Session 6

Minimally Important Differences Dave Cella Dennis Revicki Jeff Sloan **David Feeny**

Ron Hays

Minimally Important Difference (MID)

- One can observe a difference between two groups or within one group over time that is statistically significance but small.
- With a large enough sample size, even a tiny difference could be statistically significant.
- The MID is the smallest difference that we care about.

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- "Smallest difference that is considered clinically important, this can be a specified difference (the minimum important difference (MID)) or, in some cases, any detectable difference" (p. 17).
- For many wide used measures (pain, treadmill distance, HamD), the ability to show any difference between treatment groups has been considered evidence of a relevant treatment effect. If PRO instruments are to be considered more sensitive than past measures, it can be useful to specify a minimum important difference (MID) as a benchmark for interpreting mean differences" (p. 19)

Distribution-Based "Estimation" of MID

- ◆ Is not an <u>estimate</u> of the MID
- Is raw score difference derived from prior information about the MID

$$- e.g., D_{measure} = ES * SD_{measure}$$

Distribution-based formulas

- Effect size (ES) = D/SD
- Standardized Response Mean (SRM) = D/SD^{\dagger}
- Responsiveness statistic (RS) = D/SD^{\ddagger}

SD = baseline SD; $SD^{\dagger} = SD$ of D; $SD^{\ddagger} = SD$ of D among "unchanged"

Standard Error of Measurement

SEM = SD * SQRT (1-reliability)

• 95% CI = Estimated true score +/- 1.96 * SEM

• 1 SEM = 0.50 SD when reliability is 0.75

Estimating the MID

- External anchors
 - Self-report
 - Provider report
 - Clinical measure
 - Intervention
- Anchor correlated with change on target measure
 - Small (r=.1), moderate (r=.3), large (r=.5)
- Anchor indicates "minimal" change

Hypothetical Change in Physical Function (T-score units) by magnitude of intervention



Getting Hit By Bike is > Minimal Getting Hit by Rock is Closer to MID



Self-Report Anchor

- People who report a "minimal" change
- How is your physical health now compared to 4 weeks ago?
- Much improved; Moderately Improved;
- Minimally Improved;
- No Change;
- Minimally Worse;
- Moderately Worse; Much Worse

Example with Multiple Anchors

 693 RA clinical trial participants evaluated at baseline and 6-weeks post-treatment.

Five anchors:

- 1) patient global self-report;
- 2) physician global report;
- 3) pain self-report;
- 4) joint swelling;
- 5) joint tenderness

Kosinski, M. et al. (2000). Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. <u>Arthritis and Rheumatism</u>, <u>43</u>, 1478-1487.

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Patient and Physician Global Reports

- How the patient is doing, considering all the ways that RA affects him/here?
- Very good (asymptomatic and no limitation of normal activities)
 Good (mild symptoms and no limitation of normal activities)
 Fair (moderate symptoms and limitation of normal activities)
 Poor (severe symptoms and inability to carry out most normal activities)
- **Very poor** (very severe symptoms that are intolerable and inability to carry out normal activities)
- --> Improvement of 1 level over time

Global Pain, Joint Swelling and Tenderness

- 0 = no pain, 10 = severe pain; 10 centimeter visual analog scale
- Number of swollen and tender joints

-> 1-20% improvement over time

Effect Sizes (mean = 0.34) for SF-36 Changes Linked to Minimal Change in Anchors

Scale	Self-R	ClinR	Pain	Swell	Tender	Mean
PF	.35	.33	.34	.26	.32	.32
Role-P	.56	.52	.29	.35	.36	.42
Pain	.83	.70	.47	.69	.42	.62
GH	.20	.12	.09	.12	<u>.04</u>	.12
EWB	.39	.26	.25	.18	.05	.23
Role-E	.41	.28	.18	.38	.26	.30
SF	.43	.34	.28	.29	.38	.34
EF	<u>.50</u>	.47	.22	.22	.35	.35
PCS	.49	.48	.34	.29	.36	.39
MCS	.42	.27	.19	.27	.20	.27 13

Use of "No Change" Group in Estimating MID

	Change #1 MID = ?	Change #2 MID = ?	Change #3 MID = 4
No Change on Anchor	Doesn' t matter	+ 2	0, +1, or + 2
Minimal Change on Anchor	0	+ 2	+ 4

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 "When defining a meaningful change on an individual patient basis (i.e., a responder), that definition is generally larger than the minimum important difference for application to group mean comparisons" (p. 30).

Change in SF-36 Scores Over Time (n = 54)



Concluding Thoughts

- It is easier to conclude that a difference is clearly or obviously important than it is to say it is always unimportant.
- No single best way to estimate MID
 - Use multiple anchors
 - Use anchors that represent minimum change
- Wide variation in estimates of MID
 - Report range, inter-quartile range, and confidence intervals around mean estimates.

The National Safety Council has determined that if installed properly this new Seat Belt will decrease traffic accidents by 45%.



And will also reduce road-rage by 75%.

Appendix A

- p. 7: iii. Assess Measurement Properties ... "identify meaningful differences in scores"
- p. 15: "FDA intends to review a PRO instrument for ... interpretability (e.g., minimum important difference)"
- p. 17: "The FDA is specifically requesting comment on appropriate review of derivation and application of an MID in the clinical trial setting."
- P. 19, "An MID is usually specific to the population under study....If an MID is to be applied to clinical study results, it is generally helpful to use a variety of methods to discover whether concordance among methods confirms the choice of an MID."

Appendix B

- p. 25: "In some cases, the FDA may request an *a priori* definition of the minimum observed difference between treatment group means (i.e., MID) that will serve as a benchmark to interpret whether study findings are conclusive."
- p. 29: "clinically meaningful in the context of the total composite and other individual component results."
- p. 30: "If the MID is truly to be the smallest effect considered meaningful, however, it would be logical to establish the null hypothesis to rule out a difference less than or equal to the MID."
- p. 31: "amount of difference or change observed in a PRO measure between treatment groups in a clinical trial that will be interpreted as a treatment benefit."

Formulas for Significance of Individual Change

SEM 95% CI	$1.96 * SD_{b} * (1 - reliability)^{1/2}$
SEp 90% CI	1.64* SD _b * (1- reliability ²) ^{1/2}
SEp 95% CI	$1.96* \text{ SD}_{b} * (1 - \text{reliability}^2)^{1/2}$
Estimated true score	Mean + reliability (score – mean)
Reliable change index	$X_2 - X_1 / \sqrt{2}$ SEM.

 $SD_b =$ standard deviation at baseline