Interpretation of Patient-Reported Outcomes

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Learning Objective

- To understand the methods for interpretation of patient-reported outcomes

Outline

- Anchor-based approaches
  - Percentage based on thresholds
  - Criterion-group interpretation
  - Statistical significance and clinical equivalance
  - Content-based interpretation
  - Clinical important difference

- Distribution-based approaches
  - Standardized effect size
  - Probability of relative benefit
  - Cumulative distribution function

- Mediation analysis

Importance of Interpretation

- PRO results must be interpreted by attaching meaning to them
- Patients and other stakeholders benefit
- Applying methods to enrich interpretation of PRO scores

Anchor-based Approaches

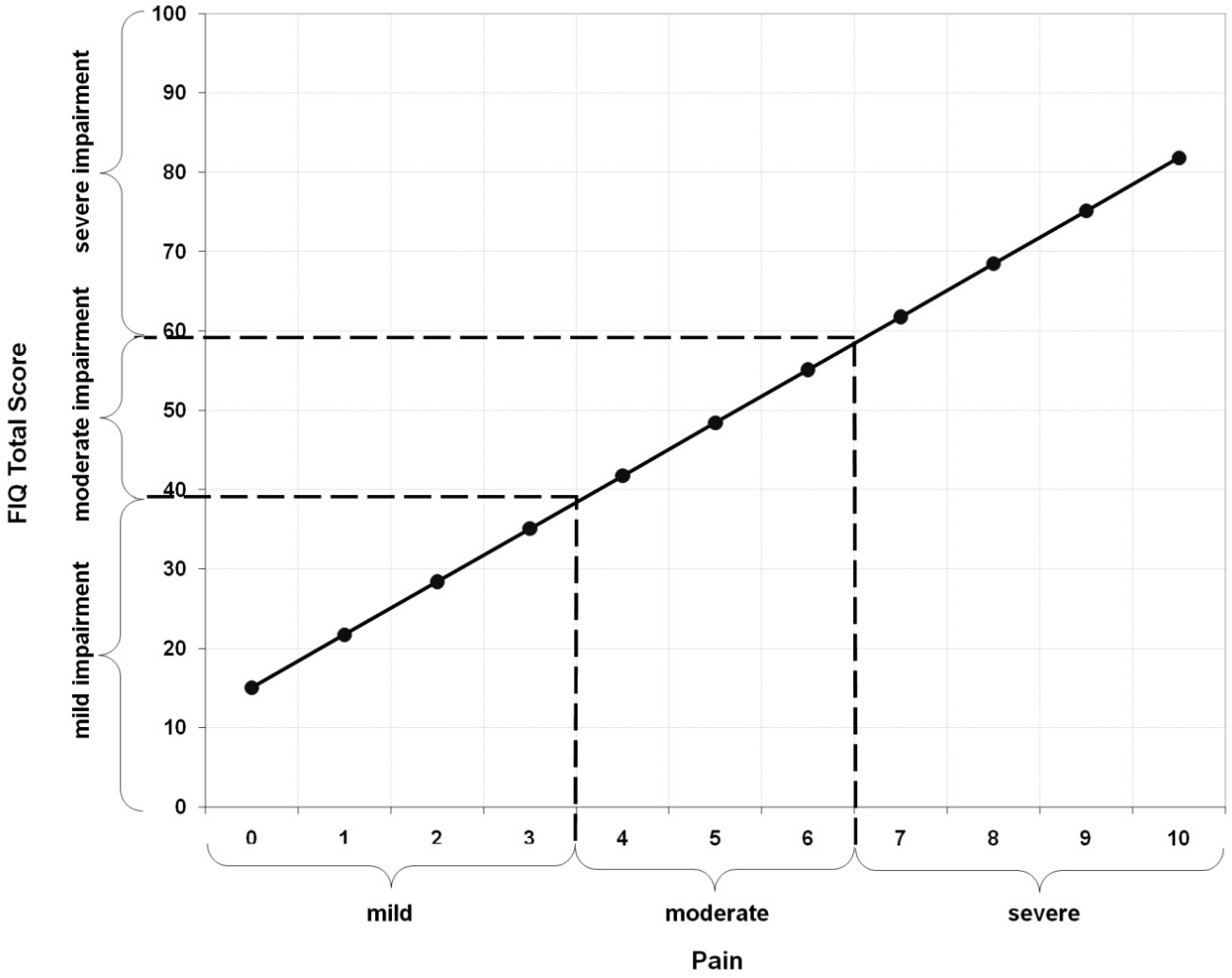
Percentage Based on Thresholds

- Show percentage of patients above and below some specified value, which is an anchored value with a meaningful criterion.

- Example: Erectile function domain of International Index of Erectile Function

- Example: Severity categorization on Fibromyalgia Impact Questionnaire (FIQ)

Severity Categorization of FIQ Total Score Using Pain Severity as an Anchor



Bennett et al. 2009

Simulated Example in SAS:
FIQ Severity Categorization (first 3 subjects)

VIEWTABLE: Work._mixed_2

	ID	Visit	Score	Pain
1	1	1	86.477679987	9.4652601914
2	1	2	73.332337615	7.9678018435
3	2	1	84.024696292	8.9303289077
4	3	1	86.354397654	9.1243845085
5	3	2	70.958155512	6.6441290133
6	3	3	52.8051996	5.8536769545
7	3	4	43.765302507	4.6849460105
8	3	5	42.117163151	3.326784542
9	3	6	16.134948499	1.9310167857
10	3	7	15.65229953	0.8598846265

SAS Code:
FIQ Severity Categorization

```
Proc Mixed data=_mixed_2;
 Class ID Visit ;
 Model Score = Pain / ddfm=kr s;
 Repeated Visit / Type=UN Subject=ID;
 Estimate " Pain =0 " Intercept 1 Pain 0 /cl;
 Estimate " Pain =1 " Intercept 1 Pain 1 /cl;
 Estimate " Pain =2 " Intercept 1 Pain 2 /cl;
 Estimate " Pain =3 " Intercept 1 Pain 3 /cl;
 Estimate " Pain =4 " Intercept 1 Pain 4 /cl;
 Estimate " Pain =5 " Intercept 1 Pain 5 /cl;
 Estimate " Pain =6 " Intercept 1 Pain 6 /cl;
 Estimate " Pain =7 " Intercept 1 Pain 7 /cl;
 Estimate " Pain =8 " Intercept 1 Pain 8 /cl;
 Estimate " Pain =9 " Intercept 1 Pain 9 /cl;
 Estimate " Pain =10" Intercept 1 Pain 10 /cl;
 Estimate " Pain =3.5 " Intercept 1 Pain 3.5 /cl;
 Estimate " Pain =6.5 " Intercept 1 Pain 6.5 /cl;
Run;
```

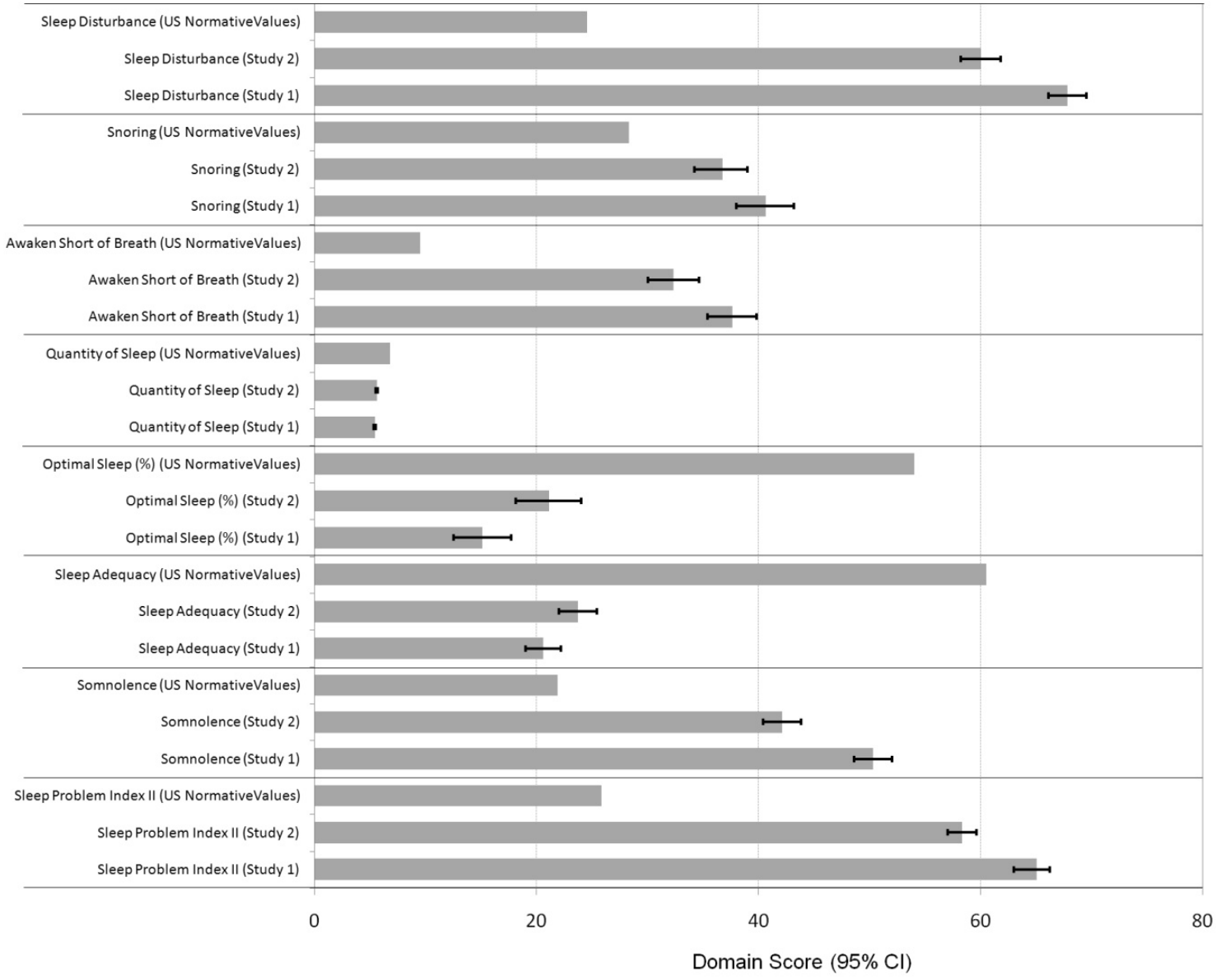
Results from Simulated Example

Label	*Estimate*	*Standard Error*	*Pr > |t|*	*Alpha*	*Lower*	*Upper*
Pain =0	6.5523	1.8715	0.0024	0.05	2.6299	10.4746
Pain =1	15.5845	1.5984	<.0001	0.05	12.2173	18.9517
Pain =2	24.6168	1.3292	<.0001	0.05	21.7971	27.4364
Pain =3	33.6490	1.0668	<.0001	0.05	31.3650	35.9330
Pain =4	42.6812	0.8179	<.0001	0.05	40.9150	44.4475
Pain =5	51.7135	0.5995	<.0001	0.05	50.4335	52.9935
Pain =6	60.7457	0.4576	<.0001	0.05	59.8182	61.6733
Pain =7	69.7780	0.4679	<.0001	0.05	68.8473	70.7087
Pain =8	78.8102	0.6229	<.0001	0.05	77.5709	80.0495
Pain =9	87.8425	0.8465	<.0001	0.05	86.1555	89.5294
Pain =10	96.8747	1.0976	<.0001	0.05	94.6826	99.0669
Pain =3.5	38.1651	0.9400	<.0001	0.05	36.1427	40.1876
Pain =6.5	65.2619	0.4408	<.0001	0.05	64.3820	66.1417

Criterion-group Interpretation

- Involves a comparison of scores from the particular group of interest to a criterion group
- Criterion group is a known group worthy of comparison which can serve as a yardstick
- For example, criterion group can be a healthy group, general population, or clinical group

Baseline Mean Scores on the Medical Outcomes Study Sleep Scale: Patients with Fibromyalgia vs. Values from the U.S. General Population

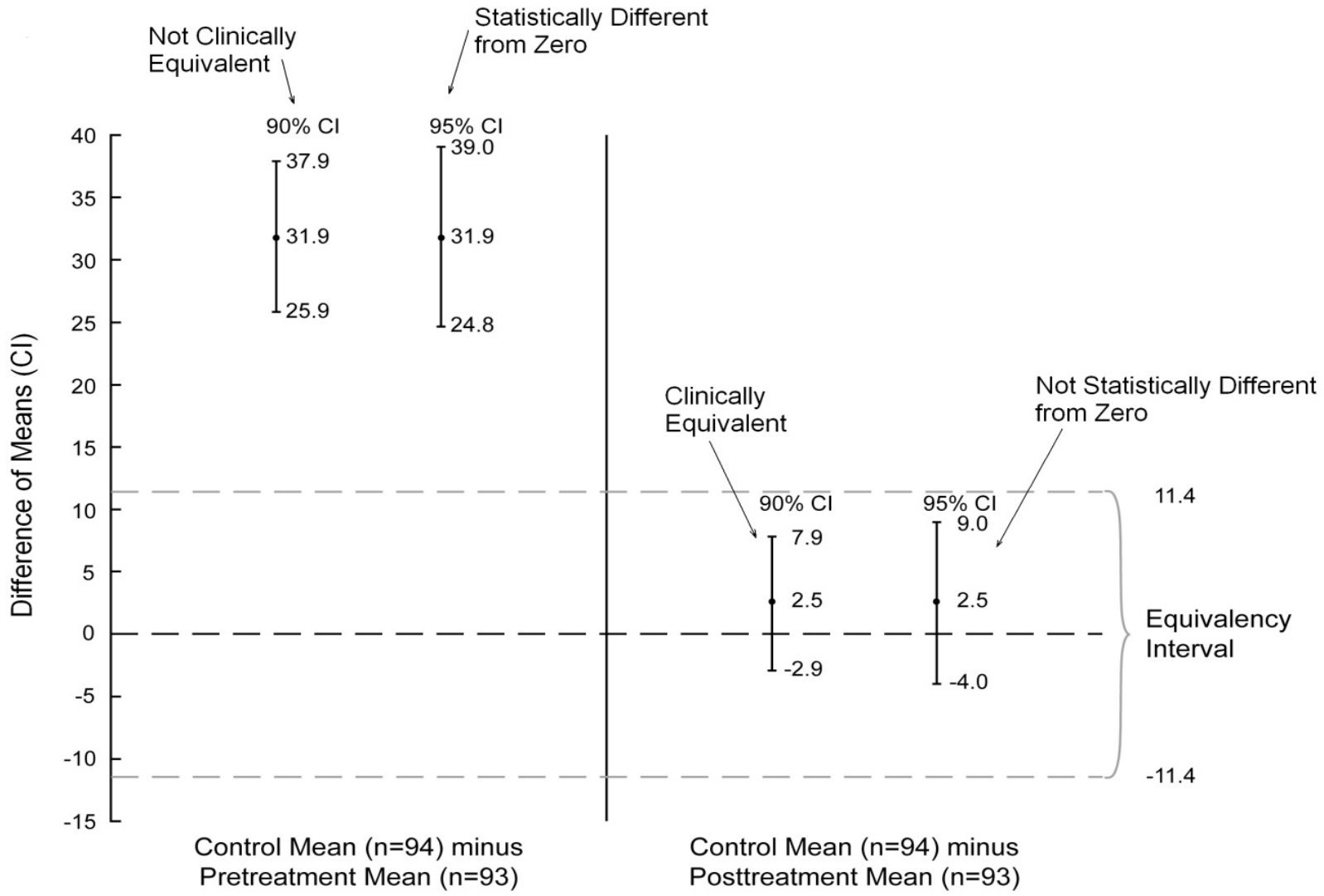


Source: Cappelleri et al. 2009

Classification of Tests on Statistical Significance and Clinical Equivalence

		Statistical Significance Test	
		Statistically Significant from 0 (95% CI excludes 0)	*Not Statistically Significant from 0 (95% CI includes 0)*
Clinical Equivalence Test	*Clinically Equivalent (entire 90% CI within region of equivalence)*	**Cell I** Clinically Equivalent and Statistically Significant	**Cell II** Clinically Equivalent and Not Statistically Significant
	Not Clinically Equivalent (entire 90% CI not within region of equivalence)	**Cell III** Not Clinically Equivalent and Statistically Significant	**Cell IV** Not Clinically Equivalent and Not Statistically Significant

Difference of Control (No ED) Mean versus Pre-treatment and Post-treatment Means on the Self-Esteem Subscale of the Self-Esteem And Relationship Questionnaire

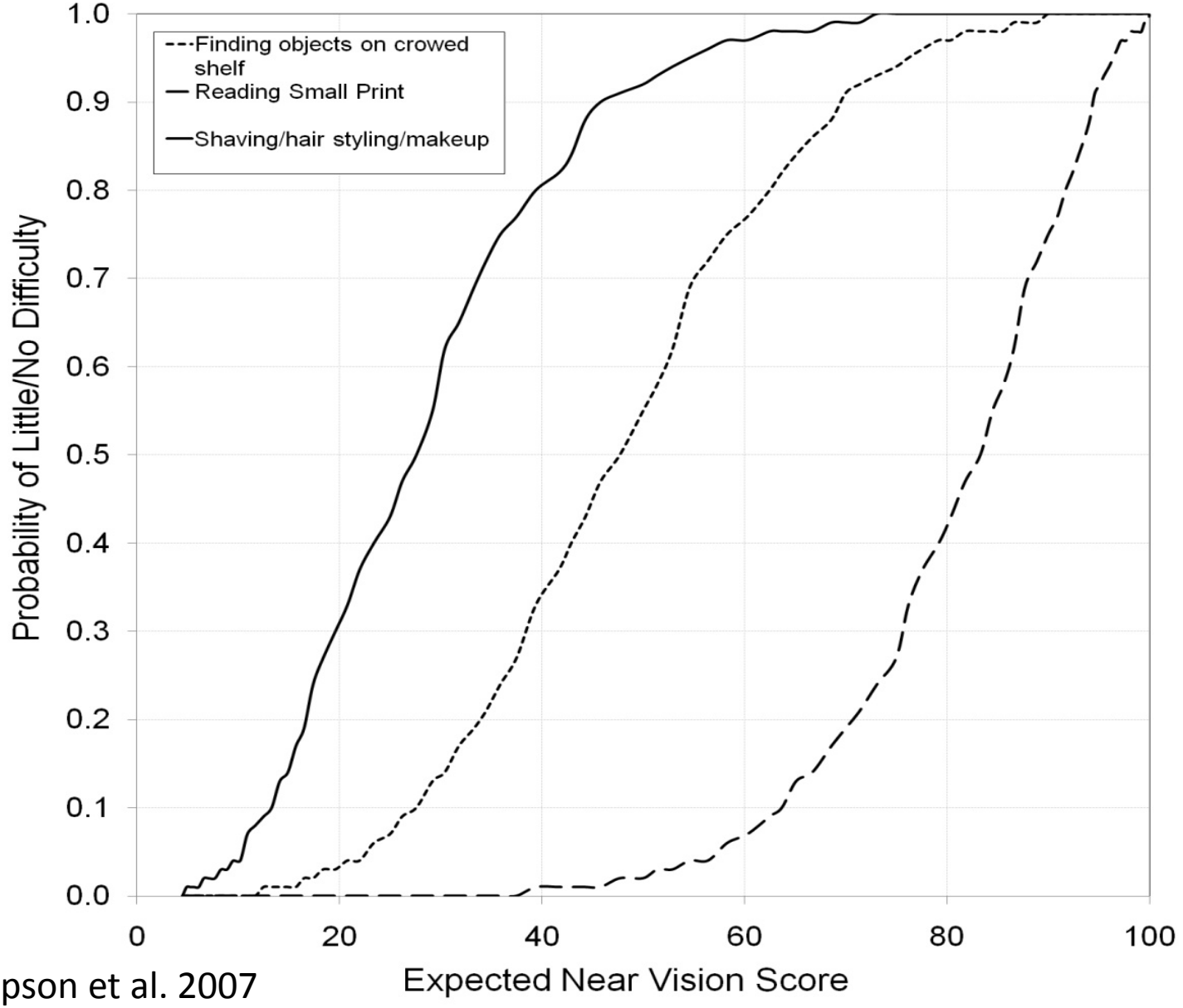


Source: Cappelleri et al. 2006

Content-based Interpretation

- Considered for a multi-item PRO measure
- Uses a representative item, along with its response categories, internal to the measure itself
- Mapping can be obtained using descriptive statistics, item response theory, ordinal logistic regression, and binary logistic regression

Probability of Little or No Difficulty: Near-Vision Subscale of the NEI-VFQ



Source: Thompson et al. 2007

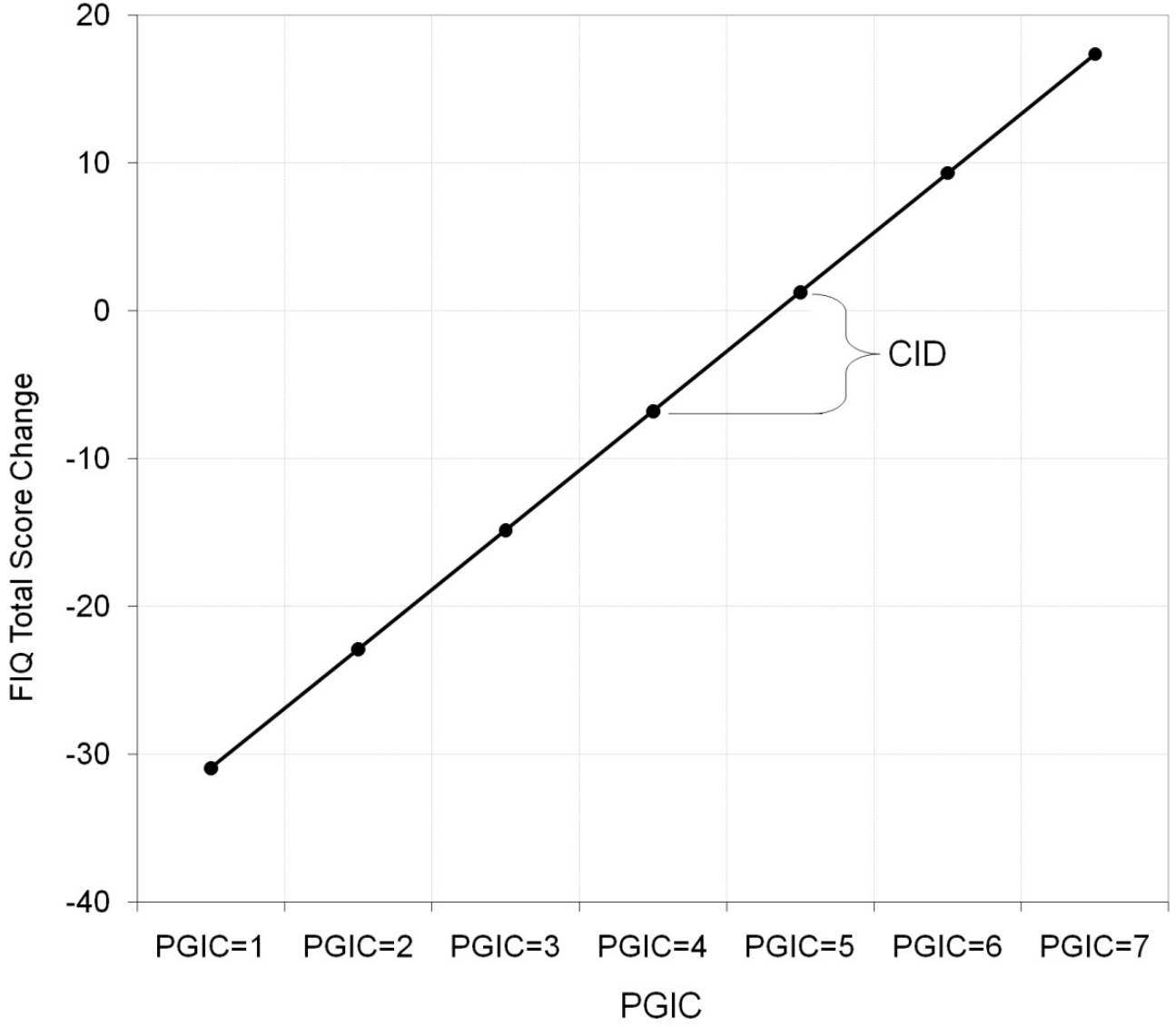
Clinical Important Difference (CID)

- Statistical significance does not imply clinical significance
- PRO score (or change in PRO score) as outcome regressed on an anchor predictor
- Anchor: Patient Global Impression of Change (PGIC, retrospective)

  1=very much improved, 2=much improved, 3=minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse
- Anchor: Patient Global Impression–Severity (PGIS, serial)

  1=none, 2=mild, 3=moderate, 4=severe
- Anchor: Clinical Global Impression–Severity (CGIC, serial)

CID on FIQ using PGIC as Continuous Anchor



CID = 8.1
(95% CI: 7.6
to 8.5)

Source: Bennett et al. 2009

Dataset Structure in Simulated Example

VIEWTABLE: Work._mixed_2

	ID	Treatment	Visit	Baseline	Y	PGIC	ChangeScore	ChangeScorePct
1	1	1	0	9.75601	.	.	.	.
2	1	1	1	9.75601	15.7728	1	6.016796888	61.6727353
3	1	1	2	9.75601	17.3098	2	7.553782138	77.4269789
4	2	1	0	10.6291	.	.	.	.
5	2	1	1	10.6291	13.8939	1	3.264826284	30.7159251
6	2	1	2	10.6291	16.0391	1	5.409958472	50.8976174
7	2	1	3	10.6291	17.6936	2	7.064543684	66.4641778
8	2	1	4	10.6291	19.0151	2	8.386011809	78.8967278
9	3	1	0	11.297	.	.	.	.
10	3	1	1	11.297	13.6029	1	2.305966046	20.4122409
11	3	1	2	11.297	15.3573	2	4.060369963	35.9420947
12	3	1	3	11.297	17.8058	2	6.508858139	57.615931
13	3	1	4	11.297	21.2385	2	9.941551256	88.0018766
14	3	1	5	11.297	22.7094	2	11.41240335	101.021751
15	3	1	6	11.297	21.6062	2	10.30918764	91.2561668
16	4	1	0	11.4949	.	.	.	.
17	4	1	1	11.4949	13.2274	1	1.732509369	15.0720212
18	4	1	2	11.4949	15.5836	1	4.088712435	35.5698858
19	4	1	3	11.4949	19.1823	1	7.687446885	66.8771924
20	4	1	4	11.4949	21.4507	2	9.955827217	86.6110403
21	4	1	5	11.4949	23.3353	2	11.84039842	103.005928
22	4	1	6	11.4949	22.335	2	10.84008614	94.3036794
23	5	1	0	9.84169	.	.	.	.
24	5	1	1	9.84169	13.5146	1	3.672902462	37.3198351
25	5	1	2	9.84169	16.7488	1	6.907063293	70.1816794
26	5	1	3	9.84169	17.0049	2	7.163168226	72.7839248
27	5	1	4	9.84169	20.6806	2	10.83886197	110.132122
28	5	1	5	9.84169	21.314	2	11.47227251	116.568115
29	5	1	6	9.84169	23.1386	2	13.29694792	135.108381
30	5	1	7	9.84169	25.3353	3	15.49361641	157.428414

Proc Mixed Longitudinal Modeling: CID Estimation (Continuous Anchor)

```
Data _mixed_3;
 Set  _mixed_2;
 Where Visit In (1 2 3 4 5 6 7);
 Run;
 Proc Mixed data=_mixed_3;
 Class ID Visit ;
 Model ChangeScore = PGIC / ddfm=kr s;
 Repeated Visit / Type=AR(1) /*UN*/  Subject=ID;
 Estimate "CID(One Category Change) = "  PGIC 1 /cl;
 Estimate " PGIC=1 " Intercept 1 PGIC 1 /cl;
 Estimate " PGIC=2 " Intercept 1 PGIC 2 /cl;
 Estimate " PGIC=3 " Intercept 1 PGIC 3 /cl;
 Estimate " PGIC=4 " Intercept 1 PGIC 4 /cl;
 Estimate " PGIC=5 " Intercept 1 PGIC 5 /cl;
 Estimate " PGIC=6 " Intercept 1 PGIC 6 /cl;
 Estimate " PGIC=7 " Intercept 1 PGIC 7 /cl;
 Run;
```

Estimated Mean Changes and CID

Label	Estimate	Standard Error	Pr > |t|	Lower	Upper
CID (one-category change)	3.9665	0.0724	<.0001	3.8242	4.1088
PGIC=1	4.9722	0.1417	<.0001	4.6939	5.2504
PGIC=2	8.9387	0.0987	<.0001	8.7445	9.1328
PGIC=3	12.9052	0.0997	<.0001	12.7090	13.1013
PGIC=4	16.8717	0.1437	<.0001	16.5893	17.1540
PGIC=5	20.8381	0.2046	<.0001	20.4363	21.2400
PGIC=6	24.8046	0.2712	<.0001	24.2719	25.3374
PGIC=7	28.7711	0.3403	<.0001	28.1028	29.4394

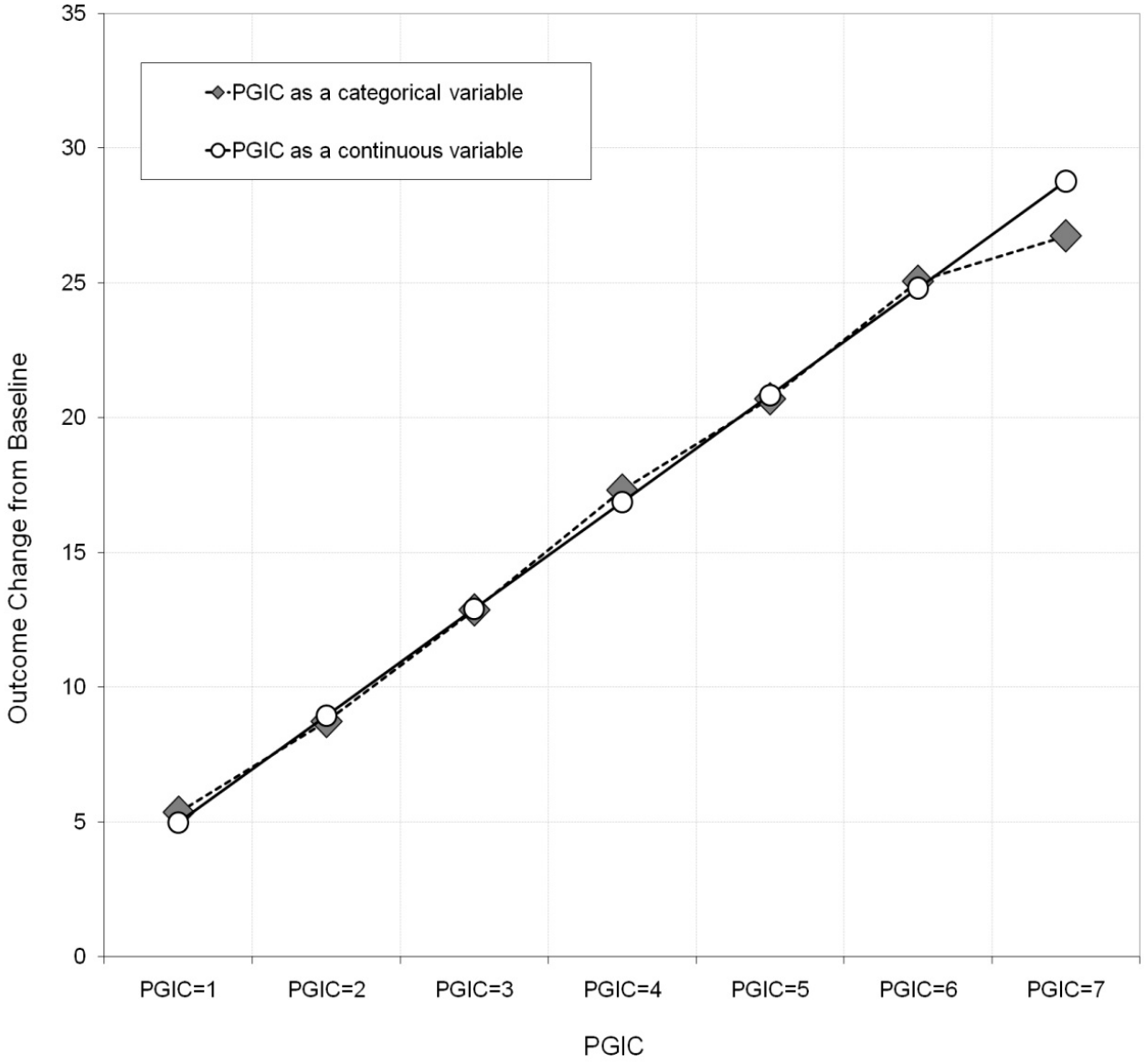
Proc Mixed Longitudinal Modeling:
CID Estimation (Categorical Anchor) – Sensitivity Analysis

```
Proc Mixed data=_mixed_3;
 Class ID Visit PGIC ;
 Model ChangeScore = PGIC / ddfm=kr s;
 Repeated Visit / Type=AR(1) Subject=ID;
 Lsmeans   PGIC /cl;
 Run;
```

Estimated Mean Changes and CID: Sensitivity Analysis (Same Simulated Data)

Effect	*PGIC*	*Estimate*	*Standard Error*	*Pr > |t|*	*Lower*	*Upper*
PGIC	1	5.3561	0.1939	<.0001	4.9757	5.7365
PGIC	2	8.7256	0.1233	<.0001	8.4836	8.9677
PGIC	3	12.8642	0.1564	<.0001	12.5572	13.1713
PGIC	4	17.3115	0.2384	<.0001	16.8438	17.7792
PGIC	5	20.6988	0.3406	<.0001	20.0305	21.3672
PGIC	6	25.0653	0.5040	<.0001	24.0764	26.0542
PGIC	7	26.7490	2.3192	<.0001	22.1987	31.2993

Mean Change in PRO Measure as Function of PGIC



Frequencies on PGIC

PGIC	*Frequency*	*Cumulative Percent*	*Cumulative Frequency*	*Percent*
1	179	14.98	179	14.98
2	518	43.35	697	58.33
3	300	25.10	997	83.43
4	114	9.54	1111	92.97
5	57	4.77	1168	97.74
6	26	2.18	1194	99.92
7	1	0.08	1195	100.00

Distribution-based Methods

Distribution-based Methods

- Based on empirical distribution and characteristics of the data
- Adjunct to, not substitute for, anchor-based methods
- Informs on meaning of difference or change in PRO measure but not whether change is *clinically* significant to patients
- Different types
  - Standardized Effect Size
  - Probability of Relative Benefit
  - Cumulative Distribution Function

Standardized Effect Size

- (Standardized) Effect size = magnitude of effect relative to variability
  - 0.2, ‘small’; 0.5, ‘medium’; 0.8, ‘large’
- Within group: before vs. after therapy
- Between groups: treatments A vs. B

Distribution-based Methods

- Within group
  - Effect = average change score on PRO
  - Variability = baseline standard deviation (SD)
  - Or variability = SD of individual changes

- Between groups
  - Effect = average difference between groups at follow-up
  - Or effect = average difference between groups from baseline to follow-up

  - Variability = pooled between-group SD at baseline
  - Or variability = pooled between-group SD at follow-up
  - Or variability = pooled SD of individual changes

Example: Effect Size

- Effect size for all subjects in single intervention study

- Effect size = $\frac{\text{Mean difference score}}{\text{SD at baseline}}$

Example: Effect Size

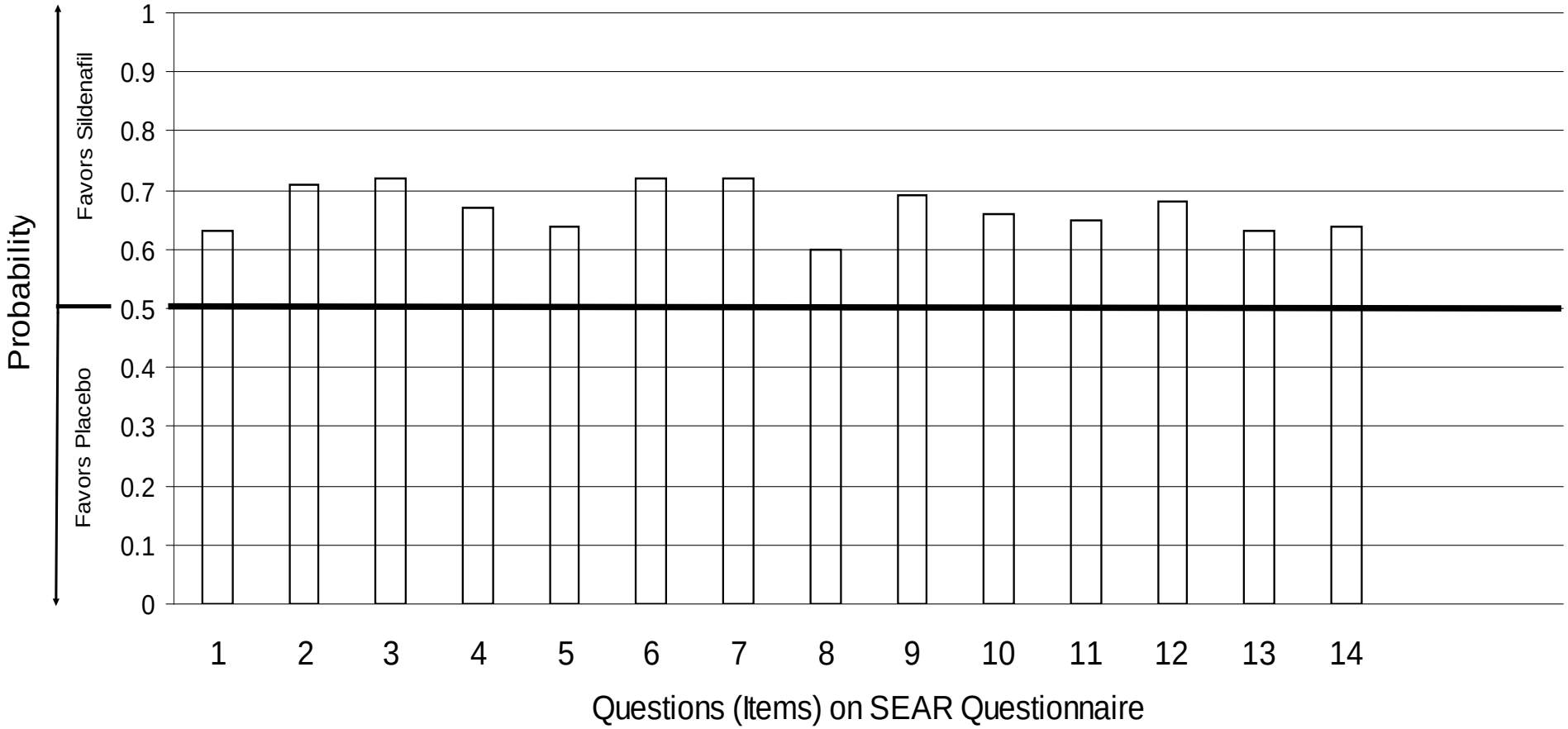
SEAR Component	Baseline Mean ± SD	End Mean ± SD	Difference	Effect Size
Sexual Relationship	42 ± 22	78 ± 21	36 ± 23	1.6
Confidence	55 ± 26	81 ± 21	26 ± 26	1.0
Self-esteem	52 ± 27	81 ± 22	29 ± 28	1.1
Overall Relationship	62 ± 30	80 ± 24	18 ± 32	0.6
Overall	48 ± 22	79 ± 20	31 ± 22	1.4

Source: Althof et al. 2003

Probability of Relative Benefit

- Based on Wilcoxon rank-sum test using ridit analysis
- Convert Mann-Whitney *U* statistic to a probability
- Probability represents the chance that a randomly selected patient from the treatment group has a more favorable response than a randomly selected patient from the control group

Example: Probability of Relative Benefit

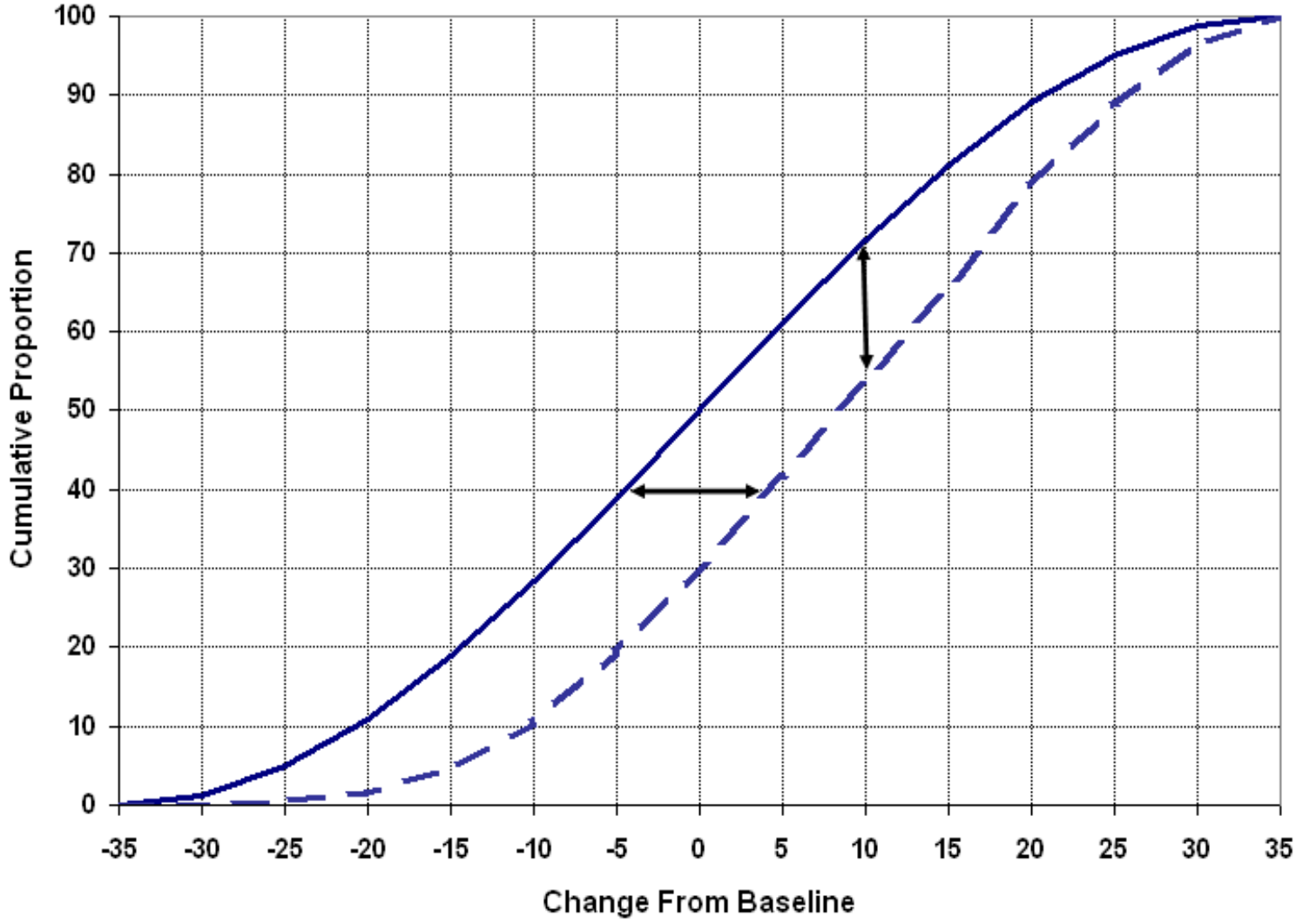


Source: Cappelleri et al. 2007

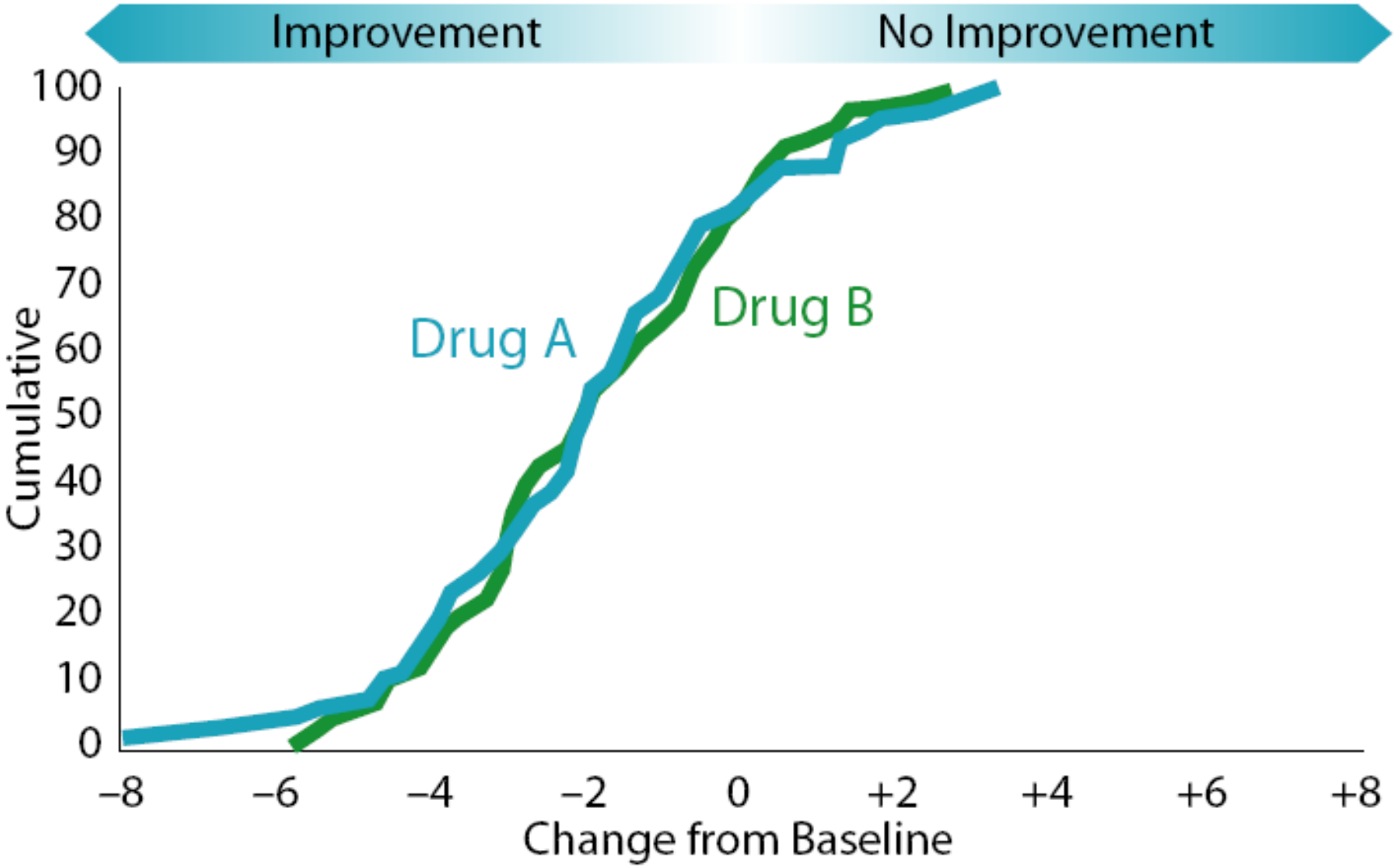
Cumulative Distribution Function

- An alternative or supplement to responder analysis
- Display a continuous plot of the percent change (or absolute change) from baseline on the horizontal axis and the cumulative percent of patients experiencing up to that change on the vertical axis
- Such a cumulative distribution of response curve – one for each treatment group – would allow a variety of response thresholds to be examined simultaneously and collectively, encompassing all available data

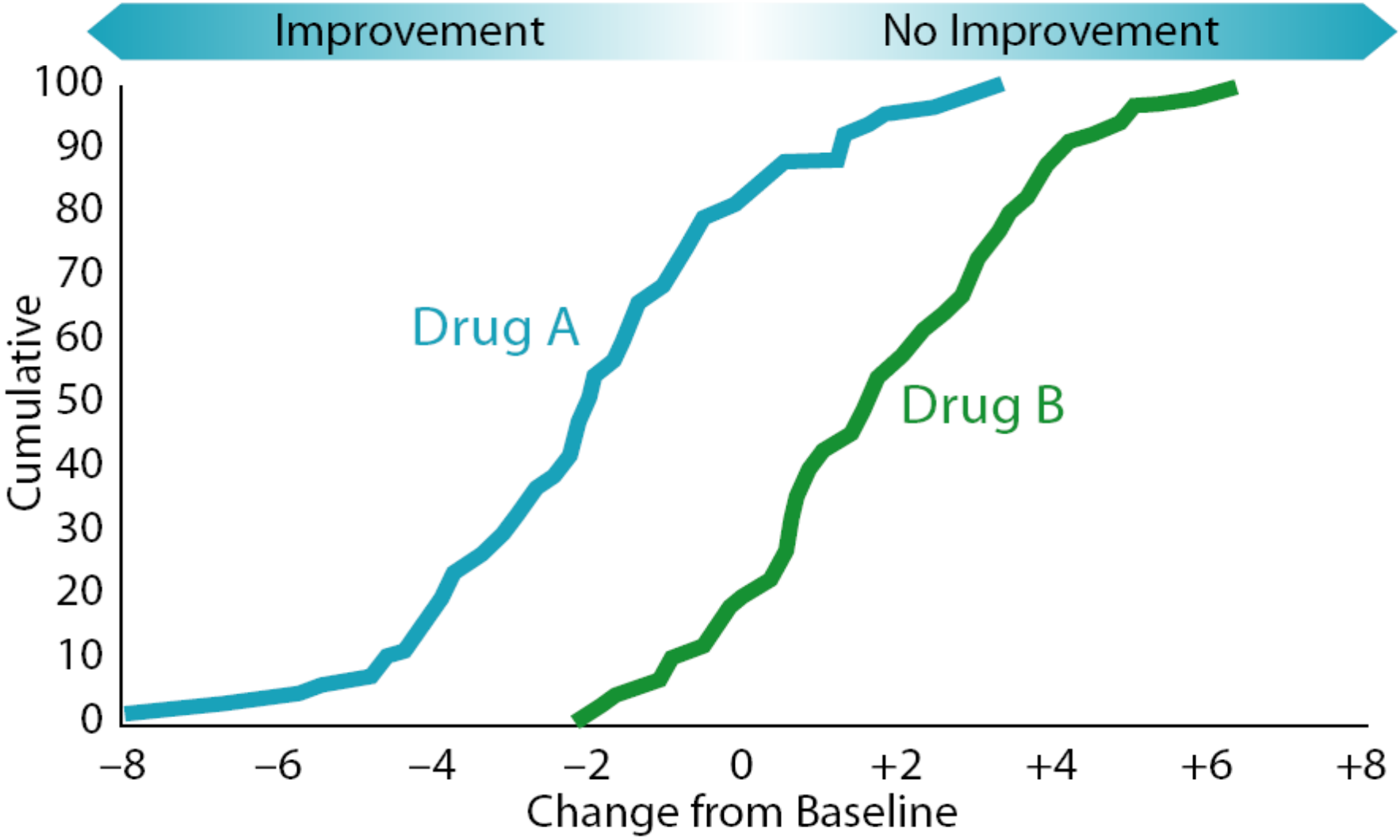
Illustrative Cumulative Distribution Function: Experimental Treatment (solid line) better than Control Treatment (dash line) -- Negative changes indicate improvement



Results showing no comparative efficacy of Drug A or Drug B



Results showing the efficacy of Drug A over Drug B



Aricept® label from 10/13/2006

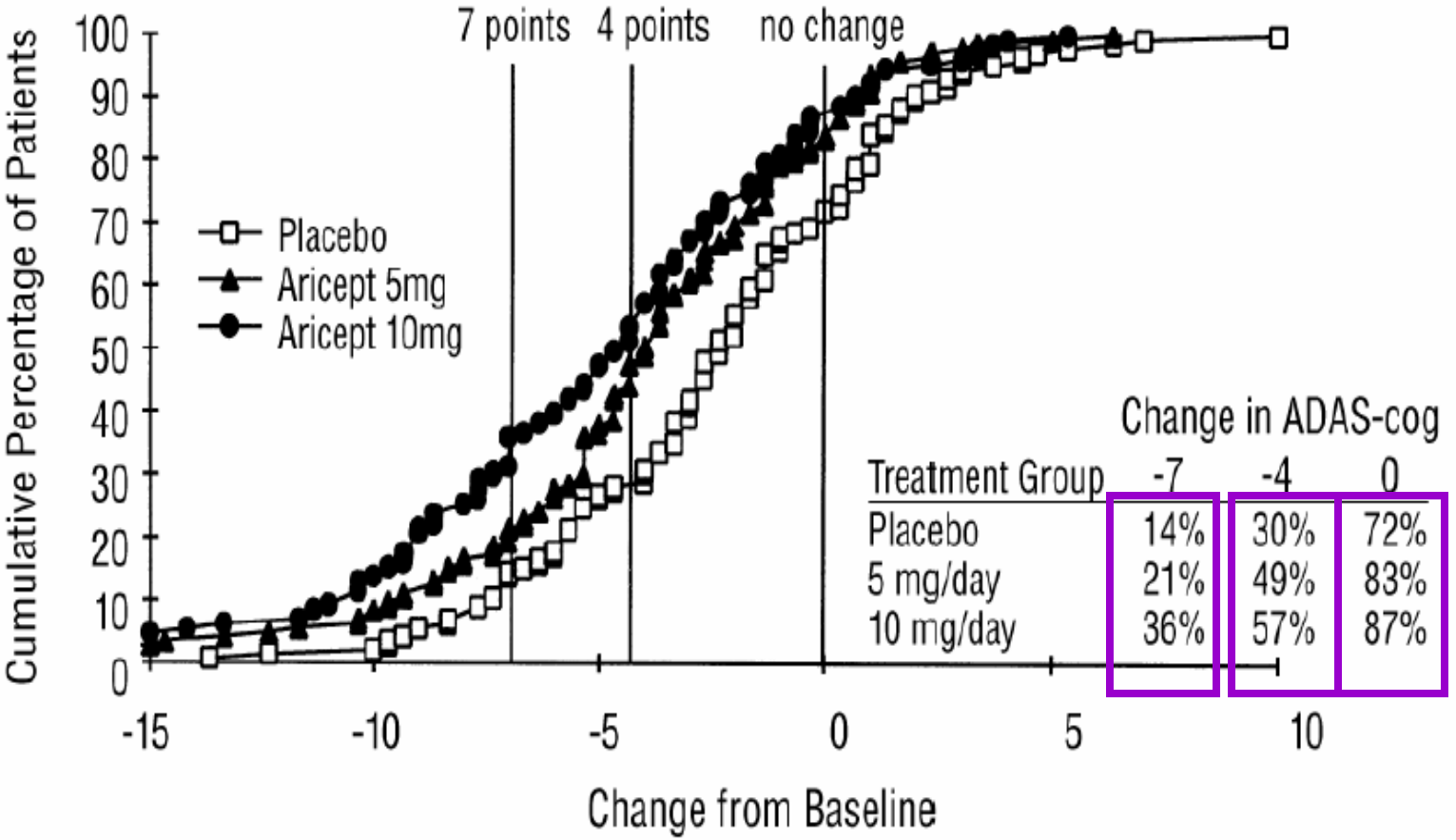


Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients Within Each Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90% and 10 mg/day 82%.

Cymbalta® label from 11/19/2009 (x-axis reversed)

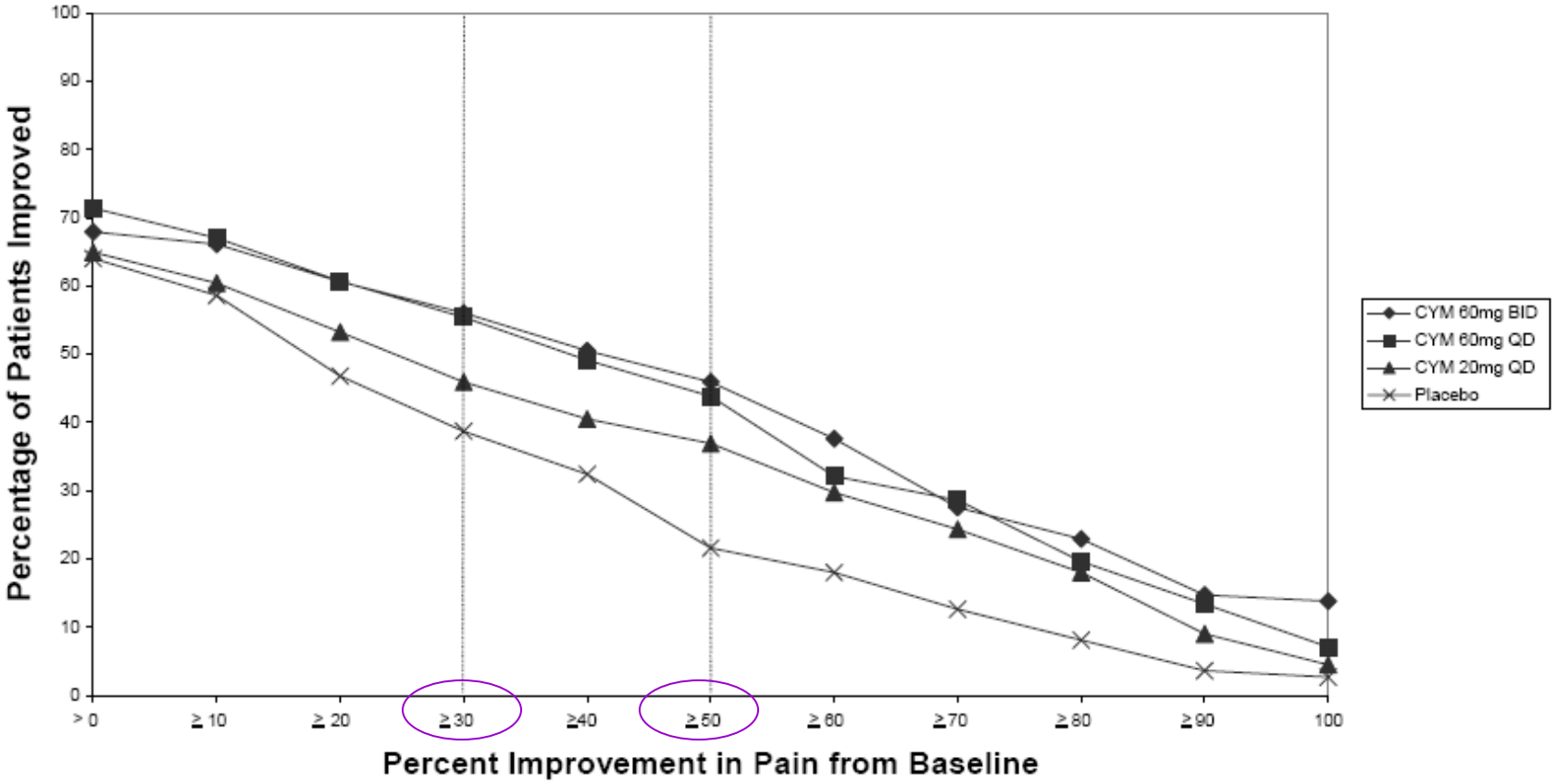
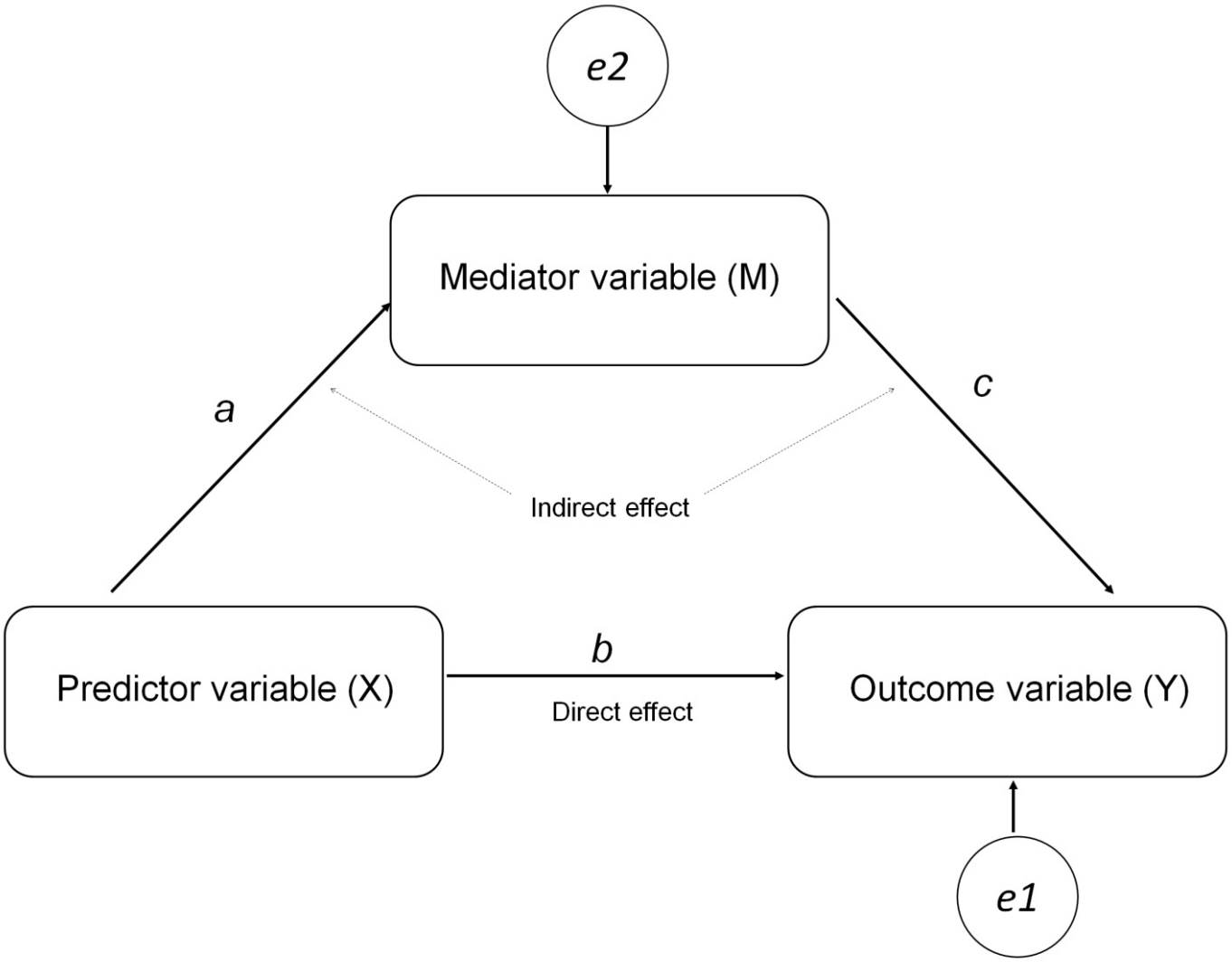


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

Mediation Analysis

Basic Mediation Model



A Few Equations

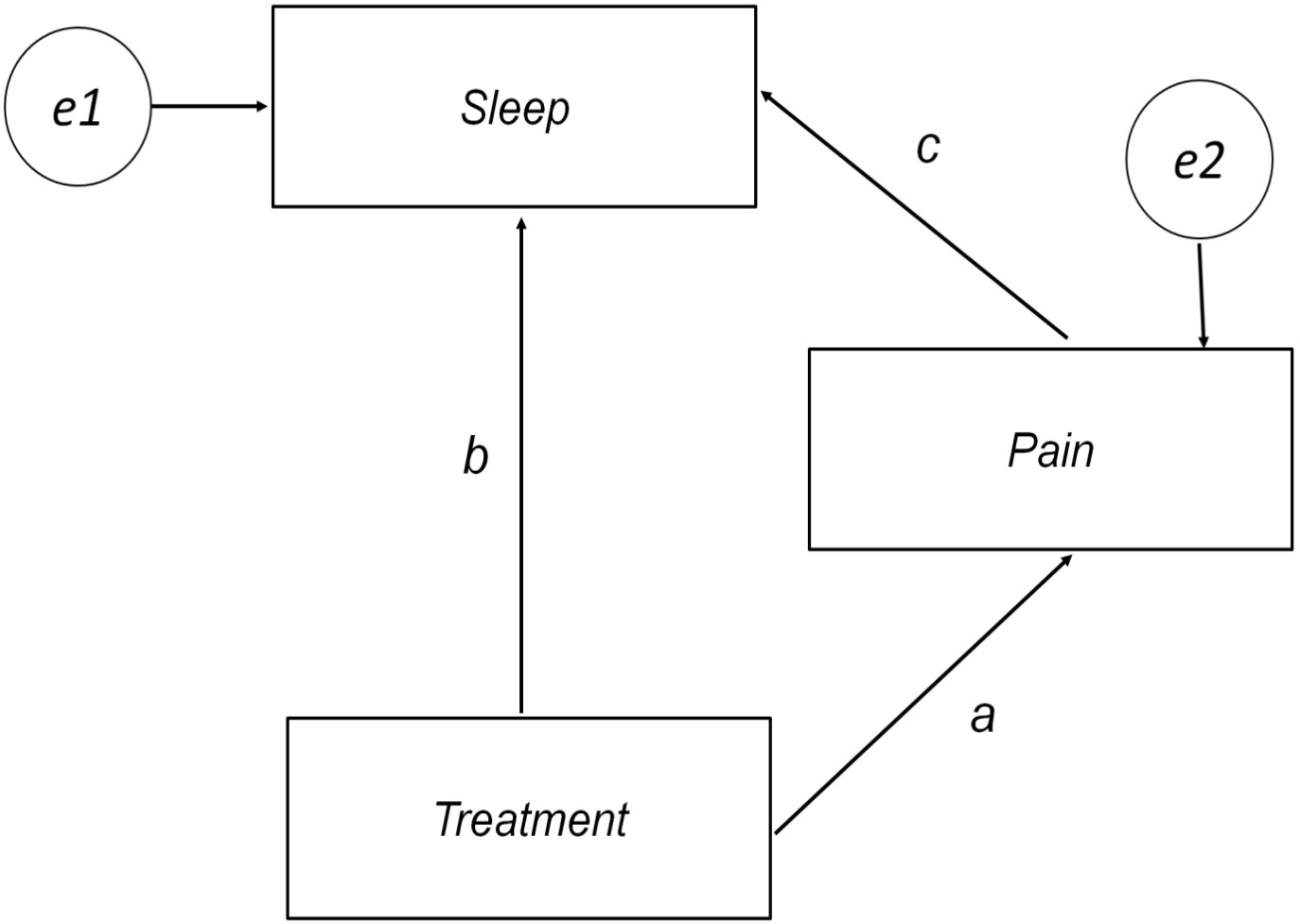
- $Y_j = i_1 + b \times X_j + c \times M_j + e_{1j}$
- $M_j = i_2 + a \times X_j + e_{2j}$

- $Y_j = (i_1 + c \times i_2) + (b + c \times a) \times X_j + (c \times e_{2j} + e_{1j})$

$$direct\ effect = 100\left(\frac{b}{b + c \times a}\right)$$

$$indirect\ effect = 100\left(\frac{c \times a}{b + c \times a}\right)$$

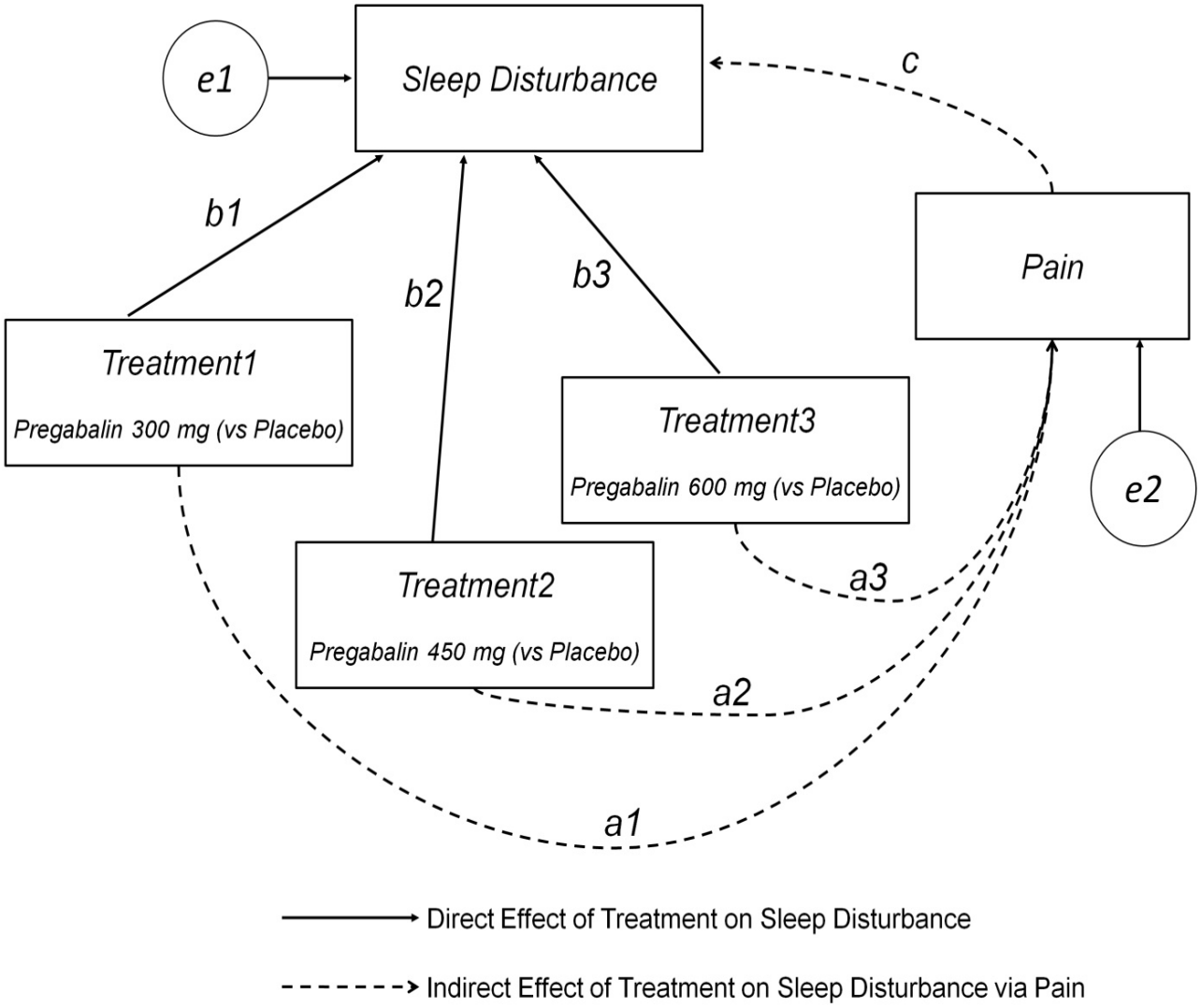
Treatment Affects *Sleep* Directly and Indirectly via *Pain*



Assumptions

- No unmeasured confounding
  - Predictor-outcome
  - Predictor-mediator
  - Mediator-outcome
- Model with no interaction is correctly specified
  - Predictor and mediator on outcome

Published Example



Source: Russell et al. 2009

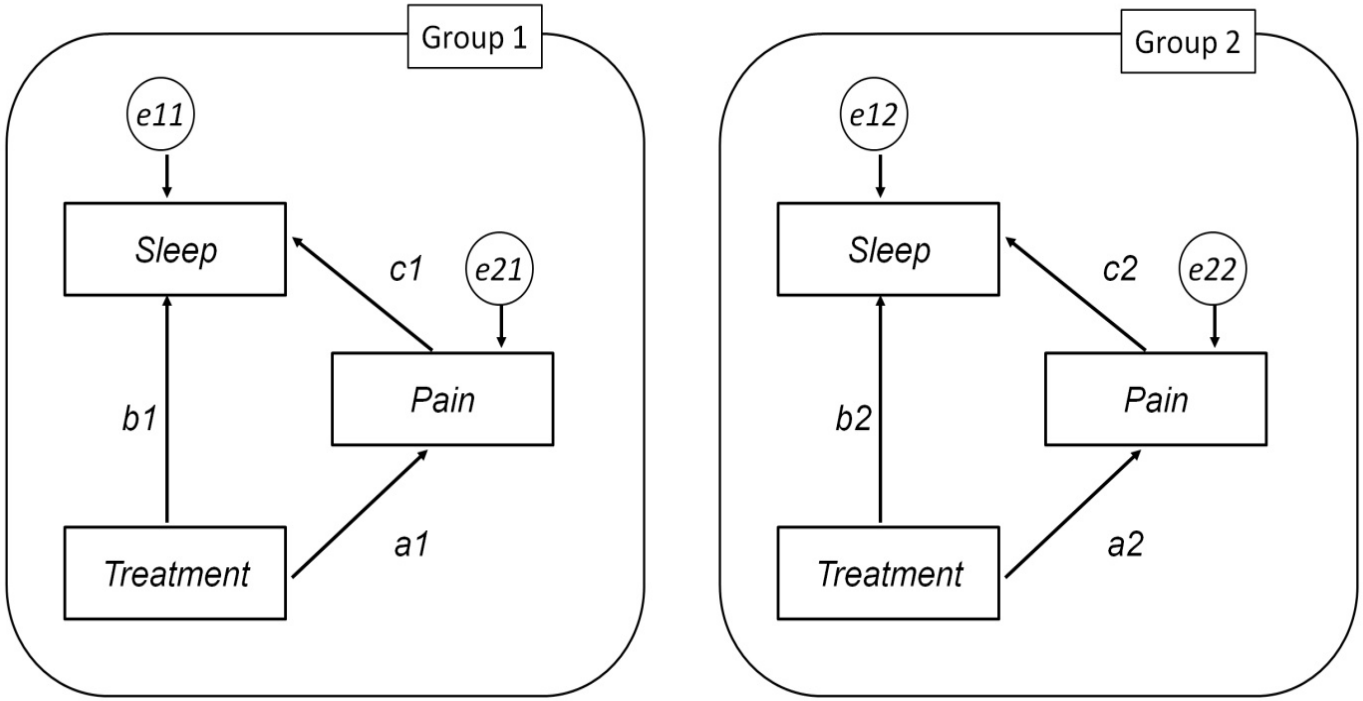
Results

Effect	Effects from TRT300 to SLEEP	Effects from TRT450 to SLEEP	Effects from TRT600 to SLEEP
Total	-9.94	-12.73	-17.79
Indirect	-1.95(*)	-3.44	-4.35
(Indirect / Total) x 100%	19.6%(*)	27%	24.4%
(Direct / Total) x 100%	80.4%	73%	75.6%

(*) indicates not statistically significant result, p-value > 0.05

Source: Russell et al. 2009

Testing for Model Invariance between Groups



$$difference\ of\ direct\ effects\ (Group\ 1\ vs\ Group\ 2):$$

$$= 100\ (\frac{b1}{b1+c1 \times a1} - \frac{b2}{b2+c2 \times a2})$$

$$difference\ of\ indirect\ effects\ (Group\ 1\ vs\ Group\ 2):$$

$$= 100\ (\frac{c1 \times a1}{b1+c1 \times a1} - \frac{c2 \times a2}{b2+c2 \times a2})$$

Summary

- Anchor-based approaches
  - Percentage based on thresholds
  - Criterion-group interpretation
  - Statistical significance and clinical equivalance
  - Content-based interpretation
  - Clinical important difference

- Distribution-based approaches
  - Standardized effect size
  - Probability of relative benefit
  - Cumulative distribution function

- Mediation analysis

Journal References: Illustrations Cited

- Althof SE. Cappelleri JC, Shpilsky A, Stecher V, Diuguid C, Sweeney M, Duttagupta S. 2003. Treatment responsiveness of the Self-Esteem And Relationship (SEAR) questionnaire in erectile dysfunction. *Urology* 61:888-893.

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- Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E, Barrett JA, Sadosky A. 2009. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Medicine 10:604-610.

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General References

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