Systematically defining research objectives and framing questions using the estimand framework

Moderators: Bellinda King-Kallimanis & Laura Lee Johnson

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Clinical Outcome Assessments in Cancer Clinical Trials

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

Defining Trial Objectives: What do we see

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.

Objective	Endpoint
• To evaluate patient reported outcomes for health-related quality of life in the two treatment arms	• Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30 • Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30

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

2.2 SECONDARY OBJECTIVES

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 safety, and health related quality of life (HRQoL) in the two treatment arms.

To compare Patient-Reported Outcomes (PRO) measures between treatment arms.

- To determine pain response rate, as assessed by the Brief Pain Inventory–Short Form (BPI-SF) and analgesic use
- To assess change in global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

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 Q3 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

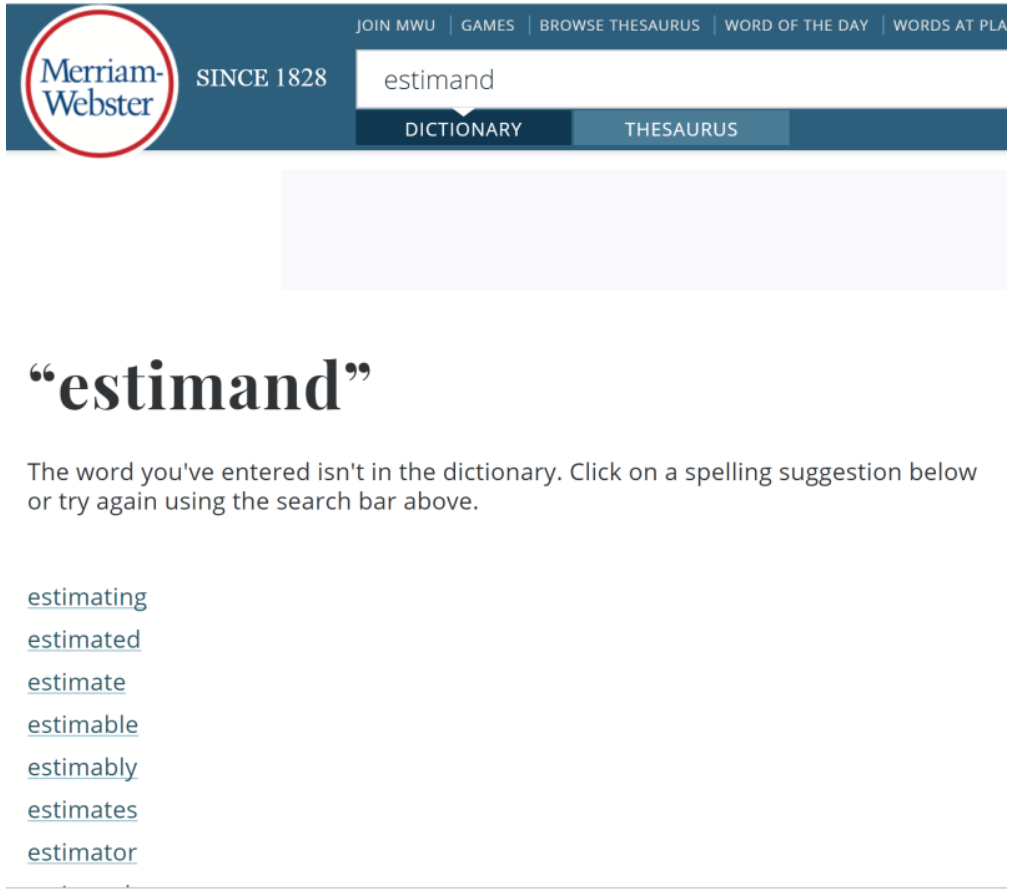
Estimand Framework

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
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf

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

Audience Poll - Question

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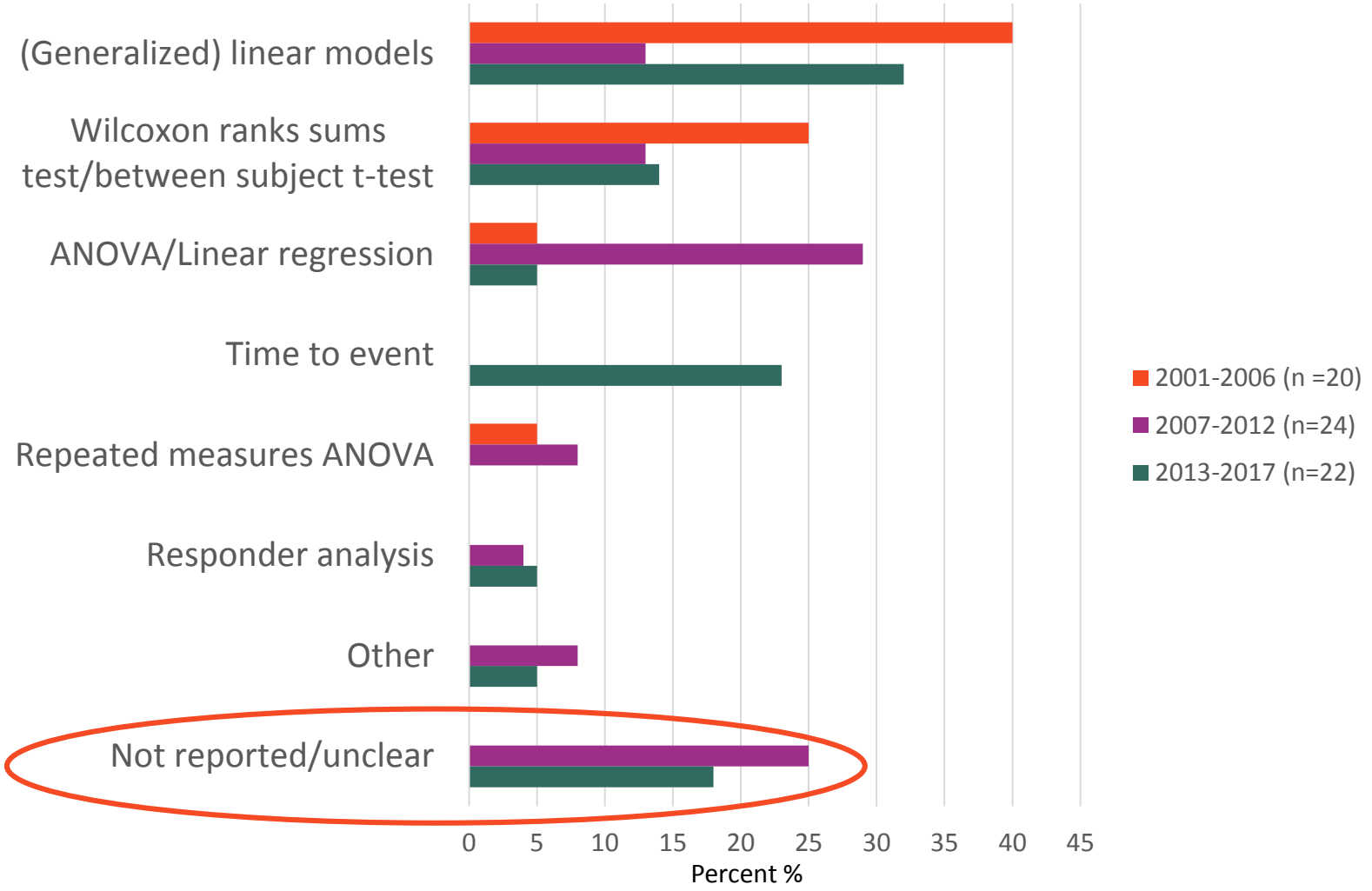
Primary Statistical Techniques in Peer Review Literature: Pe et al - SISAQOL



Pe, Dorme, Coens et al. 2018. Lancet Oncology. 19:e459-69

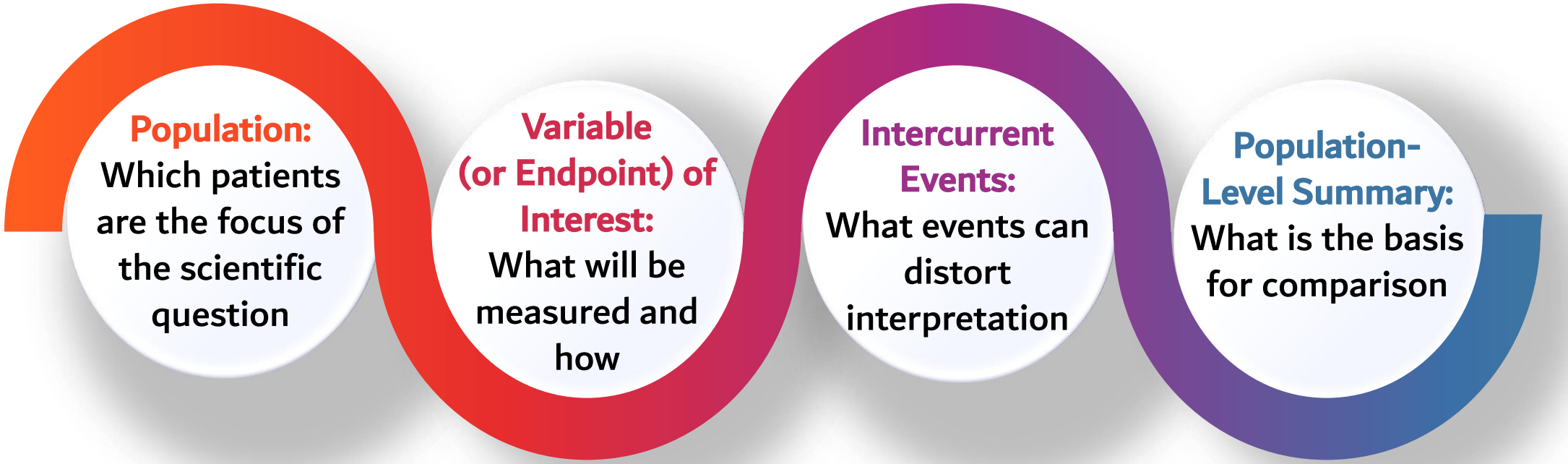
Panel Discussion

Using our case study - If this trial had captured 12 months of physical function data (i.e., each cycle of therapy) and concluded:

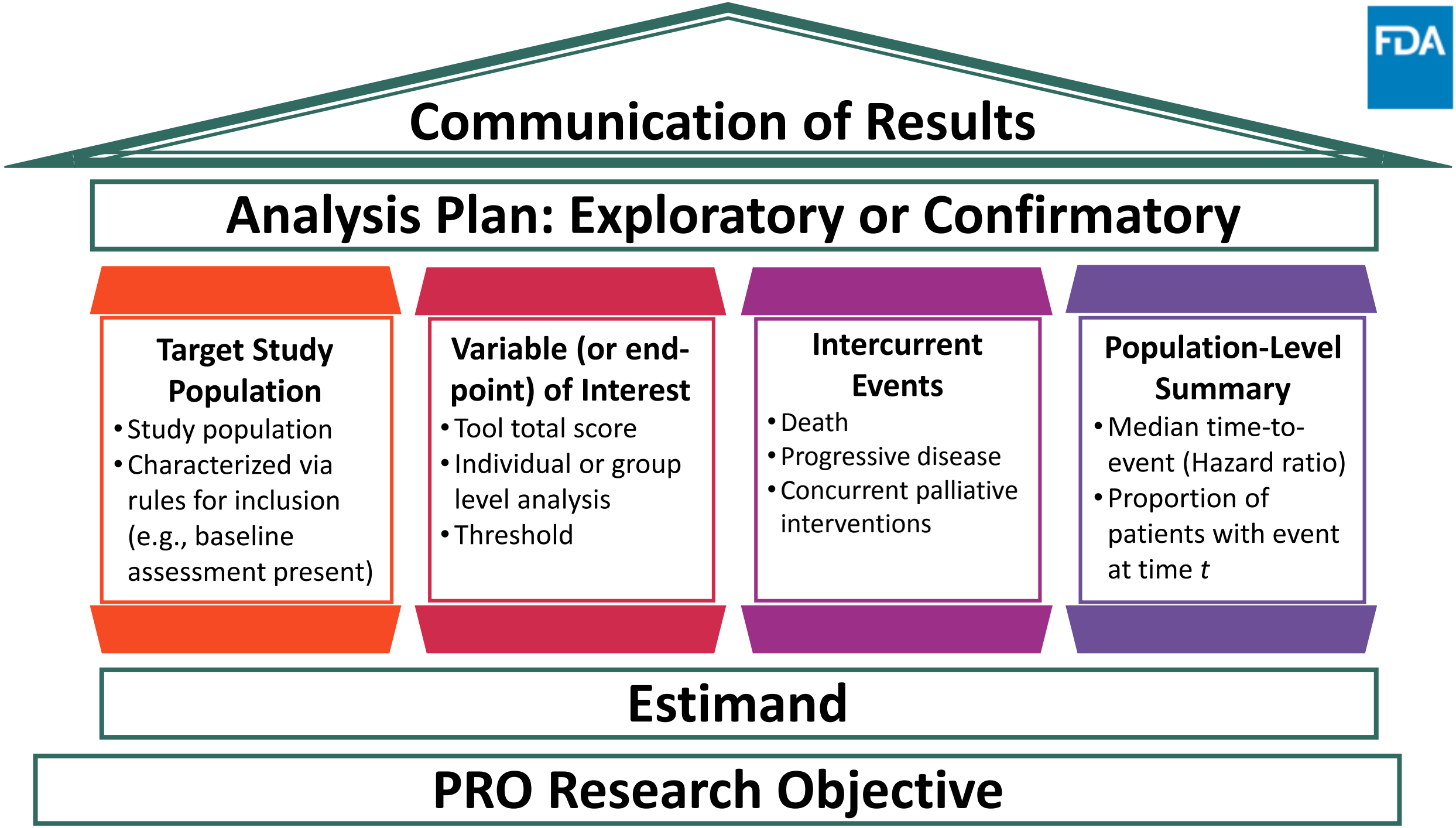
There was no difference between the two treatment arms on physical function

What conclusion would each stakeholder draw?

Estimand Framework Attributes



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

Audience Poll - Question

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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