N-of-1 trials: planning, conduct, and evaluation

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Learning Objectives

1. To learn about N-of-1 trial design and when it is appropriate

2. To learn about the newly developed CONSORT Extension for N-of-1 Trials (CENT guidelines)

3. Measuring individualized therapies....

To learn about the new U of A Integrative Health Institute
Overview

• Background

• N-of-1 study design and analysis

• CONSORT statement

• CENT
  – Development
  – Draft checklist

• Integrative Health Institute
Background: “N-of-1”

• An N-of-1 trial is a randomized, multiple crossover evaluation performed in a single individual

• Balances patient needs with methodological rigor
Single-case experimental design (SCED) scale

Tate et al. Neuropsychological Rehabilitation. 2013.
Determining optimal therapy for individual patients

- N-of-1 trials are patient-centered and an ideal way to promote rational pharmacotherapy
- Chronic diseases often require multiple medications for prolonged periods
- Offers patients and health care providers opportunity to refine medication regimens to those of maximal effectiveness
- N-of-1 trials promote patient safety by reducing polypharmacy
When is N-of-1 relevant?

- **Paediatrics and/or rare diseases**
  - Large RCTs challenging; difficult to reach adequate sample size

- **Co-morbid conditions and concurrent therapies**
  - RCTs often exclude these populations

- **Chronic diseases**
  - To re-evaluate long-term therapy

- **Patient-safety**
  - Reduce polypharmacy

- **Complementary and alternative medicine**
  - Individualized therapies not amenable to RCT; lack to evidence to support RCT

Many more...
Example: individual vs. population data

- Large trials cannot predict individual responses
- In RCT, all participants assumed to improve by same amount
When is N-of-1 appropriate?

- Lack of confidence that a current treatment is providing a benefit
- Uncertain a proposed treatment will work in a particular patient
- Patient insists on taking a treatment that the clinician thinks will not work or is harmful
- Suspect side effect is from a treatment but are unsure
- Unsure of the optimal dose

Guyatt et al, 1988
N-of-1 study design

- Treatment pairs
- Treatment periods
- Randomization and blinding
- Outcome assessment
- Stopping
Treatment Pairs

• Pairs of treatment periods
  – Active vs. Placebo
  – Low dose vs. High dose
  – Treatment A vs. Treatment B
Treatment Pairs

• Determine number of treatment pairs
  – Does not necessarily have to be specified
  – Replicated until convinced treatment is:
    • Effective
    • Harmful
    • Has no effect
  – Minimum two pairs for statistical analysis
  – Ideally three to five pairs
  – Analysis strengthened if specified in advance
Treatment Periods

• Length based on length of time for treatment to reach full effect and cease to act

• If unknown – periods should be as long as feasible (4-6 weeks)
  – Length can then be adjusted after a couple of treatment periods

• For conditions that have “attacks”, treatment period needs to be long enough to include an attack
  – Inverse rule of 3s – if an event occurs once every $x$ days we need to observe $3x$ days
Outcome assessment

• Identified prior to commencing the trial
• Need to be relevant to both patient and provider
• Patient identifies most troubling symptoms/problems they would like alleviated with the treatment = the target outcome
• Target outcomes form the basis of the disease and patient specific questionnaires
Outcome assessment

• MYMOP2 (Measure Yourself Medical Outcome Profile)
  – Patient Generated - outcomes important to patient
  – Problem specific
  – 7 point scale

Choose one or two symptoms (physical or mental) which bother you the most. Write them on the lines. Now consider how bad each symptom is, over the last week, and score it by circling your chosen number.

SYMPTOM 1: ..................  0  1  2  3  4  5  6
................................................................. As good as it could be
................................................................. As bad as it could be

SYMPTOM 2: ..................  0  1  2  3  4  5  6
................................................................. As good as it could be
................................................................. As bad as it could be

Now choose one activity (physical, social or mental) that is important to you, and that your problem makes difficult or prevents you doing. Score how bad it has been in the last week.

ACTIVITY: ......................  0  1  2  3  4  5  6
................................................................. As good as it could be
................................................................. As bad as it could be

Lastly how would you rate your general feeling of wellbeing during the last week?

.................................................................  0  1  2  3  4  5  6
As good as it could be
As bad as it could be

How long have you had Symptom 1, either all the time or on and off? Please circle:

0 - 4 weeks  4 - 12 weeks  3 months - 1 year  1 - 5 years  over 5 years

Are you taking any medication FOR THIS PROBLEM? Please circle: YES/NO

IF YES:
1. Please write in name of medication, and how much a day/week

........................................................................................................

2. Is cutting down this medication? Please circle:

Not important  a bit important  very important  not applicable

IF NO:
Is avoiding medication for this problem:

Not important  a bit important  very important  not applicable
When to Stop a N-of-1?

- When note dramatic difference between treatment arms (better or worse – NB preferable to remain blinded before deciding)
- If a minimal difference is observed between the two periods may need to complete several more to confidently make conclusions
- After completion of the number of pairs that was determined *a priori*
Early Stopping

- If there is a dramatic difference in the target outcome from one period to the next
- If there is minimal difference
- If there are serious side effects
- Conclusions made after a single pair could lead to false positives/negatives
Ethics of N-of-1

Research?
- Randomization, blinding, placebo
- Intention to publish results
- Typically altruistic

Versus

Clinical care?
- Idealized patient care (compared to status quo)
- Informed consent
- Intended for patient’s benefit
# N-of-1 trial service compared with research and routine clinical care

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Routine Clinical Care&lt;sup&gt;*&lt;/sup&gt;</th>
<th>N-of-1 Clinical Service&lt;sup&gt;a,b,c&lt;/sup&gt;</th>
<th>N-of-1 Trials Conducted as Research&lt;sup&gt;d,e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motivation</strong></td>
<td>Self-interest&lt;br&gt;Intend is to help patient</td>
<td>Self-interest&lt;br&gt;Intend is to help patient</td>
<td>Altruism (greater good)&lt;br&gt;May or may not be helpful to patients</td>
</tr>
<tr>
<td><strong>Goal</strong></td>
<td>Optimal patient care&lt;br&gt;(individualized)</td>
<td>Optimal patient care&lt;br&gt;(individualized)</td>
<td>Generalizable data&lt;br&gt;(population estimates of treatment effect)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Based on clinical expertise&lt;br&gt;Consult based&lt;br&gt;Referral based</td>
<td>Based on clinical expertise&lt;br&gt;Consult based&lt;br&gt;Referral based</td>
<td>Inclusion/exclusion criteria&lt;br&gt;Recruit (i.e., advertise)</td>
</tr>
<tr>
<td><strong>Informed consent</strong></td>
<td>Yes&lt;br&gt;Procedures, etc.</td>
<td>Yes, n-of-1 approach is a choice&lt;br&gt; NB: Secondary analysis will require separate IRB approval</td>
<td>Yes, participation in research is a choice</td>
</tr>
<tr>
<td><strong>Intervention</strong>&lt;br&gt;(dose, duration, frequency, route)</td>
<td>Individualized</td>
<td>Individualized</td>
<td>Standardized</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Informal</td>
<td>Formal outcomes (will be part of informed consent)</td>
<td>Formal outcomes (data collection)</td>
</tr>
<tr>
<td><strong>Publish results</strong></td>
<td>Yes (case reports, series)</td>
<td>Yes (suggest obtain consent a priori)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cost of product</strong>&lt;br&gt;(discussed further in Chapter 3: Financing)</td>
<td>Varies per jurisdiction</td>
<td>Varies; optimally no charge to patient</td>
<td>No charge to patient</td>
</tr>
<tr>
<td><strong>Oversight</strong></td>
<td>Physician licensing board or regulatory college&lt;br&gt;Ensures standard of care</td>
<td>Physician licensing board or regulatory college oversees standard of care; IRB would be involved for secondary analysis</td>
<td>IRB</td>
</tr>
</tbody>
</table>

Overview

- Background
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- CONSORT statement
- CENT
  - Development
  - Draft checklist
- Summary
CONSORT Statement

- A minimum set of recommendations for reporting RCTs
- Offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation

Moher, 2010
CENT Checklist

• CONSORT Extension for N-of-1 Trials (CENT)
• Intended to apply to N-of-1 trials with multiple crossover (i.e. ABAB) design
• Goals:
  – Improve quality of published N-of-1 reports
  – Promote evidence-based decision-making in healthcare
  – Help researchers design of N-of-1 trials
CENT Guidelines Development

• In collaboration with the CONSORT working group, the development process recommended by CONSORT has been employed:
  – Phase 1: Systematic reviews of N-of-1 conduct, analysis, and meta-analysis
  – Phase 2: Modified Delphi survey
  – Phase 3: In-person meeting of international experts
Advantages of N-of-1 trials

- Individualized approach
- Relatively inexpensive to conduct
- Not as disruptive to patient – provider relationship
- Only one participant required – limits exposure to therapy of unknown benefit
- Provides methodologically sound results
- Potential for the results of several N-of-1 to be meta-analysed
Disadvantages of N-of-1 trials

- Only applicable to the individual patient (i.e. not necessarily generalizable to a population)
- Preferably used for chronic, stable conditions
- Preferably used for treatments with rapid onset/termination of effect
- Potential for carry-over effects
  - Multiple random cross-over periods
  - Use average of all measurements within each period in the analysis
  - Can be quantified in the analysis
The Future of N-of-1

• Can we meta-analyze N-of-1 trials? (yes)
• Can N-of-1 trials contribute to systematic reviews? (yes)
• Can a series of N-of-1 trial compete with RCTs to generate population-based estimate? **
• Should they be registered?
• What about other single subject trial designs?
N-of-1 systematic reviews

• Salima Punja, University of Alberta
• Margaret Sampson, Children’s Hospital of Eastern Ontario
• Larissa Shamseer, Ottawa Health Research Institute
• Cecilia Bukutu, University of Alberta
• Nicholas Barrowman, Children’s Hospital of Eastern Ontario
• David Moher, Ottawa Health Research Institute
• Sunita Vohra (PI), University of Alberta
CENT Guidelines

- Larissa Shamseer, Ottawa Health Research Institute
- Margaret Sampson, Children’s Hospital of Eastern Ontario
- Cecilia Bukutu, University of Alberta
- Nick Barrowman, Children’s Hospital of Eastern Ontario
- Jane Nikles, University of Queensland, Australia
- Robyn Tate, University of Sydney, Australia
- Doug Altman, University of Oxford
- David Moher, Ottawa Health Research Institute
- Sunita Vohra (PI), University of Alberta
Funders

• **N-of-1 systematic reviews**
  - Alberta Innovates-Health Solutions
  - Canadian Institutes for Health Research
  - Hecht Foundation

• **CENT Guidelines**
  - Alberta Advanced Education and Technology
  - Boiron
  - Canadian Agency for Drugs and Health Technologies
  - Afexa (formerly CV Technologies)
  - HEEL
  - Pfizer Inc.
  - Schwabe Pharma
References

What is Integrative Health?

• Patient-centred, evidence-informed, inclusive approach to health and healing

• While open-minded, pursues inquiry and evidence

• Established field with university-based institutes and centres around the world (CAHCIM >57):
  - Canada: Toronto, McMaster, Calgary
  - Europe, Australia, China
Examples of complementary and alternative therapies

- **Whole systems of care** (e.g., Traditional Chinese Medicine, Aboriginal health practices, Ayurveda)
- **Natural health products** (e.g., herbs, vitamins, probiotics) and functional foods
- **Health care practices** (e.g., mindfulness, spirituality, arts-based therapies)

Integrative Health combines conventional and complementary approaches in an evidence-informed, patient-centred fashion.
What we have now: dis-integrative health

70% of Canadians use a variety of practices and products, often with no communication with their health care providers.

A global issue recognized by the World Health Organization:

• Widespread and increasing use of traditional and complementary medicine
• Growing economic importance
• Integration into health systems
• Recent advances in research
The bottom line: Why does this matter?

• Patient-centred care
  • Requires respect for patients’ health-related preferences/priorities/values/beliefs

• Patient safety
  • Demands awareness of all therapies patients are using

• Culturally competent care
  • Many different ways of achieving health and healing

Scholarship is essential to inform policy and practice
Thank you