Strategies to Examine Moderators of Treatment for PTSD

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Disclosures

Past 12 months

Data and Safety Monitoring Boards

AstraZeneca, Dainippon Sumitomo Pharma America, Pfizer

Consultant/Advisor

Cyberonics, FDA, MedAvante, NIMH, and Takeda

Outline

- Roles of Moderators in RCTs
- Contrast Designs for RCTs with Moderators
- Consider Hypotheses that each Addresses
- Compare Required Sample Size for each Design

Moderator of Treatment

Mediators and Moderators of Treatment Effects in RCTs.

Kraemer et al., Arch Gen Psych, 2002

Moderator is a baseline characteristic of subject that is associated (positively or negatively) with response.

Example

Males: active = placebo

Females: active > placebo

Hypothesized Moderators of Voc Rehab For PTSD

Interventions:

Individual Placement and Support

vs. Standard Vocational Rehabilitation Program

The between intervention effect size is hypothesized to be *smaller* for subjects with any of the following:

1) inadequate transportation
2) inadequate housing
3) little to no financial reserve/means
4) family care burden

Moderators in RCTs: Two Approaches

1) Design RCT to examine Moderator by Treatment Interaction with Hypothesis testing

2) Exploratory hypotheses in RCT protocol:

Specify hypothesized moderators of treatment

Exploratory Analyses of a Moderator

Moderator is a baseline characteristic of subject that is associated with response.

Exploratory analyses* will focus on magnitude of effect and not on p-values.

Magnitude of effect: R^2, Cohen's *d,* Number needed to treat *(NNT),* Number needed to harm *(NNH), AUC*

Kraemer & Kupfer, Biol Psych , 2006

* Exploratory Results are not for treatment decision making

Kraemer et al., *Mediators and Moderators of Trt Effects in RCTs*. Arch Gen Psych, 2002

Presence of Cluster C Diagnosis as Moderator of Panic Focused Psychodynamic Psychotherapy

Cluster C	Tx	N	PDSS Δ Mean (sd)	Between Tx Group Effect Size
No	PFPP	16	7.3 (5.2)	.69
	ART	14	3.6 (5.5)	
Yes	PFPP	10	9.4 (4.9)	1.35
	ART	9	2.6 (5.2)	

Milrod, J Clin Psych 2007

PDSS: Panic Disorder Severity Scale

Exploratory Results: Not for treatment decision making

Small sample size results in imprecise estimates (wide 95% CI)

$\approx d$ +/- [4 /sqrt(N*)]

where *d* is Cohen's *d*, a between group effect size and N* is total sample size.

Cluster C+ N=19: 95% CI is approximately *d* +/- 0.92:

d=1.35; 95% CI: 0.43 to 2.27

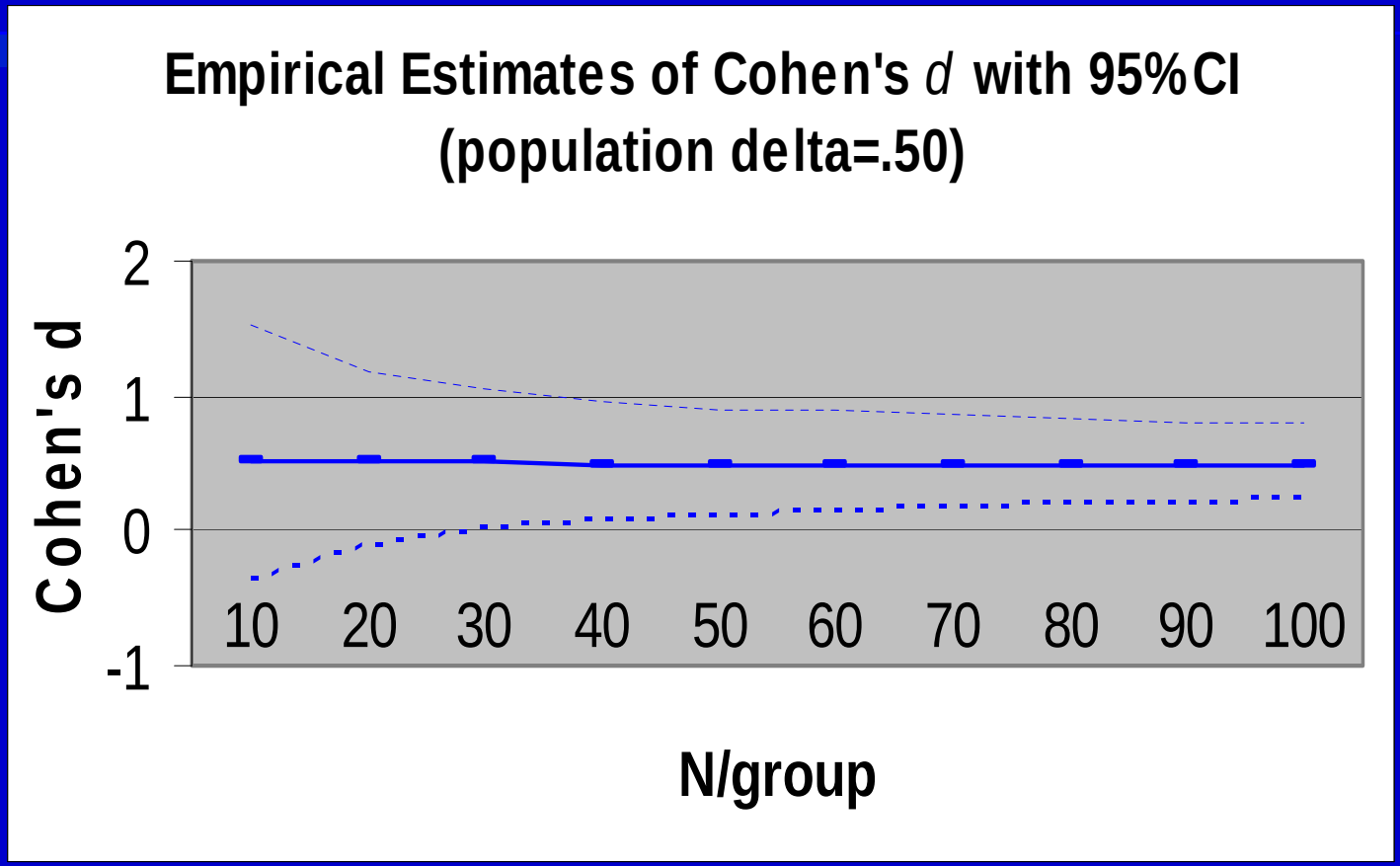
95% probability that the true population effect size falls between:

0.43 (a moderate advantage for PFPP)

2.27(an enormous, unprecedented advantage for PFPP)

Exploratory results are not for treatment decision making.

Exploratory or Pilot to Estimate Future Effect Size?

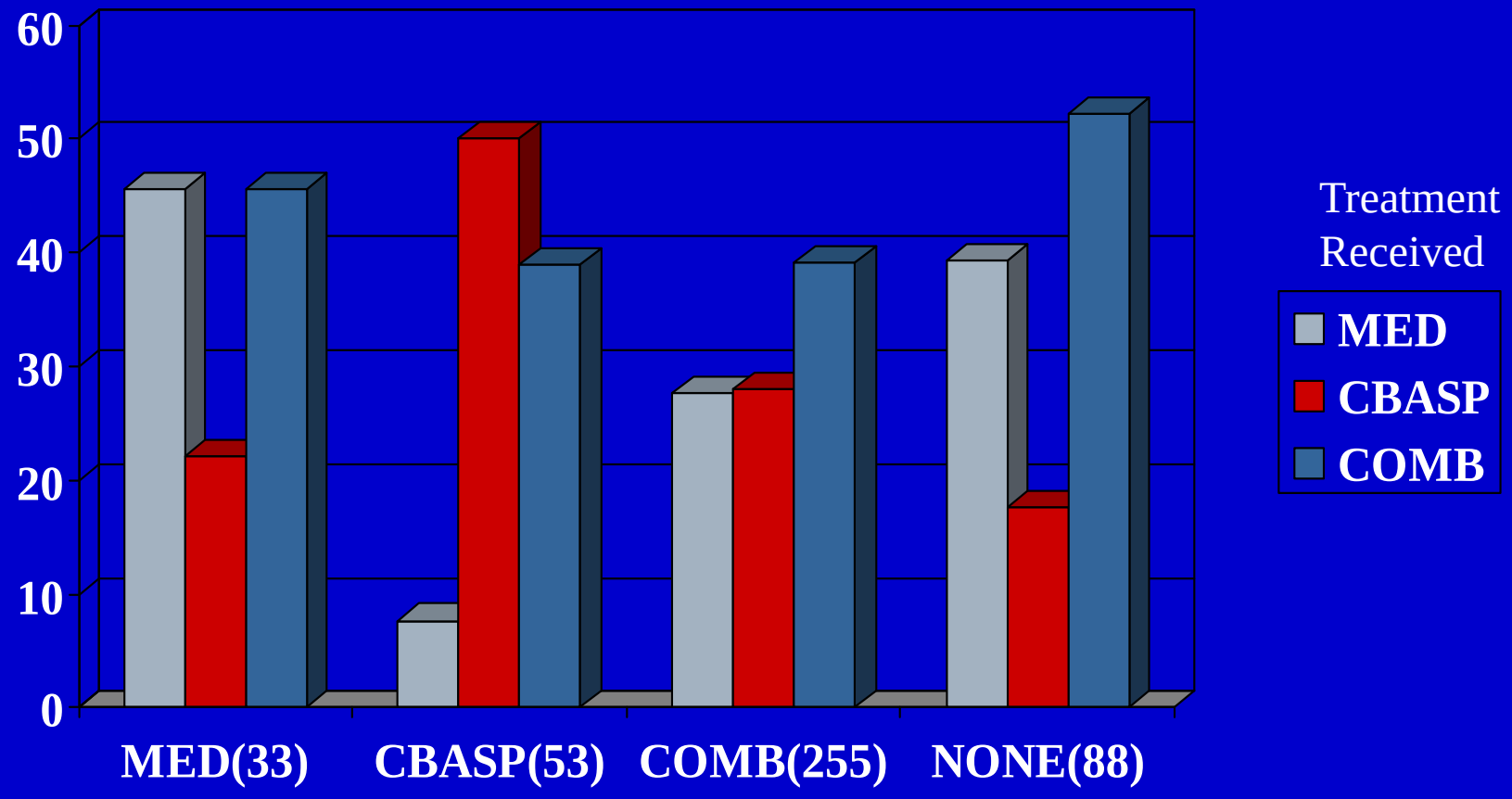


10,000 simulated data sets/N (Leon, 2008, Schz Bull)

95% CI: $\approx d$ +/- [4 /sqrt(N*)] (Kraemer, AGP 2006 63:484-9)

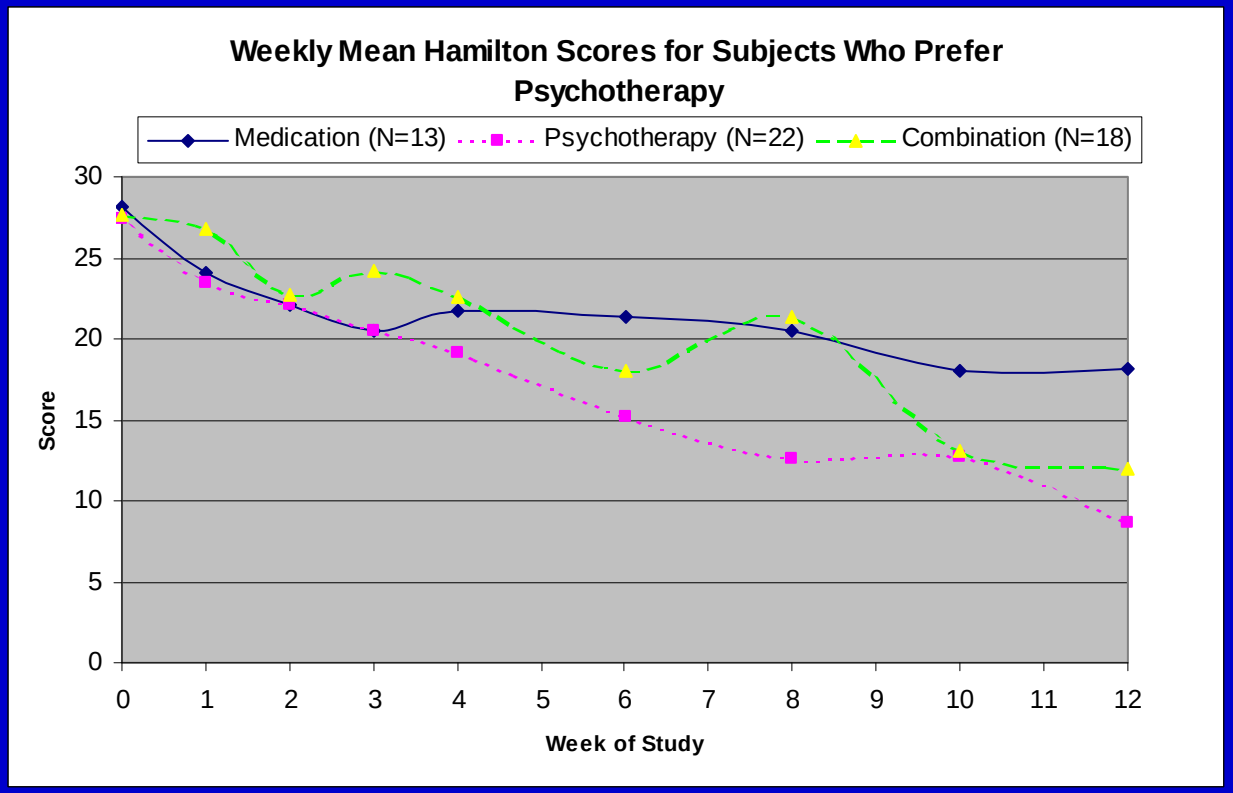
Moderators of Tx for Chronic Depression

ITT Remission Rates by Tx Preference & Tx Received

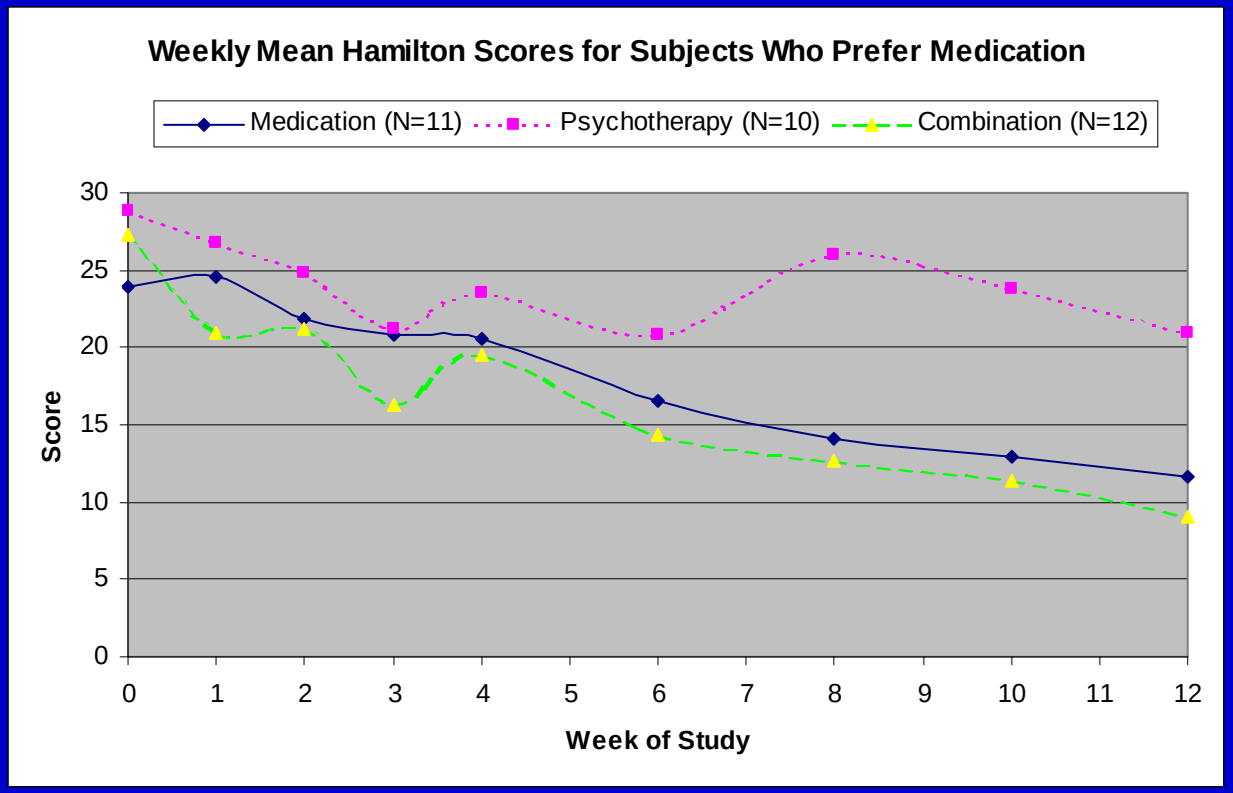


Kocsis et al: JCP 2009

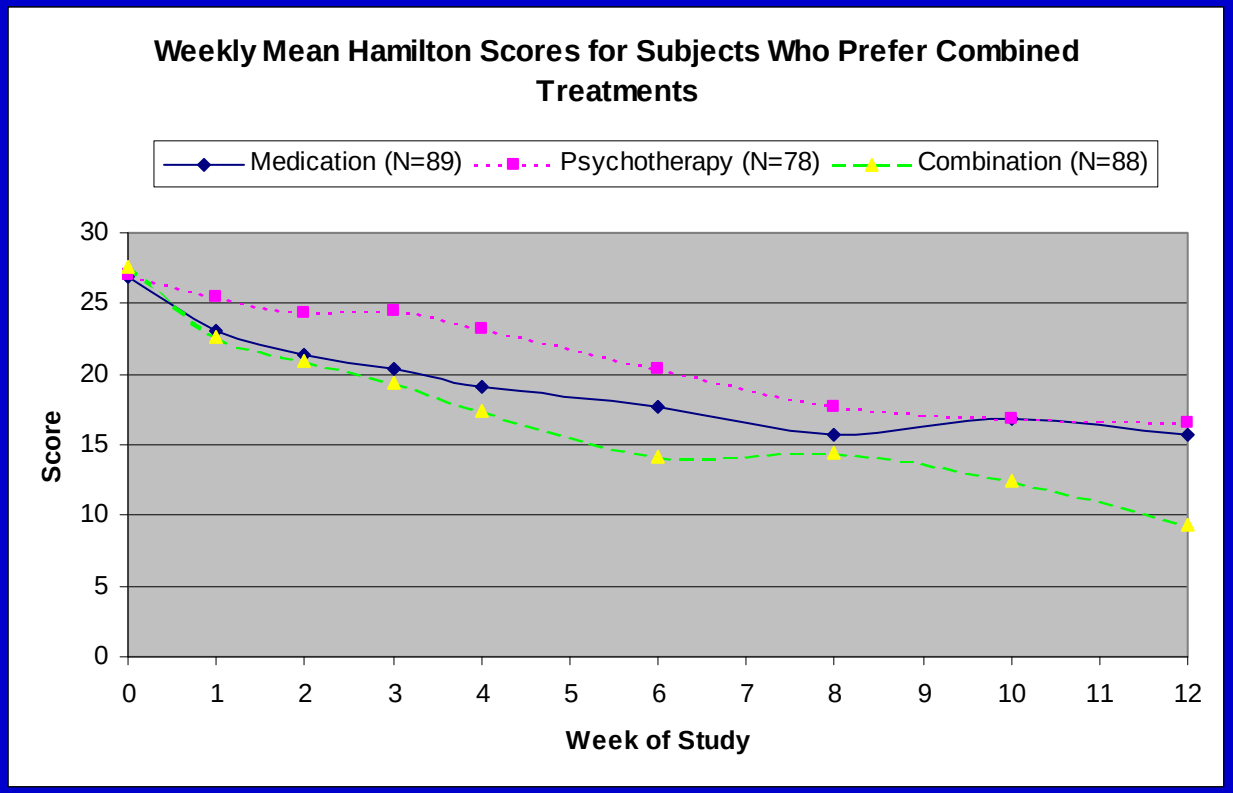
Moderators of Tx for Chronic Depression



Moderators of Tx for Chronic Depression



Moderators of Tx for Chronic Depression



If Exploratory Analyses Support Moderating Effect

Consider 2 subsequent designs:

2 x 2 factorial RCT

Main effect design

Design for Examining a Moderator:
2 x 2 factorial RCT

	Treatment	
	Active	Control
SNP+		
SNP-		

Randomize subjects to: Active vs. Control

Stratify randomization by SNP+/-

* Is there differential treatment effect for SNP+ & SNP-

H_0: $Active_{SNP+}$ - $Control_{SNP+}$ = $Active_{SNP-}$ - $Control_{SNP-}$

Significance test: *Treatment by SNP interaction*

Sample Size Required to Detect Clinically Meaningful Differences: **Interaction**

H_0: $Active_{SNP+}$ - $Control_{SNP+}$ = $Active_{SNP-}$ - $Control_{SNP-}$

Significance test: *Treatment by SNP interaction*

	Treatment	
	Active	**Control**
SNP+		
SNP-		

Interaction N is fourfold that of main effect

ANOVA - Fleiss, 1986. Design & Analysis of Clinical Experiments

Mixed-effects models - Leon & Heo, CSDA, 2008 (2 level)

Heo & Leon, Stat Med, 2009 (3 level)

Cost of 1 RCT for Interaction ≈ Cost of 2 or 3 RCTs for Main Effects

Consider Main Effects Strategy

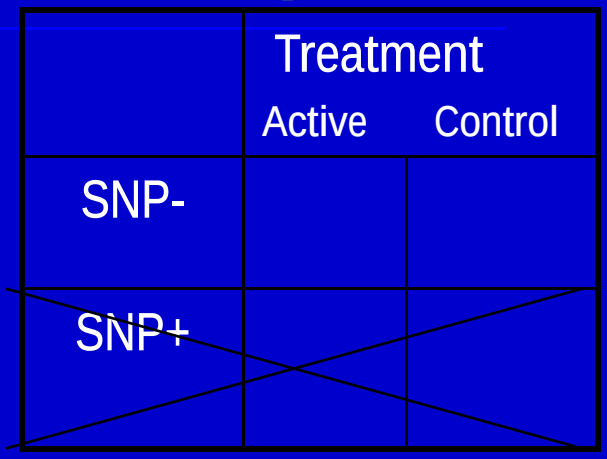
1) Exploratory hypotheses in an RCT protocol

2a) If results suggest moderator is associated with enhanced response, use in design of subsequent RCT

2b) If moderator is associated with decreased response, use to select (or develop) a novel intervention and test in subsequent RCT

3) Attempt to replicate RCT results in subsequent trial

Alternative RCT Design:
Only Enroll S's Expected to have Enhanced Response



Only recruit those with characteristics of enhanced response (as identified in Exploratory)

Randomize subjects: Active vs. Control

* Is there treatment effect for SNP- ?

H_0: $Active_{SNP-} = Control_{SNP-}$

Significance test: *Main effect of Treatment*

Generalizability limited to SNP-

Main effect N is 25% N for interaction. Opportunity to replicate.

Test a Novel Intervention for those Expected to have Decreased Response

	Treatment	
	Active	Control
SNP-		
SNP+		

Only recruit those with characteristics of decreased response (as identified in Exploratory)

Randomize subjects: Novel Active vs. Control

* Is there treatment effect for SNP+ ?

H_0: $Active_{SNP+} = Control_{SNP+}$

Significance test: *Main effect of Treatment*

Generalizability limited to SNP+

Main effect N is 25% that of interaction.

Hypothesized Moderators in Ongoing RCT of Voc Rehab For PTSD

Interventions:

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vs. Standard Vocational Rehabilitation Program

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Summary

Moderators are baseline characteristics of subjects.

Initially exploratory analyses of RCTs examine moderators.

Results can guide design of subsequent RCT, particularly the inclusion and exclusion criteria.

Summary

N required to detect interaction is 4x N for main effect.

Consider recruiting only S's with target characteristic (e.g., genotype), but this limits generalizability.

Develop and evaluate novel treatments for those with characteristic associated with decreased or adverse response.