

• Lack of clarity about what we want to measure leads to confusion for all stakeholders

• The estimand framework provides a common language that we can all talk in to better describe our research findings

• Ensures that the research question we want to answer is answerable once the data is collected
THANK YOU