A Prelude to Randomized Controlled Trials: Clinical Research Pilot Studies

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Pilot study or feasibility study?

- Feasibility studies are pieces of research done before a main study in order to answer the question *'Can this be done?'*
- Feasibility studies try out pieces of the planned RCT.
- Pilot studies try out the operation of all pieces as they will be implemented in the planned RCT.
- Terms are often used synonymously.

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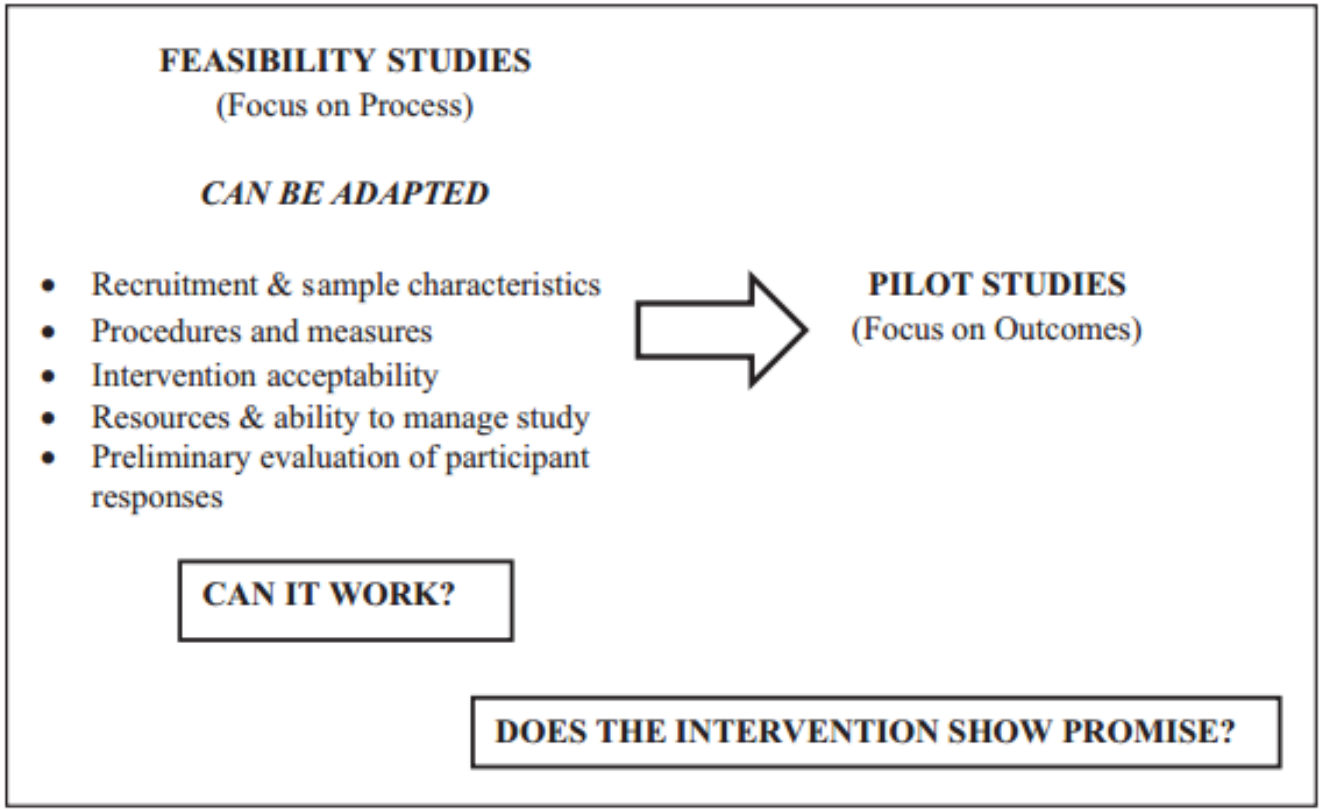

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Areas of Focus

- Eight general areas of focus addressed by feasibility studies:
- Acceptability looks at how the intended individual recipients—both targeted individuals and those involved in implementing programs—react to the intervention.
- Demand can be assessed by gathering data on estimated use or by actually documenting the use of selected intervention activities in a defined intervention population or setting.
- Implementation concerns the extent, likelihood, and manner in which an intervention can be fully implemented as planned and proposed, often in an uncontrolled design.
- Practicality explores the extent to which an intervention can be delivered when resources, time, commitment, or some combination thereof are constrained in some way.

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Areas of Focus

- Adaptation focuses on changing program contents or procedures to be appropriate in a new situation.
- Integration assesses the level of system change needed to integrate a new program or process into an existing infrastructure or program.
- Expansion examines the potential success of an already-successful intervention with a different population or in a different setting.
- Limited-efficacy testing may be conducted in a convenience sample, with intermediate rather than final outcomes, with shorter follow-up periods, or with limited statistical power.

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Why we do feasibility studies – the long answer

- Feasibility studies are used to determine whether an intervention is appropriate for further testing.
- Performing a feasibility study may be indicated when:
  - There is limited existing data using a specific intervention technique.
  - Prior studies were not guided by in-depth research or knowledge of the impact of an intervention on a population.
  - Prior studies were performed by researchers unfamiliar with the population of interest.
  - previous interventions using a similar method were not successful, but improved versions may be successful, or previous interventions had positive outcomes but in different settings than the one of interest.

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This is why we do feasibility studies – the short answer

- Can identify problem areas and fix/refine prior to engaging in pilot or full scale study.
- Provides some preliminary data that may help with sample size calculations.
- Introduces study staff to the actual logistics of what is going to be involved.

My study is feasible, but is it acceptable?

FEASIBILITY IS THE EASE OR CONVENIENCE OF EXECUTION

Primarily concerned with the researcher's ability to execute the plan.

ACCEPTABILITY IS THE SUITABILITY OR FAVORABILITY OF RECEPTION

Concerned with the suitability of the intervention or the research design from the perspective of the recipients, intervention providers, or health-care professionals.

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Assessing feasibility & acceptability.

Definitions	
Assessment of feasibility	Determines whether the intervention, study design, and procedures can be successfully executed by the researcher and delivered to the participants as planned.
Assessment of acceptability	Determines the suitability of the intervention and the study procedures from the perspective of the clinical populations of interest, the intervention providers, of the health professionals who provide care to the population of interest.
Assessment of intervention fidelity	Determines the extent to which the intervention can be provided as intended. These data can be used as indicators of feasibility in a pilot RCT.

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Assessing the feasibility & acceptability of the intervention.

FEASIBILITY

The dose (i.e., number, frequency, and timing)

Content

Methods of delivery

Percentage of sessions delivered to participants

INTERVENTION FIDELITY

The extent to which the intervention can be delivered as intended

- Can assess with checklists, audio recordings, etc.

ACCEPTABILITY

Satisfaction or perceptions of the helpfulness, credibility, comprehensiveness, comprehensibility, and user-friendliness of the intervention.

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Assessing the feasibility and acceptability of the study design and procedures.

FEASIBILITY

Recruitment of participants – percentage of eligible persons agreeing to participate

- Administer a questionnaire at the time of recruitment to identify specific reasons for refusal (i.e., study procedures too time-consuming or intervention not appropriate).
- Rate of recruitment can be useful in determining the overall timeline for the full-scale RCT and creating a budget.
- Inclusion and exclusion criteria can be scrutinized.
- Contamination – when participants in either group receive the intervention intended for those in the other group.

ACCEPTABILITY

Participant burden

Staff burden

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Potential outcomes.

Main study not feasible.

Feasible with modifications.

Feasible with close monitoring.

Feasible as is.

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From feasibility to pilot study.

Four primary purposes of pilot studies

To test the:

1. Process
2. Resources
3. Management
4. Scientific basis of the RCT

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Example of pilot study aims

Optimized Sleep After Brain Injury (OSABI)

- Aim 1: To characterize and estimate the incidence of sleep disturbance in the early rehabilitation phase of recovery after TBI.
- Aim 2: To determine the feasibility of implementing a sleep hygiene protocol on an inpatient TBI rehabilitation unit.
- Aim 3: To demonstrate selected outcome measures' ability to sufficiently detect change by examining variability in measures over time within groups.
- Aim 4: To explore the relationship of sleep quality and quantity to the recovery of cognitive function of individuals with TBI.

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Process

Assesses the feasibility of the processes that are key to the success of the main study.

- Recruitment rates
- Refusal rates
- Failure/success rates
- (Non)compliance or adherence rates
- Eligibility criteria
  - Too restrictive?
- Understanding of study questionnaires or data collection tools
- Length of time to fill out the study forms

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Resources

Assessing time and resource problems that can occur during the main study.

- Determining capacity
- Is equipment readily available?
- What happens when equipment breaks or gets stolen?
- Determine facility's willingness and capacity

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Management

Assessing potential human and data management problems.

- What challenges do study personnel have?
- Are there any problems with data management or entry?
- Can data coming from different sources be matched?
- Do data show too much or too little variability?

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Scientific

Assessment of treatment safety, dose, response, effect, and variance of the effect.

- What is the safe dose level?
- Do patients respond to the drug/treatment?
- What is the estimate of the treatment effect?
- What is the estimate of the variance of the treatment effect?

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So now you're doing a pilot study…

- Protocol is approved
- You have some funding to support this work (hopefully)
- Staffing is in place
- All necessary supplies, materials, incidentals are ready to go
- Potential participants are identified, interested, and ready to be consented/enrolled
- We have identified possible glitches and have some contingency plans in place, but….

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Something's not right

- The flow of events isn't working
- The participants are dropping out
- The study staff aren't following through with the procedures
- The IRB will have to be informed of protocol deviations, etc.
- You are encountering unexpected OTHER issues
- So what can be done to salvage this pilot?

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What makes a pilot successful?

- Lots of planning
- Critical review
- Realistic expectations
- Implementation plan
- Ability to address issues as they arise
- Patience, patience, patience

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Clinical Pilot Study Program at Craig Hospital

Review process

- Develop a concept proposal that is reviewed by those familiar with research processes
- Incorporate feedback
- Present a well-developed full proposal that clearly identifies
  - Knowledge of literature/background information
  - Theoretical approach (if appropriate)
  - Methodology
  - Dissemination plan
  - Budget

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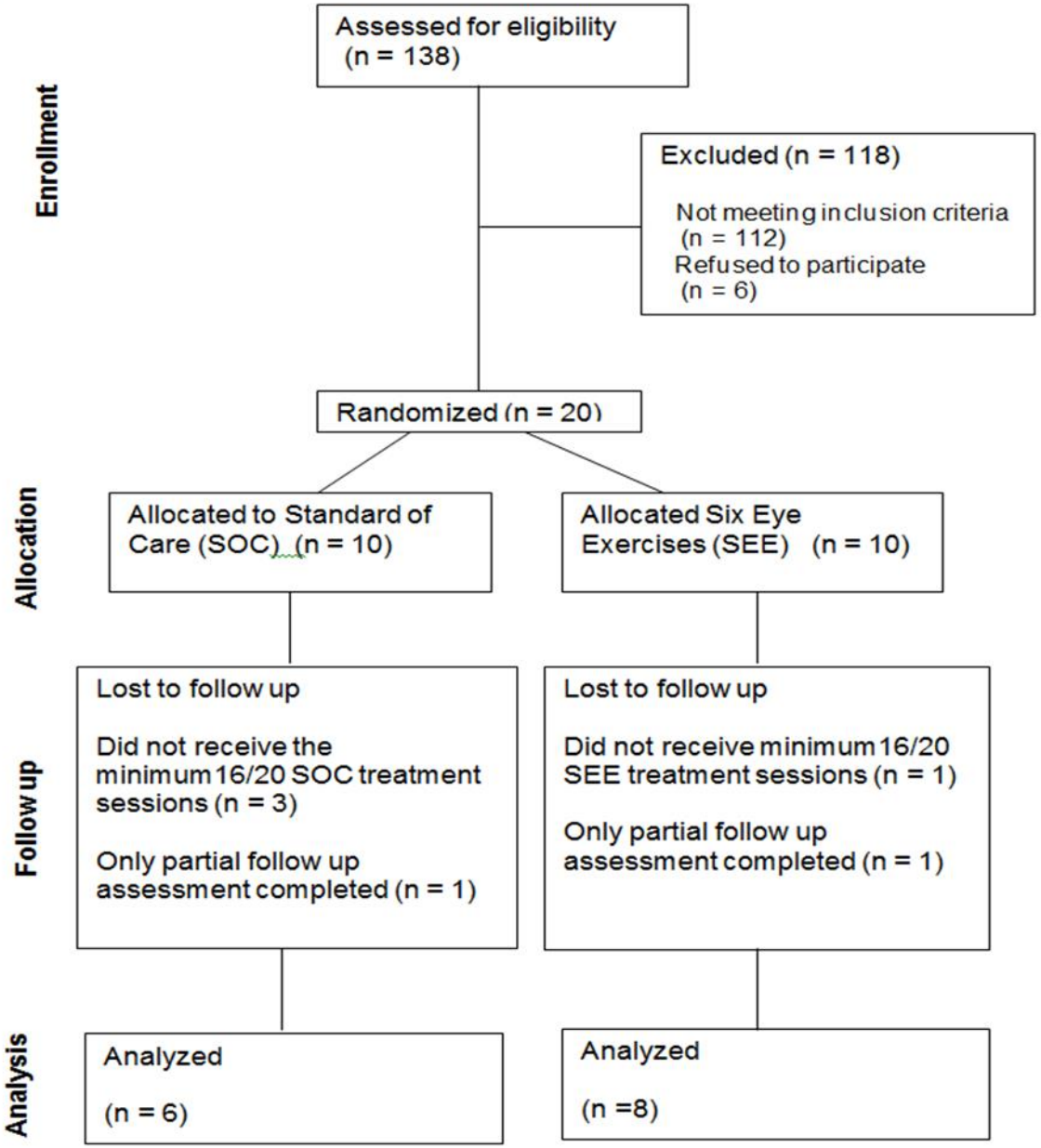
How do I interpret my pilot data?

Interpreting Pilot Studies

- The analysis should focus on answering feasibility objectives.
- Need to define criteria for achievement of feasibility objectives.
  - Recruitment (inclusion/exclusion criteria)
  - Enrollment (consent rate)
  - Protocols (control and treatment fidelity)
  - Withdrawal/completion rates
  - Resource burden
  - Signal of treatment effect

Diagram 1

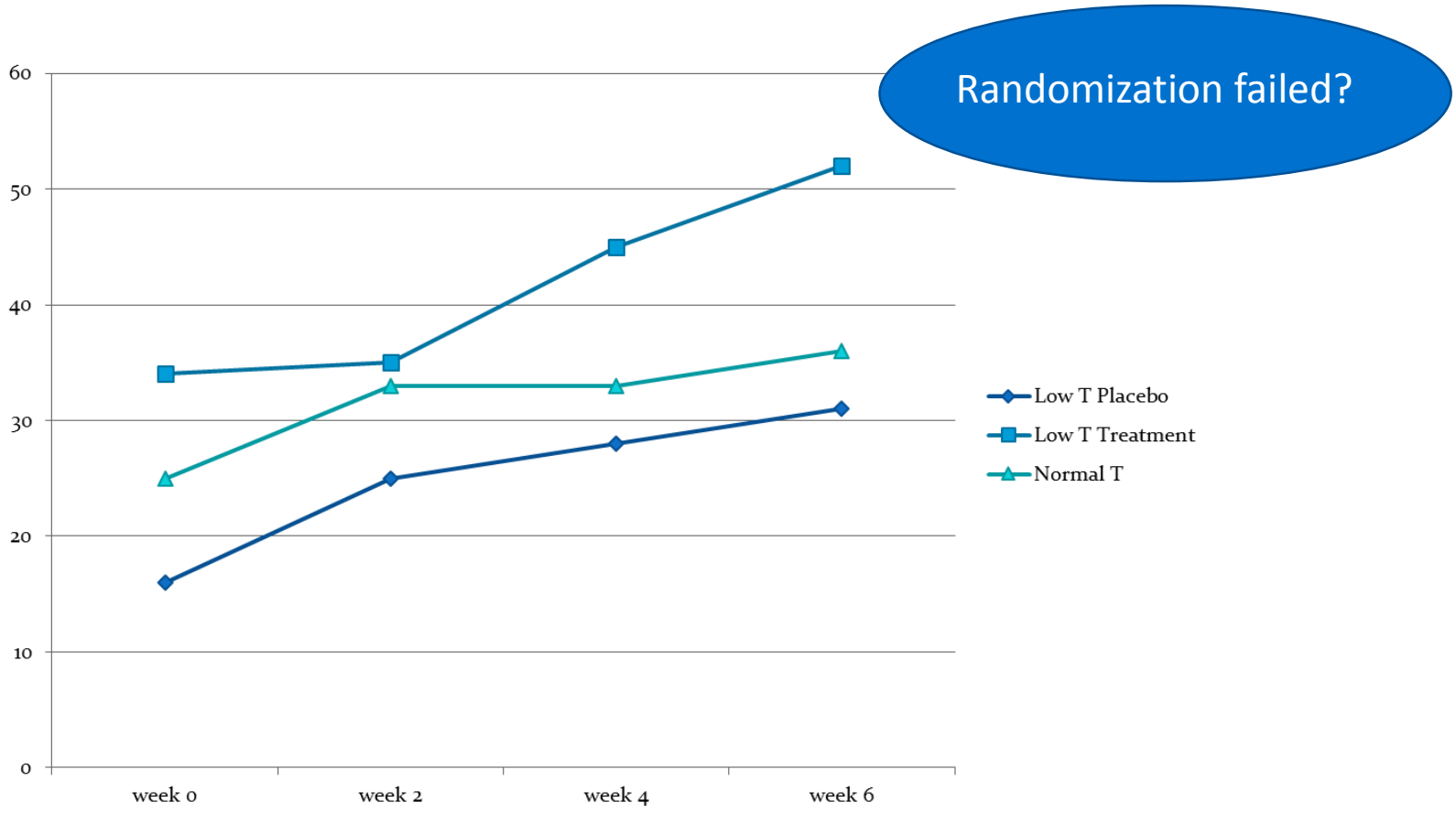


ConSORT Diagram

The problem of randomization in pilot studies

- A problem with randomization in small n studies is imbalance among the treatment groups with respect to some prognostic factors that invalidates trial results or that necessitates complex secondary analysis of covariance to eradicate the imbalance (which makes it less clinically interpretable).

Testosterone FIM change by group



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Minimization

Adaptive or dynamic allocation

- Method used in clinical trials to balance the arms simultaneously over several prognostic factors.
- The first participant is allocated randomly an arm of the study. Subsequent participants are allocated to the arm that reduces prognostic factor imbalances between the arms.

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The Consolidated Standards of Reporting Trials (ConSORT) 2010

- Minimization has the advantage of making small groups closely similar in terms of participant characteristics at all stages of the trial.
- Minimization offers the only acceptable alternative to randomization, and some have argued that it is superior
- Nevertheless, in general, trials that use minimization are considered methodologically equivalent to randomized trials, even when a random element is not incorporated.

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How does minimization work?

Prognostic Factor	Intervention	Control
Sleep Efficiency (SE)		
0-40	3	5
41- 80	4	2
Time Post Injury		
1-23	4	3
24- 45	3	4

8th participant: SE = 64 Days Post Injury = 23

Intervention grp: 4 + 4 = 8 Control grp: 2 + 3 = 5

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Prognostic Factor	Intervention	Control
SE		
0-40	3	5
41- 80	4	3
Time Post Injury		
1-23	4	4
24- 45	3	4

9th participant: SE = 35 Days Post Injury = 42

Intervention grp: 3 + 3 = 6 Control grp: 5 + 4 = 9

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Data analysis

- The analysis used to detect a treatment signal should be mainly descriptive and not hypothesis testing.
- Pre-post change scores
  - Frequencies
  - Medians with ranges
  - Means with 95% confidence intervals
  - Effect sizes (if relatively normally distributed and SDs similar)

Table 2 Primary and Secondary Outcome Measures											
	SOC (n=6)						Tx (n=8)				
	BASELINE	POST-TREATMENT					BASELINE	POST-TREATMENT			
	Median	Median	Median Δ	% Improved	% No Impairment		Median	Median	Median Δ	% Improved	% No Impairment
VSS # of Symptoms	2.0	1.0	-0.5	50.0 (3/6)	16.7		5.5	1.0	-2.5	75.0 (6/8)	37.5
VSS Severity Total	2.5	2.0	-0.5	50.0 (3/6)	16.7		14.5	1.5	-7.5	87.5 (7/8)	37.5

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Table 3 Mean Pre-Post Change with SD and 95% CI				
	SOC		Tx	
	Mean (SD)	95% CI	Mean (SD)	95% CI
DK	12.1 (20)	-12.7 to 37.0	16.6 (9)	8.9 to 24.4
ND	33.7 (38)	-6.0 to 73.3	49.9 (43)	13.2 to 86.5
Sx #	0.8 (1)	-0.4 to 2.1	3.5 (3)	0.8 to 6.2

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$$\text{Cohen's } d = \frac{M_1 - M_2}{SD_{pooled}}$$

$$\text{Glass's } \Delta = \frac{M_1 - M_2}{SD_{control}}$$

$$\text{Hedges' } g = \frac{M_1 - M_2}{SD^*_{pooled}}$$

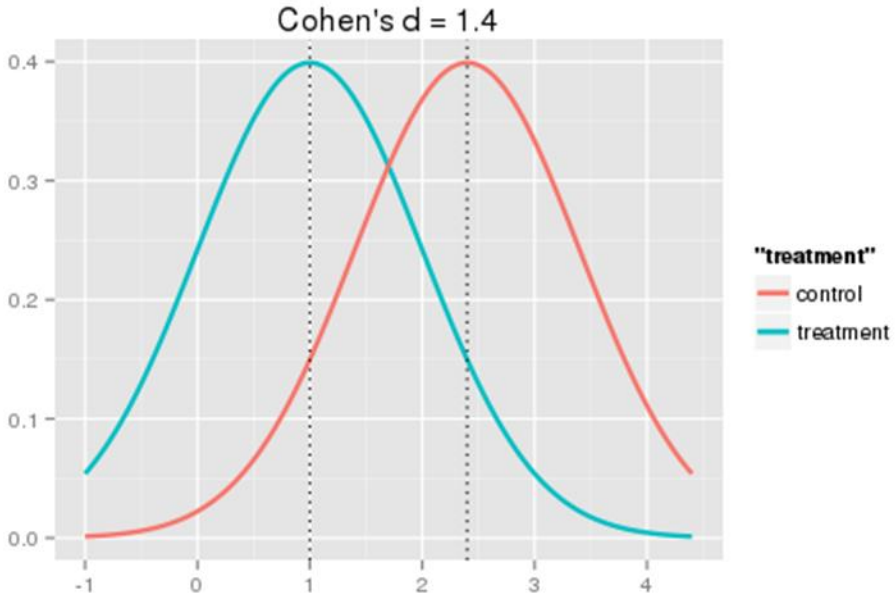

Table 3 Pre-Post Change Effect Size				
	SOC		Tx	
	Mean (SD)		Mean (SD)	*d*
DK	12.1 (20)		16.6 (9.3)	0.29
ND	33.7 (37.8)		49.9 (43.8)	0.40
Sx #	0.8 (1.2)		3.5 (3.3)	1.09

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frequently asked QUESTIONS

Is my pilot study publishable?	YES
Can the pilot data be used in the main study?	POSSIBLY
Are the results of my pilot study valid on their own?	YES
Can the results from my pilot study be used to treat patients?	NOT A GOOD IDEA

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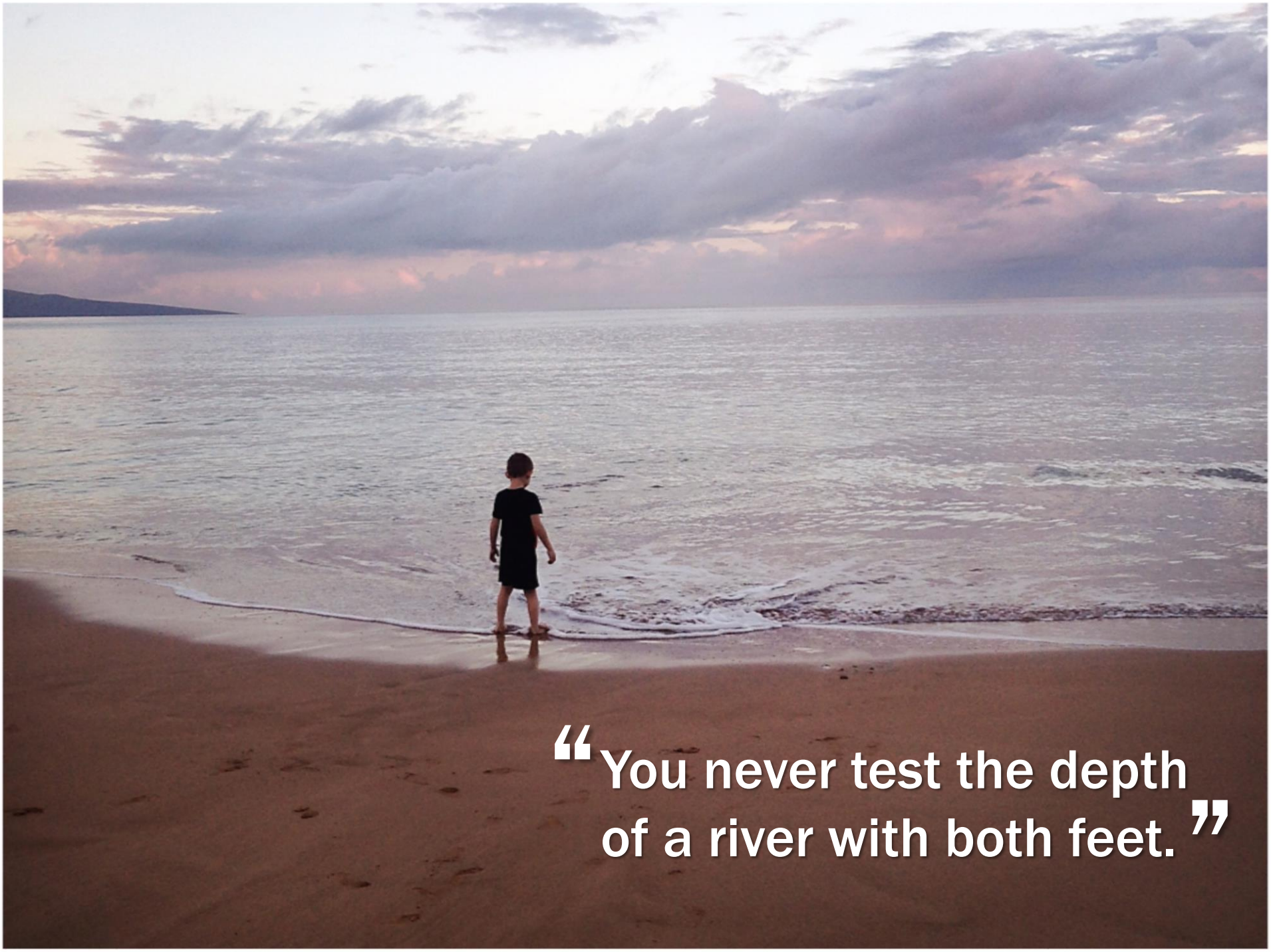
“You never test the depth
of a river with both feet.”

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