Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Webinar

Technological Updates in the Treatment of Mental Health Conditions

July 28, 2016
1 – 2:30 p.m. (ET)

Presenters, Moderator

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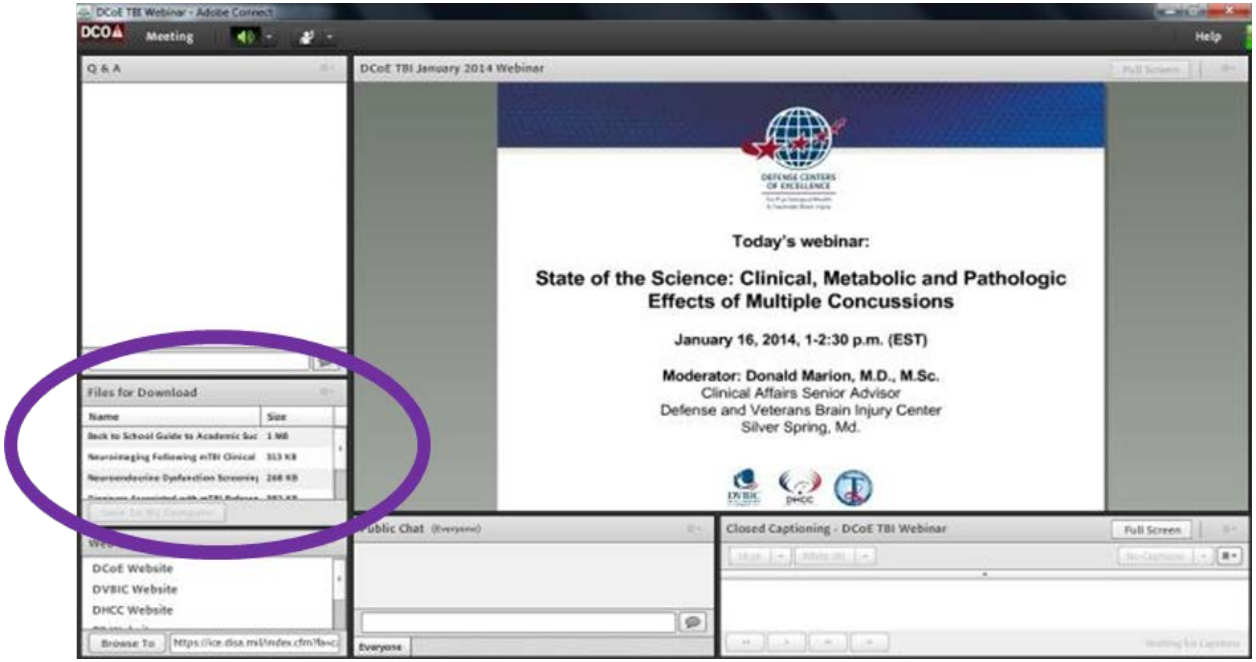

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  - Currently, only those contractors with scope of work or with commensurate contract language are permitted in this training.

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(continued)

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(continued)

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Physical Therapists
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Psychologists
This Conference is approved for up to 1.5 hours of continuing education. APA Division 22 (Rehabilitation Psychology) is approved by the American Psychological Association to sponsor continuing education for psychologists. APA Division 22 maintains responsibility for this program and its content.

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This activity is approved for up to 0.15 ASHA CEUs (Intermediate level, Professional area).

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Webinar Overview

Evidence-based treatments are a requirement in clinical practice and technological innovations in the delivery of psychotherapy are no exception to this rule. Clinical trials that use a null or waitlist control group are appropriate in the absence of an established standard of care. Technical adaptation of an evidence-based practice, however, negates the use of a null or waitlist control group. In this case, direct comparison of active treatments is required. One approach that is becoming more prominent in the literature is the non-inferiority trial. The goal is to demonstrate that an experimental alternative is no less efficacious when compared to the standard of care. Unfortunately, the reports of their application demonstrate confusion or a lack of awareness of the technical and philosophical nuances of this trial design. In this webinar, we will develop the tools needed to evaluate the quality of the evidence base to inform clinical practice. We will use trials of technological methods of administering psychotherapy compared to the in-office standard of care as a practical case study.

At the conclusion of this webinar, participants will be able to:

- Identify the key design elements of a non-inferiority study
- Interpret the results of a non-inferiority trial
- Evaluate the credibility of the evidence base for a treatment approach based on non-inferiority designs

Derek J. Smolenski, Ph. D., M.P.H.

Derek J. Smolenski, Ph. D., M.P.H.

- Epidemiologist with interests in applied multivariate analysis and behavioral epidemiology
- Earned advanced degrees at the University of Texas Health Science Center at Houston and completed postdoctoral work at the University of Minnesota
- Has worked in several content areas including sexual health, alcohol abuse, behavioral assessment, depression and suicide
- Lead quantitative asset with the National Center for Telehealth and Technology since 2012
- Serves as the lead analyst for the Department of Defense Suicide Event Report and has been the lead methodologist on several clinical trials including a non-inferiority trial which serves as the impetus for this webinar

Disclosures

- Dr. Smolenski has no relevant financial relationships to disclose.

- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense, nor the U.S. Government.

Introduction

- Delivery of psychological health interventions via technological methods (i.e. videoconferencing, telephone) and use of internet based interventions have gained attention and use in DoD and VA.
- What is the level of evidence base regarding use of these technological methods ?
- How can clinicians evaluate the current evidence-base?
- What do clinicians need to know about non-inferiority trials to effectively evaluate the evidence base?

Structure of today's presentation

- Concepts of non-inferiority
- Critical review of recent trials of technology use in psychotherapy
- Summarize recommendations for reviewing non-inferiority trials as a part of the evidence base for clinical practice

Central questions in clinical trials

- Is there a difference between X and Y? (Superiority)

$$H_0: \mu_X - \mu_y = 0 \quad H_1: \mu_X - \mu_y \neq 0$$
$$H_0: \mu_X - \mu_y \leq 0 \quad H_1: \mu_X - \mu_y > 0$$
$$H_0: \mu_X - \mu_y \geq 0 \quad H_1: \mu_X - \mu_y < 0$$

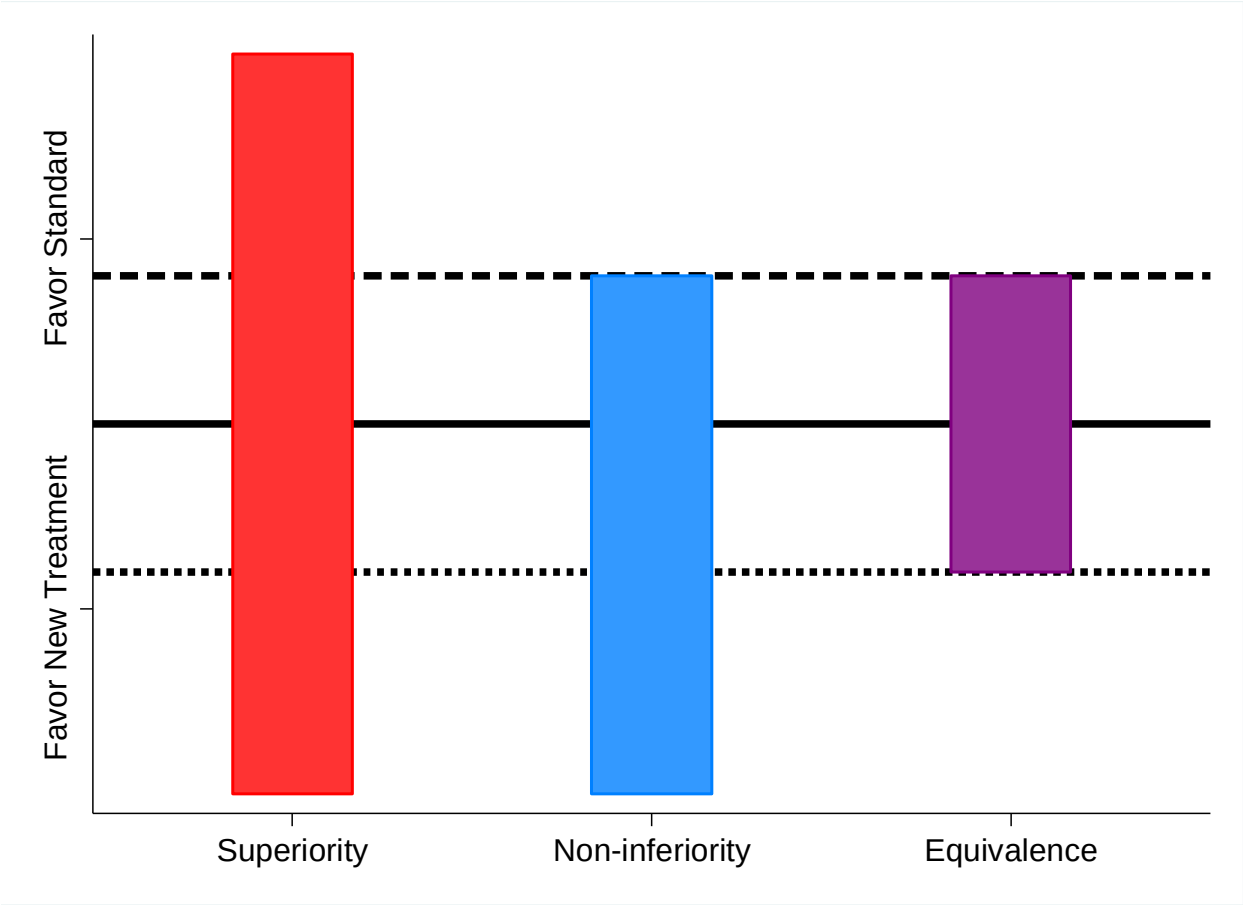
- Is X no worse than Y? (Non-inferiority)

$$H_0: \mu_X - \mu_y \geq \delta \quad H_1: \mu_X - \mu_y < \delta$$

- Is X no worse and no better than Y? (Equivalence)

$$H_0: \mu_X - \mu_y \geq |\delta| \quad H_1: \mu_X - \mu_y < |\delta|$$

Central questions in clinical trials



Pass the margin

- Goal in non-inferiority
  - Reject a difference of a magnitude specified a priori
- Planned difference to reject (δ) is the **margin**
- How is a margin defined? (D'Agostino, 2003; Greene, 2008)
  - Clinical and statistical considerations
  - No perfect answer
  - Should not exceed **minimal expected effect** of standard treatment

Margin, or butter?

- Many studies use minimum ‘clinically meaningful difference’
  - Example: Difference in BDI-II score of 5

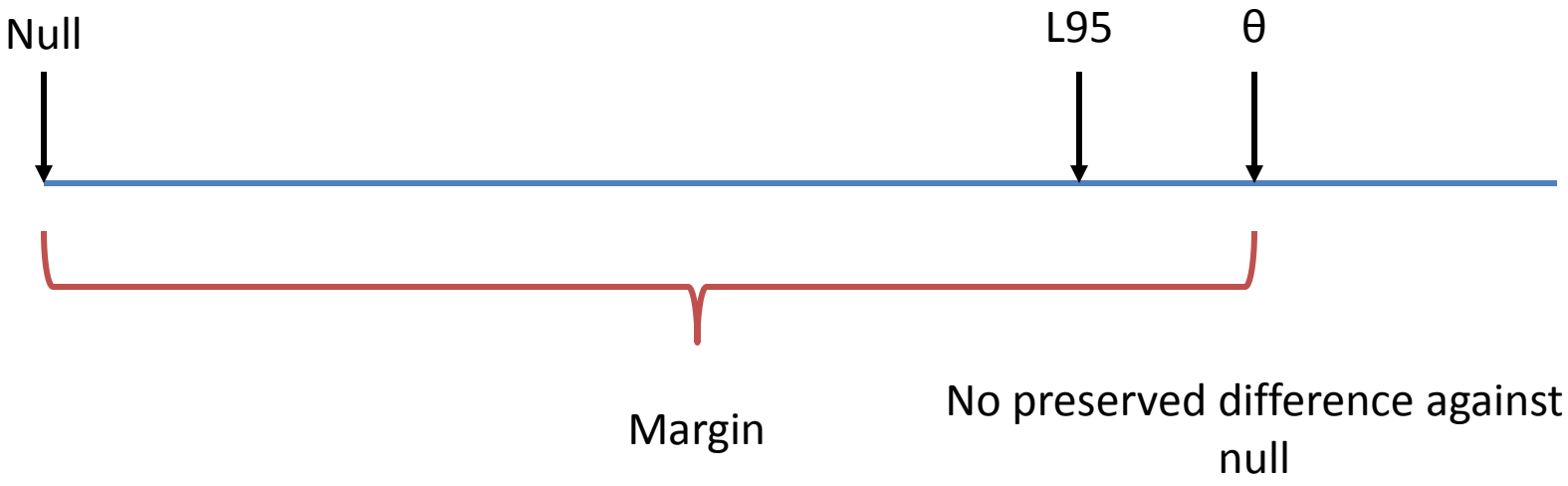
- Ignore statistical issues
  - Expected difference of standard of care against null or waitlist control
  - Variability
  - Preservation of effect

I can't believe it's margin

- Use a meta-analysis
  - Examine lower bound of 95% confidence interval
  - Use a proportion of value to set margin
    - 50% is common; preserves half of the effect
    - 25% would preserve 75% of effect
- Consider interpretive implications of margin

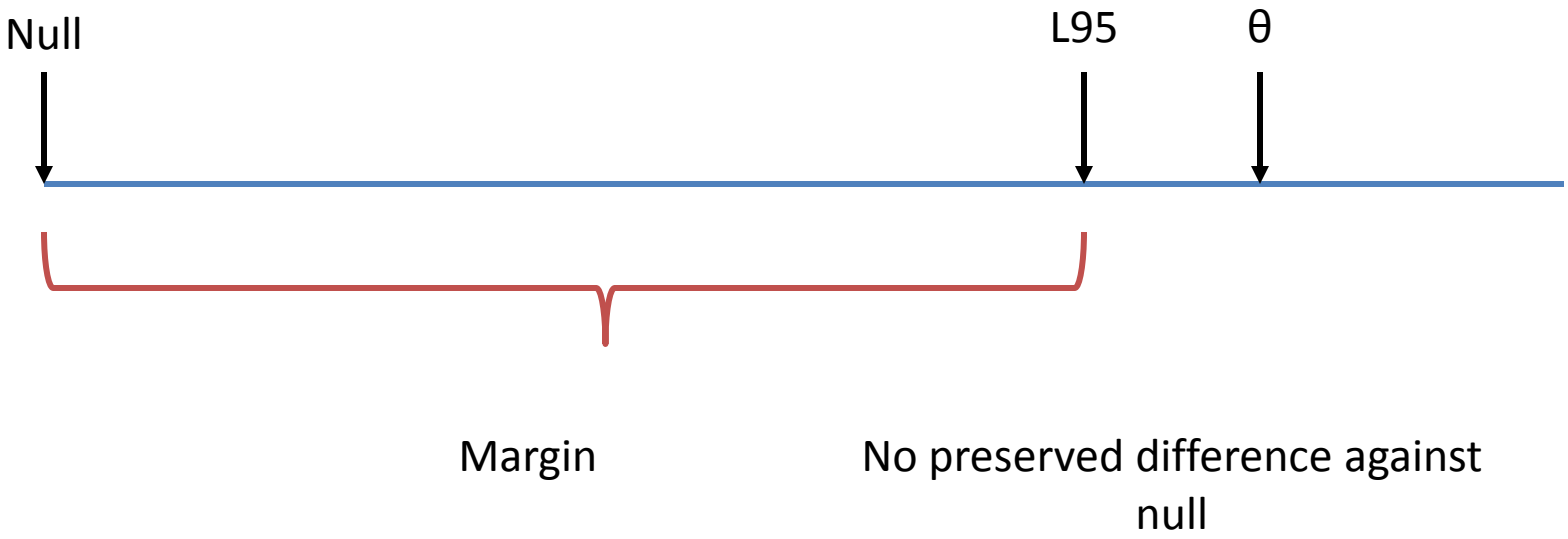
Scenario 1

Margin = θ



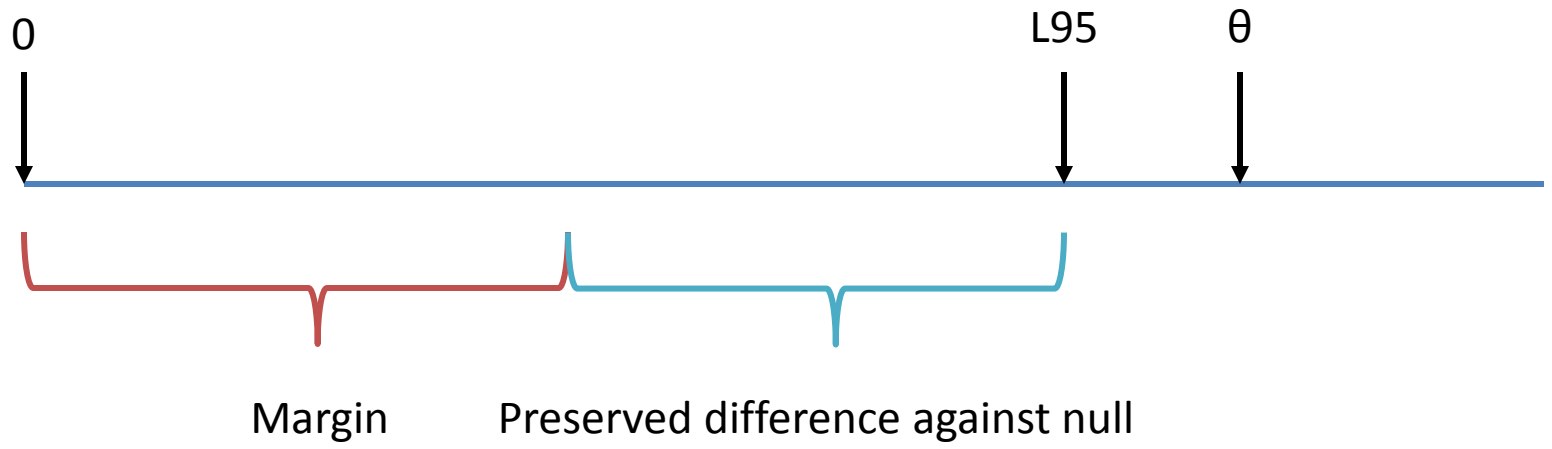
Scenario 2

Margin = L95



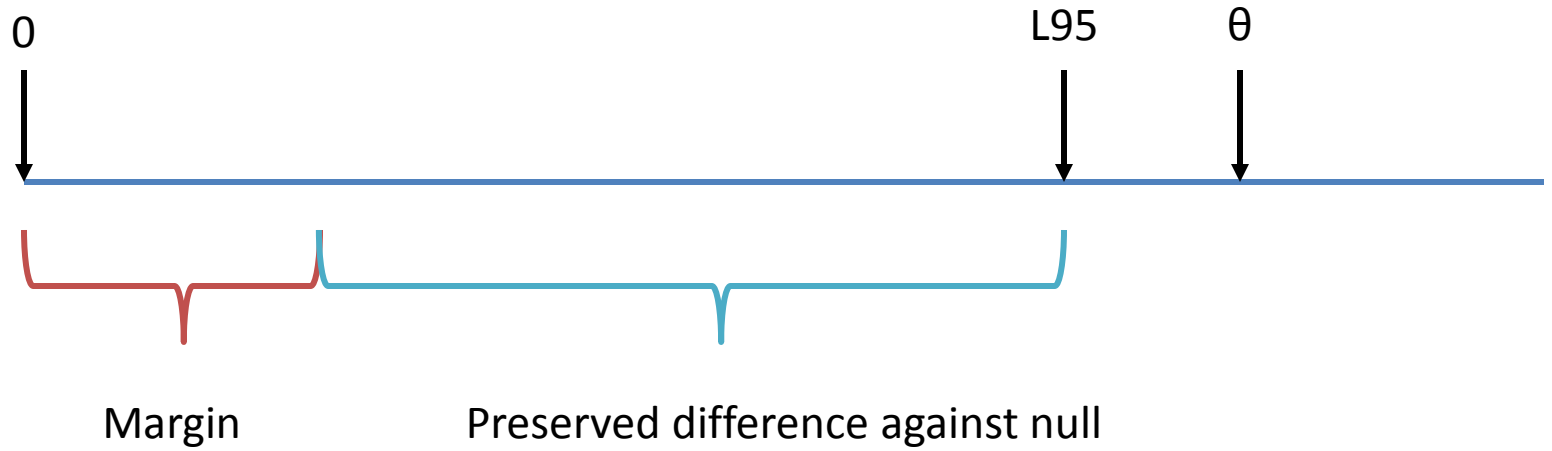
Scenario 3

Margin = L95 x 0.5



Scenario 3

Margin = L95 x 0.25



Final words on the margin

- Use raw score differences
  - Avoid issues with multivariate standardization
  - Independent from sample-specific standard deviations
  - Tend to relate more directly to clinical meaning

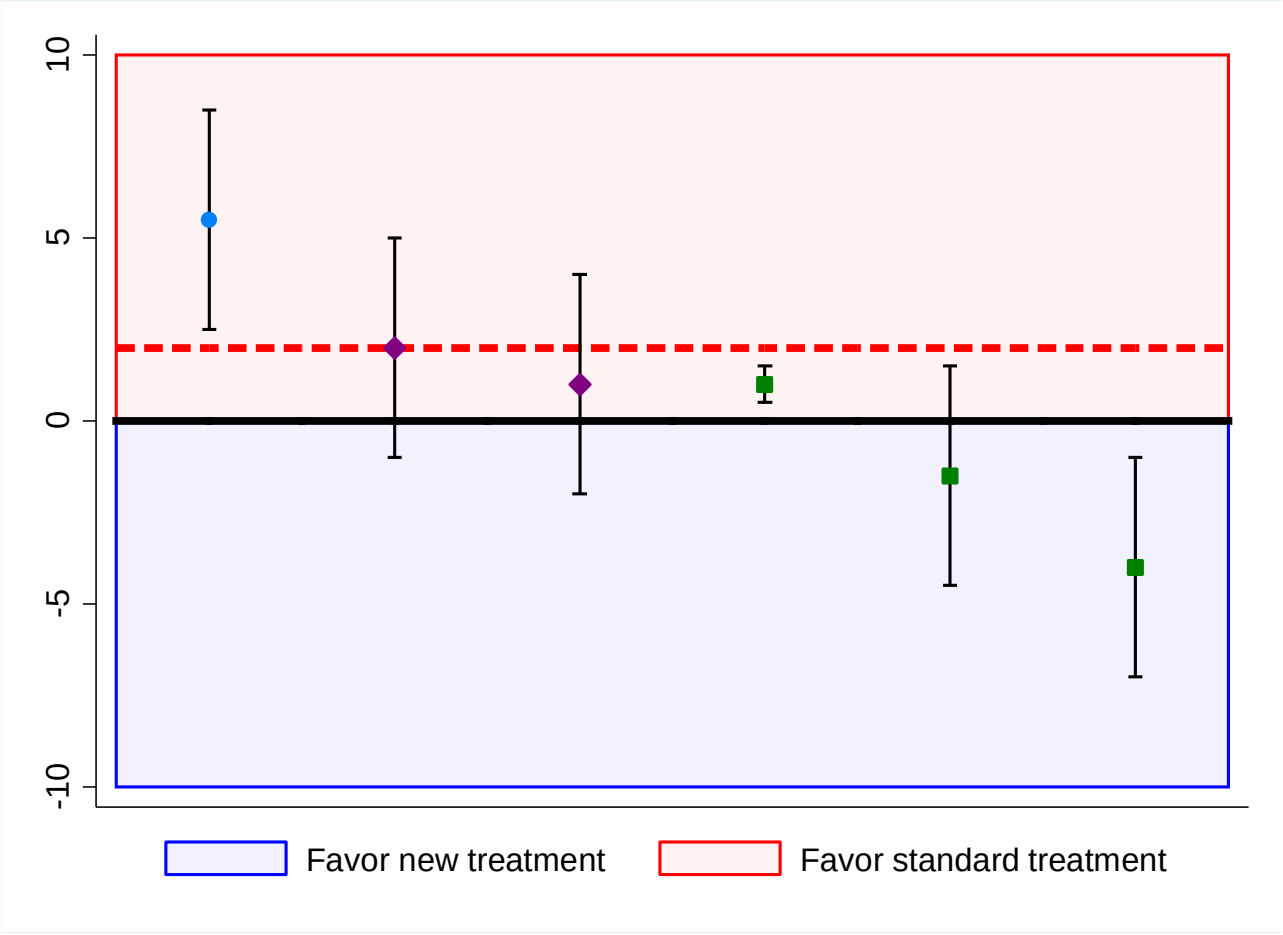
- A priori
- Use meta-analysis if possible
- Clinical significance alone does not address preservation of effect

Interpreting results

- Focus on lower bound of 95% confidence interval if $\delta < 0$
- Focus on upper bound of 95% confidence interval if $\delta > 0$

- 95% confidence interval allows for two tests:
  1. Non-inferiority
  2. In non-inferior, examine superiority

Interpreting results



Sample size

- Considerations
  - α – Type I error
  - β – Type II error
  - δ – Margin
  - θ – Anticipated **actual difference** in point estimates
- Traditional methods focused on **one-tailed test** and used **conventional power**
  - $\alpha = 0.05$
  - $1 - \beta = 0.80$

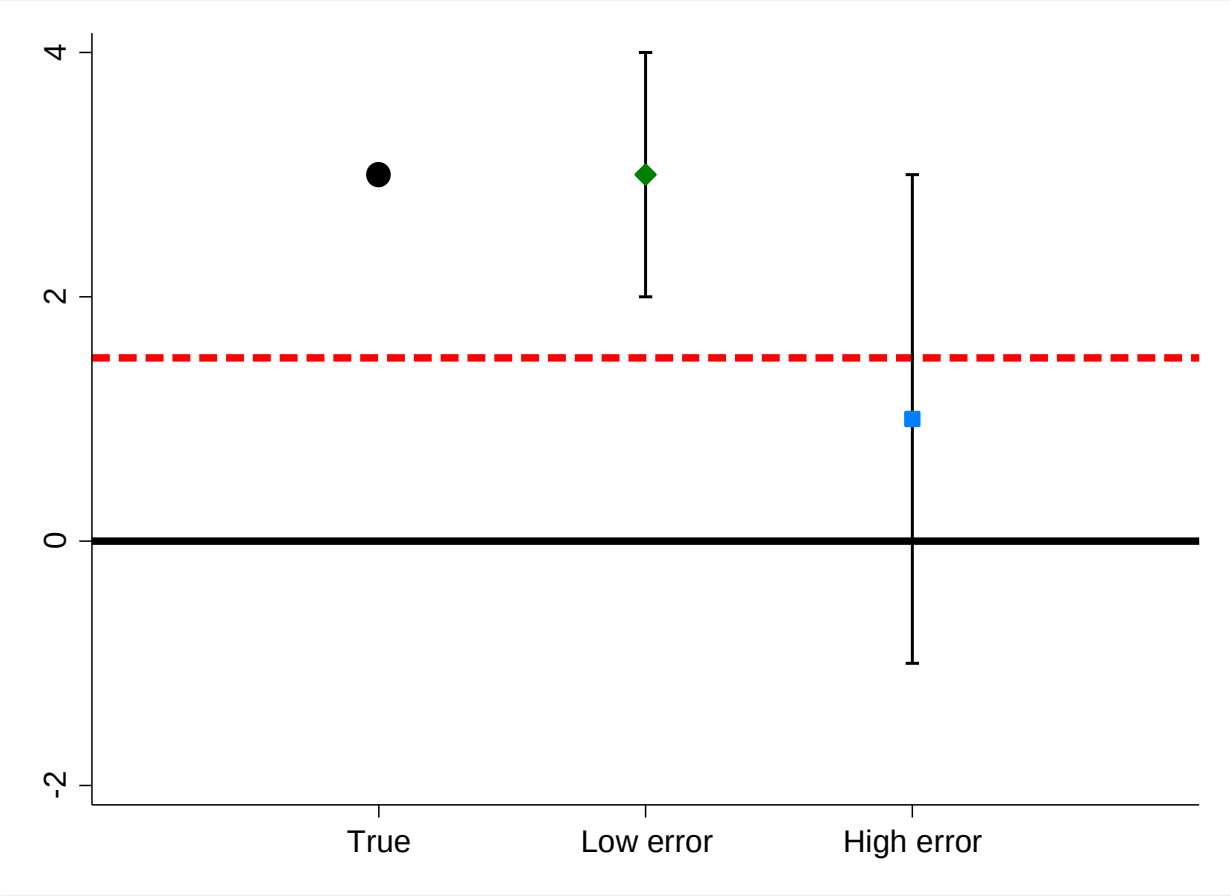
Problems with original approach

- Errors are reversed
  - Superiority/inferiority
    - **Type I** – Reject null of no difference when there is no difference
    - **Type II** – Fail to reject null of no difference when there is a difference
  - Non-inferiority
    - **Type I** – Reject null of inferiority for a treatment that is inferior
    - **Type II** – Fail to reject null of inferiority for a treatment that is not inferior

Why is the reversal of errors important?

- Traditional thinking in research
  - Nondifferential error biases to the null
  - Conservative because error gives us lower estimates in research than are probably true
- This creates the opposite problem in a non-inferiority trial
  - Estimates biased toward 0 bias results in favor of non-inferiority

Why is the reversal of errors important?



A final word on analysis

- Per protocol and intent-to-treat analyses are both important
  - Intent-to-treat
    - Benefit – random allocation
    - Drawback – conservative (lower estimate than if perfect compliance)
  - Per protocol
    - Benefit – seeing difference among actual treatment users (stronger difference is general result, so better test of non-inferiority)
    - Drawback – selection bias

Recommendations on sample size

- Per Greene et al, 2008,
  - Two-tailed $\alpha = 0.05$
  - $1 - \beta = 0.10$

$$n_{group} = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 s^2}{(\theta - \delta)^2}$$

- Major difference from traditional trial is in denominator

Technology and psychological health

- Use of telehealth growing in behavioral medicine
- Benefits of access to care, increased privacy, flexibility (Arnberg, 2014).
- How do we determine if this is useful?

Technology and psychological health

- Non-inferiority trial is a good option
  - Avoid ethical problem of using null or waitlist control
  - Evidence base is robust for most standard treatments

- Brief review of trials on technology and delivery of psychological health interventions
  - 11 studies reviewed

Overview of studies

First author, year	Target condition	Therapy
Acierno, 2016	Posttraumatic stress	Behavioral activation
Andersson, 2013	Depression	Cognitive behavioral
Blom, 2015	Insomnia	Cognitive behavioral
Egede, 2015	Depression	Behavioral activation
Hedman, 2011	Social anxiety	Cognitive behavioral
Lappalainen, 2014	Depression	Acceptance and commitment
Lovel, 2006	Obsessive compulsive disorder	Cognitive behavioral
Ly, 2015	Depression	Behavioral Activation
Turner, 2014	Obsessive compulsive disorder	Cognitive behavioral
Wagner, 2014	Depression	Cognitive behavioral
Yuen, 2015	Posttraumatic stress	Prolonged exposure

Types of telehealth considered

- Videoconferencing (3 studies)
  - All 3 against individual, in-person therapy
  - 2 used behavioral activation (Acierno, 2016; Egede, 2015)
  - 1 used prolonged exposure (Yuen, 2015)
- Telephone (2 studies)
  - Both cognitive behavioral therapy for obsessive compulsive disorder (Lovell, 2006; Turner, 2014)
- Self-paced, Internet-based (6 studies)
  - 4 cognitive behavioral studies (Andersson, 2013; Blom, 2015; Hedman, 2011; Wagner, 2014)

Types of comparisons

- Videoconferencing and telephone
  - Same content for both treatment groups
  - Same sequencing
  - Same timing
- Self-help/Internet
  - Similar content for both groups; active treatment engaged in *in-person group therapy* (Andersson, 2013; Blom, 2015; Hedman, 2011).

Methods critique

First author, year	Total N	Measure	Tails	Margin specified	Reported power
Acierno, 2016	184	PCL	1	Y	0.91
Andersson, 2013	69	MADRS-S	2	Y	0.79
Blom, 2015	48	ISI	2	Y	None reported
Egede, 2015	204	BDI	1	Y	0.85
Hedman, 2011	126	LSAS	2	Y	<0.80
Lappalainen, 2014	38	BDI	2	N	None reported
Lovell, 2006	72	Yale Brown	2	Y	0.80
Ly, 2015	93	BDI	2	Y	None reported
Turner, 2014	72	CY-BOCS	2	Y	0.80
Wagner, 2014	62	BDI	2	N	None reported
Yuen, 2015	52	CAPS	1	Y	None reported

Findings at post treatment

First author, year	Measure	Margin	Baseline SD Control	Approx. *d*	Estimate [95% CI]	Conclusion
Acierno, 2016	PCL	-8.8	14.0	0.63	-0.11 [-3.50, 3.50] (approx)	Non-inferior
Andersson, 2013	MADRS-S	2	5.0	0.40	-4.07 [-8.63, -0.77]	Non-inferior
Blom, 2015	ISI	4	3.9	1.03	-1.31 [-3.99, 1.36]	Non-inferior
Egede, 2015	BDI (percentage)	-15	-	-	0.88 [-10.13, 11.89]	Non-inferior
Hedman, 2011	LSAS	-10	22.9	0.44	5.60 [0.68, 17.66]	Non-inferior and superior
Lovell, 2006	Yale Brown	5	5.8	0.86	-0.59 [-3.51, 2.34]	Non-inferior
Ly, 2015	BDI	2.5	7.89	0.32	2.42 [-2.19, 7.03]	Cannot reject non-inferior
Turner, 2014	CY-BOCS	5	4.02	1.24	1.00 [-2.80, 4.80] (approx)	Non-inferior
Yuen, 2015	CAPS	d=-0.42		.42	0.13 [-0.32, 0.59]	Non-inferior

Observations from the research

- Language is problematic
  - Absence of a statistically significant difference **DOES NOT EQUAL**
    - No true difference
    - Equivalence or non-inferiority
  - Equivalence is not the same as non-inferior
    - Equivalence requires no exceeding the margin on *either* side of 0 and needs to be planned a prior
  - Non-inferiority cannot be used to describe a study that does not have a margin

Observations from the research (cont.)

- Broad heterogeneity in margin widths once consideration of study variation is considered
- Several studies with small sample sizes
  - Justified given larger margins, repeated measures
  - Are the MARGINS justified?
  - Randomization will probably not resolve imbalance issues with small samples

Observations from the research (cont.)

- Most studies relied on a 'clinically meaningful minimal difference' as the margin criterion
  - 2 studies used the lower bound of 95% CI from a meta-analysis as the margin (Hedman, 2011; Yuen, 2015)
    - Preservation of effect?
- Only one study failed to reject null hypothesis
  - Truly no difference in efficacy?
  - Many studies are biasing estimates toward zero?
  - Margins are too generous?

Things to consider

- Assumptions
  - Active control is faithful representative
  - Effect from meta-analysis (if consulted) is constant
  - Active control represents best available standard or alternative
- Margin
  - Reasonable value
  - Sources of information
  - Practical meaning of value

Recommendations for evaluating evidence base

- Best measures available to reduce error
- Thorough (and explicit) calculation of sample size
  - Use two-tailed α and $\beta = 0.10$
- Avoid mixture of exposures
- With non-inferiority, bad studies had a stronger chance of giving a desirable outcome than with superiority/inferiority studies
- Defense of margin selection

Summary

During this webinar, participants learned to:

- Identify the key design elements of a non-inferiority study
- Interpret the results of a non-inferiority trial
- Evaluate the credibility of the evidence base for a treatment approach based on non-inferiority designs

References

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Questions

- Submit questions via the Q&A box located on the screen.
- The Q&A box is monitored and questions will be forwarded to our presenters for response.
- We will respond to as many questions as time permits.

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Save the Date

Next DCoE Traumatic Brain Injury Webinar

Animal-Assisted Therapy: An Alternate Treatment to TBI Rehabilitation

August 11, 2016; 1-2:30 p.m. (ET)

Next DCoE Psychological Health Webinar Theme:

Combating Compassion Fatigue

August 25; 1-2:30 p.m. (ET)

Save the Date

2016 Summit State of the Science: Advances, Current Diagnostics and Treatments of Psychological Health and Traumatic Brian Injury in Military Health Care

September 13 – 15, 2016

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