PED (Patient Experience Data) / (Patient Reported Outcomes) as primary endpoints in clinical trials – What is a clinical meaningful change ? -statistician's view

John P.A. Ioannidis, MD, DSc – Stanford University

February 19, 2025

ESC
European Society of Cardiology

Statistician's view

- The primary endpoint should be decided primarily based on clinical and patient-centered, not statistical, considerations.
- There is a temptation to consult with the statistician to retrofit selection of endpoints and of their clinically meaningful change based on anticipated power
- Or worse to ask statisticians to justify (provide excuses) for the selection of an outcome and "suitable" clinically meaningful change, often implausible sample size calculations (e.g. implausibly large effect, or implausibly wide non-inferiority margin).

Annals of Internal Medicine®

Research and Reporting Methods | 9 October 2018

Researcher Requests for Inappropriate Analysis and Reporting: A U.S. Survey of Consulting Biostatisticians

Authors: Min Qi W
INFORMATION

Publication: Annal

Results:

Of 522 consulting biostatisticians contacted, 390 provided sufficient responses: a completion rate of 74.7%. The 4 most frequently reported inappropriate requests rated as "most severe" by at least 20% of the respondents were, in order of frequency, removing or altering some data records to better support the research hypothesis; interpreting the statistical findings on the basis of expectation, not actual results; not reporting the presence of key missing data that might bias the results; and ignoring violations of assumptions that would change results from positive to negative. These requests were reported most often by younger biostatisticians.

Some types of clinical trials, e.g. non-inferiority designs, almost always favor the sponsor:

Among trials published in 2011, 55/57 of non-inferiority trials with head to head comparisons sponsored by the industry demonstrated non-inferiority

Success rate > 96%

Flacco et al. JCE 2015

What a statistician/methodologist can do

- May point to already existing patient-centered endpoints that have been previously validated and where there is already documentation and validation of clinically meaningful changes
- May point to existing endpoints that have not been validated and thus should be avoided (unless they can be validated and justified for the specific trial being designed)
- Discuss the potential for measurement error in different outcomes and how these may erode treatment effects
- Discuss the potential for missing data in different outcomes and measurements
- Discuss the need, pros and cons of having more than one primary endpoints and/or composite endpoints

Systematic review before the new trial

Assess what endpoints have been used in which trials

Examine treatment effects recorded

Perform synthesis of data on treatment effects

Determine the need for a new trial and if so with what outcomes

Completeness of main outcomes across randomized trials in entire discipline: survey of chronic lung disease outcomes in preterm infants

John P A Ioannidis,[1] Jeffrey D Horbar,[2,3,4] Colleen M Ovelman,[4] Yolanda Brosseau,[4] Kristian Thorlund,[5] Madge E Buus-Frank,[6,7] Edward J Mills,[8] Roger F Soll[2,4]

ABSTRACT

OBJECTIVE
To map the availability of information on a major clinical outcome—chronic lung disease—across the randomized controlled trials in systematic reviews of an entire specialty, specifically interventions in preterm infants.

DESIGN
Survey of systematic reviews.

DATA SOURCES
Cochrane Database of Systematic Reviews.

STUDY SELECTION AND METHODS
All Cochrane systematic reviews (as of November 2013) that had evaluated interventions in preterm infants. We identified how many of those systematic reviews had looked for information on chronic lung disease, how many reported on chronic lung disease, and how many of the randomized controlled trials included in the systematic reviews reported on chronic lung disease. We also randomly selected 10 systematic reviews that did not report on chronic lung disease and 10 that reported on any such outcomes and identified whether any information on chronic lung disease appeared in the primary reports of the randomized controlled trials but not in the systematic reviews.

MAIN OUTCOME MEASURES
Whether availability of chronic lung disease outcomes differed by type of population and intervention and whether additional non-extracted data might have been available in trial reports.

RESULTS
174 systematic reviews with 1041 trials exclusively concerned preterm infants. Of those, 105 reviews looked for chronic lung disease outcomes, and 79 reported on these outcomes. Of the 1041 included trials, 202 reported on chronic lung disease at 28 days and 200 at 36 weeks postmenstrual; 320 reported on chronic lung disease with any definition. The proportion of systematic reviews that looked for or reported on chronic lung disease and the proportion of trials that reported on chronic lung disease was larger in preterm infants with respiratory distress or support than others ($P < 0.001$) and differed across interventions ($P < 0.001$). Even for trials on children with ventilation interventions, only 56% (48/86) reported on chronic lung disease. In the random sample, 45 of 84 trials (54%) had no outcomes on chronic lung disease in the systematic reviews, and only 9/45 (20%) had such information in the primary trial reports.

CONCLUSIONS
Most trials included in systematic reviews of interventions on preterm infants are missing information on one of the most common serious outcomes in this population. Use of standardized clinical outcomes that would have to be collected and reported by default in all trials in a given specialty should be considered.

Introduction

Many randomized controlled trials report only a portion of their primary and secondary outcomes.[1-5] This creates substantial potential for bias in the available evidence.[6,7] Trials can be misinterpreted when crucial information is missing. Selective reporting further distorts the systematic reviews and meta-analyses of the evidence. The impact of missing information on outcomes is even more influential when the respective outcomes are clinically the most important ones for the patients and setting examined. Some outcomes are so important that all trials, and thus also all systematic reviews, should consider, collect data, and report results on them. Their

Patient-relevant outcomes are usually understudied

Chronic lung disease in preterm infants reported in only 320/1041 trials

Methodological safeguards

- Proper discussion of potential effects of blinding of patients and of providers on the primary endpoint and relevant pros and cons.
- Pragmatism versus protection from bias.
- Ensuring detailed, pre-registered statistical analysis plan, taking into account any adjustments or peculiarities in chosen endpoint and trying to anticipate potential problems.
- Design and reporting according to accepted standards, e.g. new SPIRIT and CONSORT guidelines.

Meta-considerations

- Considering the conduct of other previous, concurrent, or future planned trials
- Any plans for integration of the evidence across multiple trials
- Harmonization or standardization of trial endpoints and other trial processes