

Creating a responder definition for patient-reported outcomes: How to select an appropriate cut-off value?

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Background

Patient Reported Outcomes (PROs) characterize information that is important to the patient, measuring symptoms that sometimes can only be assessed by the patient, such as pain.

Standard clinical trial endpoints may not reflect the patient's experience. Objective measures (e.g., imaging results) may be poorly correlated or fail to capture a patient's condition or wellbeing following treatment intervention.

Collection of patient outcomes may be paper-based, computer-assisted or telephone-based and can be self administered, via interview or a combination of both. Depending on the assessments captured, PRO data may be collected daily (e.g., via eDiaries) or at frequent intervals.

Most health technology assessment (HTA) bodies rely on PRO data in order to provide recommendations regarding access to new therapies.



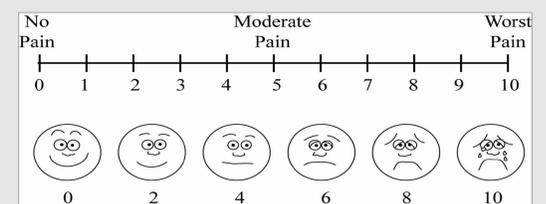
Content Validity & Psychometric Evaluation

Content Validity

- Item generation
- Recall period
- Response options (Checklist, Likert Scale, VAS, Pictorial)
- Scoring algorithm

Psychometric Evaluation

- Reliability (Test-retest, internal consistency)
- Construct Validity (discriminant validity, convergent validity, known group validity)
- Ability to detect change



Selecting a Responder Cut-off

Response definition: Individual patient PRO score (e.g absolute, change) at a predetermined time period that should be interpreted as a treatment benefit.

This poster explores the 3 main methods commonly used to define a responder cut-off. The process requires statistical and clinical judgement and by no means is an exact science!

Distributional Based Methods (Supportive)

The between-person variation and measure of error can provide a change value on a scale, which can be quantified as small, medium or large to provide confidence in the responder definition.

- Cohen's Moderate Effect Size (1/2 Standard Deviation)
- Standard Error of Measurement

Note, distributional methods do not inform the clinical importance and should be used alongside empirical methods.

Anchor Based Methods (Preferred Method)

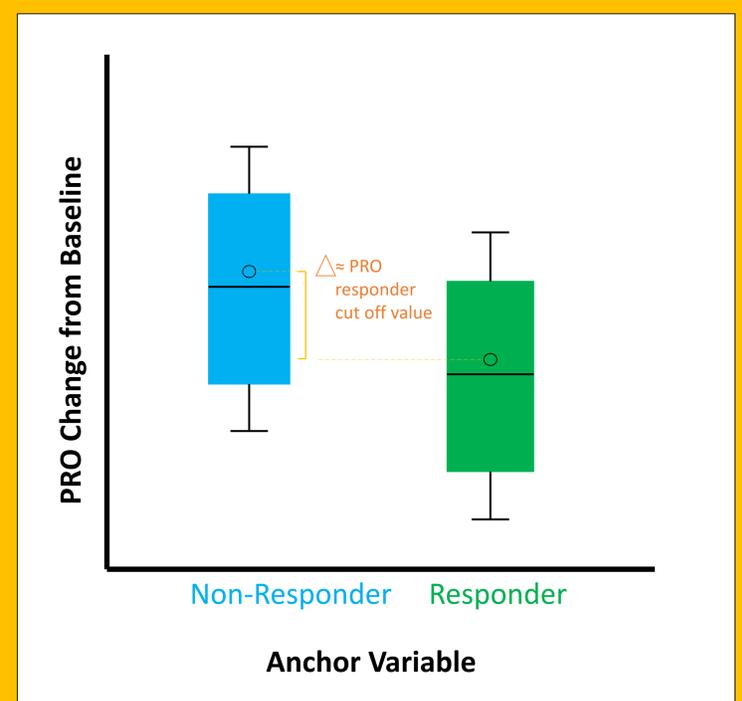
Anchor-based methods explore the associations between the targeted concept of the PRO instrument and the concept measured by the anchors.

- Identify anchors that are well established, meaningful, easy to interpret and have an accepted MCID.
- Anchors should show moderate correlation with the PRO instrument (e.g. $r > |0.3|$). Low correlation suggests the anchoring will not be meaningful, whilst a very high correlation suggests redundancy in the PRO.
- For each anchor, produce summary statistics for different response subgroups (e.g. below MCID vs. above MCID.) The cut-off for the PRO response definition can be established by taking the difference in means between the two response subgroups.
- ROC curves can be generated to assess the sensitivity and specificity of a change in the PRO scale in predicting whether patient is a responder or non-responder on the anchor variable.

Cumulative Density Function (Supportive)

To evaluate the robustness of the cut-off value selected.

- Plot the cumulative proportion of patients (Y axis) achieving PRO response over a range of possible response cut-off values (X axis).



Difference between MCID and Responder Definitions



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References

- FDA Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
- PSI PRO Webinar 8th May 2018