Beyond RCTs: Producing high level evidence using single case experimental design trials

Peter Rosenbaum, CanChild, Canada
Helene Polatajko, University of Toronto, Canada
Lynn Logan, Upstate Medical University, USA
Hortensia Gimeno, King’s College London, UK

The RCT: A Great Approach... Sometimes
But
What to do when it is not?
What are high level alternatives?

What is an RCT?
In health care research, an experiment designed to test an intervention.

- Randomly allocate 'enough' people to the 'arms' of the intervention – assuming that on average people in each group will be similar enough...
- Randomization is meant to control/balance as many of the 'relevant' (as well as the as-yet unknown) factors as possible

What are high level alternatives?

A great approach, sometimes...

- A clear and specific research question
- A clearly defined target group for the Rx
- A discrete replicable intervention
- A reasonable alternate intervention or placebo Rx
- A specific, discrete, relevant and measurable impact, assessed by people who are 'masked' to groups
- A time-course that allows people to argue logically for a causal connection between exposure and outcome

An Example: The Collet et al. HBOT Study

A clear and specific research question:
The primary objective was to determine whether 40 treatments could improve gross motor function and to verify whether any improvement persisted for 3 months after the end of the intervention.

A clearly defined target group for the Rx:
Children with CP aged 3-12 years

A discrete intervention accepted as ‘appropriate’:
40 ‘dives’ at 1.75 ATA – 5x/week for 8 weeks

A reasonable alternate intervention or placebo:
40 ‘dives’ at 1.3 ATA – 5x/week for 8 weeks (enough to be perceptible but assumed to be of no clinical value)
The Collet et al. HBOT Study

A specific, discrete, relevant and measurable impact:
The ‘primary’ outcome was gross motor function assessed by trained, masked evaluators with the GMFM-66
Several ‘secondary’ outcomes looked at ADLs, attention, working memory and speech
A time-course that allows people to argue logically for a causal connection between exposure and outcome:
Outcomes assessed at the end of the 8 weeks and three months later

What are the Usual Realities?
• A clear and specific research question?
  This should always be possible, but may be too focused or too big!
• A clearly defined target group for the Rx
  Can be very challenging
  Availability – RCTs need ‘large’ numbers!
  Heterogeneity – a perennial challenge, especially with small Ns
  How to stratify to enable ‘comparable’ groups
• A discrete replicable intervention
  HBOT is the exception – our Rxs usually have several potential ‘active ingredients’

What are the Design Challenges?
There is a significant mismatch between the well-deserved stature and glory of the RCT and the realities of our childhood disability field!
• Questions are complex...
• Heterogeneity of the kids and families with whom we work adds complexity
• There are ‘too many’ kids in clinic – we are all busy – but they ‘disappear’ the minute the grant is funded (Murphy, once again!)
• The time-course of change in our field is long – meaning other things (growth, development, co-interventions, changing goals, new Rxs…) all are operating
• Too many ‘sources of variation’ (the ‘Yes, but what about…’ questions)

But…The realities of rehabilitation intervention research
Population issues
• Small populations
• Highly variable
• Highly dispersed
• Real-world goals
• Non-randomizable circumstances

Intervention issues
• Unclear
• Under developed
• Untested/reflective
• Personalized | Individualized
• Complex
• Multidimensional
• Personalized real-world outcomes
• Non-randomizable circumstances
The realities of rehabilitation intervention research... your situation

Population issues
- What is your population?
- What are the issues...
  - numbers
  - heterogeneity
  - access
  - randomisation potential

Intervention issues
- What is your intervention?
- What are the issues....
  - Untested | ineffective
  - Complex
  - Multidimensional
  - No gold standard

The realities of rehabilitation intervention research... the CO-OP example

Population issues
- DCD
- What are the issues....
  - numbers: large but difficult to access
  - heterogeneity
  - real world individualised goals
  - randomisation allocation

Intervention issues
- SM based approaches
- What are the issues....
  - No or weak evidence
  - Old theories pervade
  - Complex
  - Multidimensional
  - No gold standard

The CO-OP example: Creating a new intervention

Population issues
- Large numbers of children
- Highly variable
- Varied real-world goals
- Specific performance deficits

Intervention issues
- Reconsider theoretical perspectives
- Design a new intervention
- Test-refine-test-refine-test

Design issues
- RCT premature - Proof of principle
- Heterogeneity
- Varied goals
- Alternatives???

Creating a new intervention: An alternative design - SCED

Single Case Experimental Design
- Specify/solidify approach
- Replication across children
- Replication across therapists
- Follow-up studies (informal)
- Pilot RCT + formal follow-up

Design Considerations: Demonstrate experimental control
- Multiple data points (repeatable measures)
- Baseline and intervention phases
- Match with theoretical basis - non-reversible
- Replication across behaviours
- Replication across children
- Replication across therapists

Design chosen
- SCED series with multiple baseline across behaviours and replication across children and therapists

Single Case Experimental Designs: High level alternatives

OBJECTIVES
1. To identify 6 different types of SCED
2. To assign levels of evidence to each type of SCED

What SCED is NOT

- Case Report
  - Carefully reported example of new intervention, diagnosis, or combination of treatments
  - Non experimental design

- SCED
  - Tightly controlled experimental design
  - Must demonstrate stability of elements of interest before beginning intervention
  - May be randomized
  - Often includes more than a single subject
Basic Definition of SCED

Systematic observation, measurement, graphing and analysis of a carefully defined target behavior during both baseline (pre-treatment) and treatment conditions.

SCED Advantage

- Stable baseline clearly identified
- Control or identification of outside influences
- May modify or compare interventions or contexts
- Randomization of timing or intervention is possible
- Multiple subjects may be studied to improve generalization

Major components of SCED

1) The sequential application and withdrawal or variation of the intervention
2) The use of frequent and repeated outcome measures

Simple Baseline (A-B) Design

A = baseline phase
B = treatment/intervention phase

SCED involves studying a single individual by taking repeated measurements of one or more dependent variables and systematically applying and sometimes withdrawing or varying the independent variable [Ottenbacher, 1986]

NOT considered an experimental design (CONSORT extension for reporting N-of-1 trials 2015)

Basic components of SCED

Baseline Phase = A phase: Initial period of observation in which the natural frequency of occurrence of the behavior is obtained

Treatment Phase = B phase: Once a stable baseline has been obtained, a new therapeutic or treatment variable is introduced and the frequency of the behavior continues to be measured.

Major components of SCED

Blind Data Collection: The strength of the design is greater when the data collectors do not know the phase of treatment in which data are being collected.

Generalizability: To increase generalizability, SCEDs must be replicated across clients, by other therapists and in other settings.
Characteristics of SCED

1) Target behaviors are clearly specified and operationally defined
2) Methods of measurement are precisely defined
3) Continuous measures are taken throughout each phase of the study
4) One intervention strategy (independent variable) is manipulated at a time
5) Extraneous variables are carefully controlled
6) Methods used in data collection must be replicable and reliable

Simple Baseline: AB Design

- The simplest and least sophisticated analysis technique in which the baseline (A) is first established followed by the treatment phase (B).
- The least powerful SCED because you cannot be sure that another confounding variable did not cause the behavior change.
- Does not allow for any randomization

Simple Baseline: AB Design

• The simplest and least sophisticated analysis technique in which the baseline (A) is first established followed by the treatment phase (B).
• The least powerful SCED because you cannot be sure that another confounding variable did not cause the behavior change.
• Does not allow for any randomization

Withdrawal or Reversal Design: ABA

• Baseline measurement is taken (A), followed by introduction of treatment (B), and then return to baseline (A).
• If treatment is effective, desired behavior will improve during B-phase and get worse again when treatment is withdrawn (second A-phase).

Withdrawal Design: ABA

• ABA is superior to AB design because it tests the effects not only of introducing the treatment but also of withdrawing it (fewer threats to internal validity than an AB design).
• Also does not allow for randomization.
Problems with ABA Design

1) Once a behavior is acquired, it may be maintained by outside behaviors (other than the intervention), e.g., developmental milestones.
2) There are ethical implications of finishing a study in a non-treatment phase.

ABAB: Withdrawal-Reinstatement Design

- Baseline measurement of the target behavior (A) is taken, the treatment is implemented (B), the treatment is withdrawn (A), and finally the treatment is reinstated (B).
- Advantage: Terminates in a treatment phase.

Alternating Treatment Design

- Two or more interventions are rapidly alternated in random fashion and their effects compared on a dependent variable within a single phase.
- This design is most powerful when a baseline condition is provided both prior to and following the intervention phase.
- Advantage: Alternations in the treatment may occur over brief periods, in contrast to ABAAB and M-B designs.

Multiple Baseline Design

- M-B design can be done across behaviors, subjects, or settings.
- M-B designs can be either concurrent or non-concurrent, with the former being the stronger of the two. Concurrent designs allow for comparison under the same conditions.
- M-B designs with random assignment are the most powerful.
- Advantage: Any change in the target behavior that occurs during intervention for Subject 1 is compared not only to his own baseline but also to the ongoing baselines of the other subjects, behaviors or settings.
Variation of Multiple Baseline
- Requires stable baseline followed by stepwise treatment interventions
- Each phase provides a baseline for the next level of treatment

Changing Criterion Design
- Essentially a SCED. Whereas SCED arose from research in the behavioral sciences, N-of-1 trials arose from the medical literature.
- Most examples of N-of-1 trials tend to address the effectiveness of drugs but could be applied also to other types of discrete interventions that do not have a carry-over effect.

N-of-1 Randomized Controlled Trial
- Can be used to select optimal treatment for an individual.
- Trials of two treatments (drugs) or a treatment and a placebo are usually conducted.
- Like SCED, requires a measurable target behavior or symptom.
- Examples of target behaviors: level of pain on a VAS, no. of episodes of a specific symptom per day, or distance walked without SOB.
- Pairs of treatment periods in which experimental treatment and alternate or placebo treatment are offered randomly.

N-of-1 Randomized Controlled Trial
- Treatment being evaluated must have a reasonably quick acting effect on the target behavior or symptom and the effect must be reversible or cease when the placebo is introduced or the treatment discontinued.
- As with SCED, generalizability is enhanced thru replication.

Value of N-of-1 RCT
- Both subject and clinician/evaluator are blind to the treatment being administered.
- As with SCED, examines effects of various treatments on individual patients or clients.
Levels of Evidence: Oxford CEBM

**Level I**: RCTs or meta-analyses of RCTs

**Level II**: Small RCTs, cohort studies, SR of cohort studies

**Level III**: Case-control studies, SR of case-control studies

**Level IV**: Case series

**Level V**: Expert opinion

---

SCED Levels of Evidence Level I

**Design**: Randomized, controlled, N-of-1 RCT, ATD, and MBD (concurrent or non-concurrent) with clear-cut results.

- Generalizability if the ATD is replicated across ≥5 Subjects and the MBD consists of at least 3 Subjects, behaviors, or settings.

- These designs can provide causal inferences.

---

SCED Levels of Evidence Level II

**Design**: Non-randomized, controlled, concurrent MBD with clear-cut results.

Generalizability if design consists of at least 3 Subjects, behaviors or settings.

Limited causal inference.

---

SCED Levels of Evidence Level III

**Design**: Non-randomized, controlled, non-concurrent MBD with clear-cut results.

Generalizability if design consists of at least 3 Subjects, behaviors or settings.

Limited causal inference.

---

SCED Levels of Evidence Level IV

**Design**: Non-randomized, controlled SCED with at least 3 phases (ABA, ABAB, BAB, etc.) with clear-cut results.

Generalizability if replicated across ≥5 Ss. Only hints at causal inferences.

---

SCED Levels of Evidence Level V

**Design**: Non-randomized, controlled AB design with clear-cut results.

Generalizability if replicated across ≥5 Ss.

Suggests causal inferences allowing for testing of ideas.
**Checklist for Reporting N-of-1 trials and SCED**

See handouts or http://www.equator-network.org/reporting-guidelines/consort-
for-N-of-1

---

**Augmenting deep brain stimulation with a cognitive approach**

SCED with replications across children with hyperkinetic movement disorders

**Current Treatment Options**

Medical-based interventions
Heterogeneity of HMD

Priorities for families and measurement of outcomes in interventions for dystonia

Priorities for children with CP

Evaluation of 57 children and young people with HMD.
Canadian Occupational Performance Measure (COPM)
Most frequent priority was self-care.

What outcomes matter for children and their families?

1. Reduction pain and discomfort
2. Accessing assistive technology
3. Dressing activities
4. Use of tools (scissors, cutlery, pencils, ...)
5. Participation in family and social activities

Significant change observed in both, motor and process skills at 1 and 2 years post DBS

Dystonia and other HMD

Current management options include

- Surgical
- Deep Brain Stimulation
- Intrathecal Baclofen
- Medical
- Oral medications
- Botulinum Toxin
**Dystonia and other HMD**

Current management options include:
- **Surgical**
  - Deep Brain Stimulation
  - Intrathecal Baclofen
- **Medical**
  - Botulinum Toxin

Functional targeted intervention potentially available as an adjunct... but paucity of evidence available

**CO-OP Approach™**

Cognitive Orientation to daily Occupational Performance

**Methodology**

**Inclusion Criteria**
- HMD post DBS
- 6-21 years
- MACS I-IV problems with activities of daily living

**Primary Outcome Measures**
- Assessment of motor and process skills (AMPS)
- Performance Quality Rating Scale (PQRS)
- Blinded rated

**Generalisation Transfer**

Functional targeted intervention
- Client Centred
- Cognitive Strategies
- Functional goals

**Methodology**

**Client Centred**

Functionally targeted intervention

**CO-OP Approach™**

**Cognitive Strategies**

**Functional goals**
CO-OP and DBS in HMD

Environmental Factors

Self-Efficacy (DBS Pts)

Cognitive Ability Measures

- PQRS
- GAS
- COPM
- PEDI-CAT
- AMPS
- ABAS-II

Anxiety Measures

- PQRS
- COPM
- GAS

Environmental Factors

- SEG-P

Self-Efficacy (DBS Pts)

- PEDI-CAT
- COPM
- GAS

Measures across the ICF

MRI Electrode position

Single Case Experimental Design/
N-of-1 trials

Single Case Experimental Design/
N-of-1 trials

Single Case Experimental Design/
N-of-1 trials

Single Case Experimental Design/
N-of-1 trials

Single Case Experimental Design/
N-of-1 trials

SCED/N-of-1 trials

SCED/N-of-1 trials

SCED/N-of-1 trials

REPLICATION

n-of-1 + 3

n-of-1 + 3

n-of-1 + 3

n-of-1 + 3

n-of-1 + 3
15/08/17

**SCED**

**Replication**

n-of-1 + 3 + 5 = 4 + 6

---

**Stage 1**

- Expert Therapist
- N-of-1 with replication
- Single Case Experimental Design

**Proof of Concept**

- Feasible
- Acceptable
- Efficacy

---

**Baseline** (Pre CO-OP)

- Post CO-OP

**During CO-OP**

**Post CO-OP**

**3M Follow Up** (After CO-OP)

---

**Did the intervention fail?**

---

**Baseline** (Pre CO-OP)

- Post CO-OP
Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?

Did the intervention fail?
**Discussion about realities of your own research relative design**

**Research Q/purpose**  
Adapting an existing intervention  
Creating a new intervention - local use only (your own practice only)

**P**  
Proof of principle  
Uptake beyond your context

**Design**  
- Proof of principle - simple SCED (SCD)  
- For broader uptake - a process that goes from the simple SCED, through the N of 1 Trial, to a full scale trial (RCT maybe)

Using CO-OP as the heuristic  
- Creating a new intervention with DCD > Trial >  
- Adopting to dystonia

**References**