Using a distribution-based approach and systematic review methods to derive minimum clinically important differences

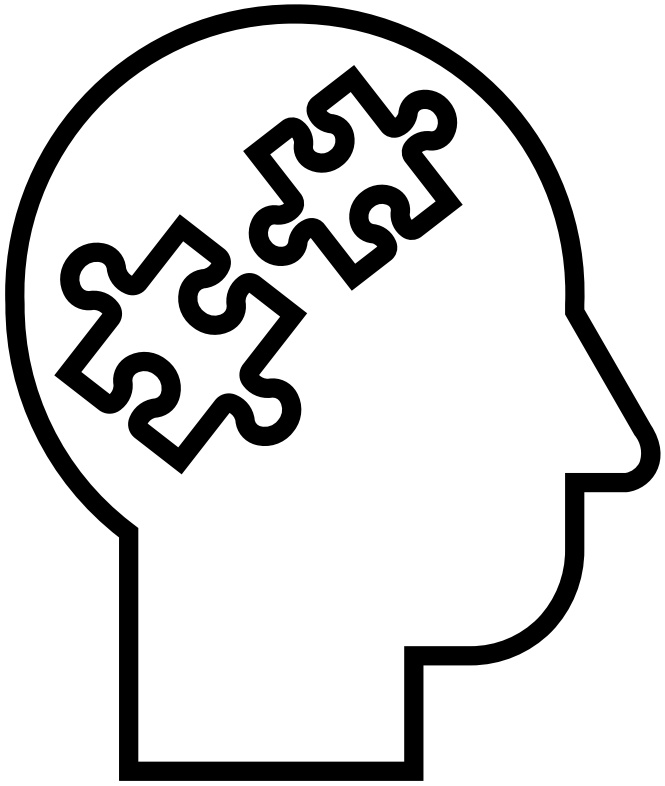
Dr. Jennifer Watt, MD, PhD, FRCPC

Assistant Professor, Department of Medicine, University of Toronto

Geriatrician, St. Michael's Hospital-Unity Health Toronto

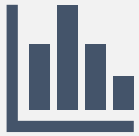
Scientist, Li Ka Shing Knowledge Institute

The Problem



Background and Rationale

Minimum **clinically important difference (MCID) for** a **scale:** threshold **above which we** perceive **a difference in an outcome**



Anchor- and distribution-based approaches to deriving a MCID

Can we improve estimation of MCIDs with knowledge synthesis methods and enhance interpretability of meta-analysis results?

Objectives

To describe an empiric example where we applied a distribution-based approach (data collected as part of a systematic review) to derive a minimum clinically important difference (MCID) for our outcomes of interest

To compare our derived MCID values to published MCID values

Methods: Dataset

We used data from a published systematic review and network meta-analysis of the comparative effectiveness and safety of cognitive enhancers (donepezil, galantamine, rivastigmine and memantine) for treating Alzheimer disease.

We included parallel randomized trials reporting a (1) baseline mean or mean change value for the MMSE or 11-item version of the ADAS-Cog, (2) standard deviation (SD) for the baseline mean or mean change value, and (3) number of participants per study arm.

We used accepted methods to calculate SDs where study authors reported other measures of uncertainty (i.e. 95% confidence interval or standard error).

Tricco AC et al. Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis. Journal of the American Geriatrics Society. 2018;66:170-178.

Methods: Calculating a Minimum Clinically Important Difference (MCID)

$$SD_{pooled} = \sqrt{\frac{\sum(n_i - 1)SD_i^2}{\sum(n_i - 1)}}$$

- n_i = number of participants per trial arm
- SD_i = standard deviation value per trial arm
- Multiply SD_{pooled} by an appropriate threshold (e.g. 0.4 or 0.5) for standard deviation (SD) values to derive a range of plausible MCID values

Furukawa TA, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59(1):7-10.

Results: Primary Analysis

	# RCTs (# Participants)	SD Range	Pooled SD	MCID: 0.4 x SD	MCID: 0.5 x SD
MMSE					
Baseline SDs	51 (12449)	0.94 to 6.8	4	1.6	2
Mean Change SDs	36 (10575)	0.33 to 6.12	3.6	1.4	1.8
ADAS-Cog					
Baseline SDs	37 (10006)	2.55 to 17.3	10	4	5
Mean Change SDs	38 (13288)	1.32 to 12.85	6.4	2.6	3.2

Abbreviations: Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog); Mini Mental State Exam (MMSE); minimum clinically important difference (MCID); randomized trial (RCT); standard deviation (SD)

MMSE MCID Results: Treatment Group

	# RCTs (# Participants)	SD Range	Pooled SD	MCID: 0.4 x SD	MCID: 0.5 x SD
Donepezil					
Baseline SDs	35 (3785)	1.08 to 5.9	4.2	1.7	2.1
Mean Change SDs	28 (3125)	0.33 to 6.12	3.6	1.5	1.8
Galantamine					
Baseline SDs	7 (1285)	1.92 to 4.12	3.9	1.6	2
Mean Change SDs	5 (1102)	2.24 to 4.05	3.9	1.5	1.9
Rivastigmine					
Baseline SDs	17 (1944)	0.98 to 4.9	3.5	1.4	1.8
Mean Change SDs	12 (1891)	0.46 to 3.6	3.2	1.3	1.6
Memantine					
Baseline SDs	9 (548)	1.6 to 6.2	4	1.6	2
Mean Change SDs	4 (442)	2.2 to 5.65	4.1	1.6	2
Placebo					
Baseline SDs	36 (4396)	0.94 to 6.8	4.1	1.6	2
Mean Change SDs	27 (3758)	0.33 to 5.76	3.7	1.5	1.8

Abbreviations: Mini Mental State Exam (MMSE); minimum clinically important difference (MCID); randomized trial (RCT); standard deviation (SD)

ADAS-Cog MCID Results: Treatment Group

	# RCTs (# Participants)	SD Range	Pooled SD	MCID: 0.4 x SD	MCID: 0.5 x SD
Donepezil					
Baseline SDs	22 (1693)	6.56 to 15.8	10.2	4.1	5.1
Mean Change SDs	20 (2215)	3.96 to 7.46	5.8	2.3	2.9
Galantamine					
Baseline SDs	16 (2296)	5.02 to 11.78	9.7	3.9	4.9
Mean Change SDs	22 (3179)	5 to 7.43	6	2.4	3
Rivastigmine					
Baseline SDs	14 (1825)	4.6 to 12.3	10	4	5
Mean Change SDs	15 (2892)	1.32 to 12.85	7.1	2.8	3.5
Memantine					
Baseline SDs	5 (706)	7.9 to 11.01	10	4	5
Mean Change SDs	3 (603)	5.46 to 9.77	8.2	3.3	4.1
Placebo					
Baseline SDs	28 (3398)	2.55 to 17.3	10.1	4.1	5.1
Mean Change SDs	29 (4315)	2.5 to 8.19	6.3	2.5	3.2

Abbreviations: Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog); minimum clinically important difference (MCID); randomized trial (RCT); standard deviation (SD)

Limitations

- It is unclear if minimum clinically important differences (MCIDs) generated by this approach are generalizable to all situations in which a scale is used.
- The anticipated distribution of uncertainty may vary based on effect modifiers.

Conclusion

- A distribution-based approach using data included in a systematic review can approximate minimum clinically important differences (MCIDs).
- Our approach performed better when we derived MCIDs from baseline as opposed to mean change standard deviations.
- This approach could facilitate clinical interpretation of outcome measures reported in randomized trials and systematic reviews of interventions.
- Future research should focus on the generalizability of this method to other clinical scenarios.

Questions?

Watt J, Veroniki AA, Tricco A, Straus S. Using a distribution-based approach and systematic review methods to derive minimum clinically important differences. *BMC Medical Research Methodology*. 2021; 41.

Dr. Jennifer Watt,
MD, PhD, FRCPC

jennifer.watt@utoronto.ca

@jennannwatt

Results: Sensitivity Analysis

	# RCTs (# Participants)	SD Range	Pooled SD	MCID: 0.4 x SD	MCID: 0.5 x SD
MMSE					
Baseline SDs	38 (9614)	1.3 to 6.8	4	1.6	2
Mean Change SDs	12 (5288)	0.33 to 4.34	3.5	1.4	1.8
ADAS-Cog					
Baseline SDs	26 (5744)	4.6 to 17.3	9.9	3.9	4.9
Mean Change SDs	8 (3320)	1.32 to 7.88	6.4	2.5	3.2

Abbreviations: Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog); Mini Mental State Exam (MMSE); minimum clinically important difference (MCID); randomized trial (RCT); standard deviation (SD)