Journal of Clinical Epidemiology 76 (2016) 47–56

Journal of Clinical Epidemiology

N-of-1 trials are a tapestry of heterogeneity

Salima Punja[a], Cecilia Bukutu[a,b], Larissa Shamseer[c], Margaret Sampson[d], Lisa Hartling[e], Liana Urichuk[f], Sunita Vohra[g,*]

[a]*Department of Pediatrics, University of Alberta, 1702 College Plaza, 8215—112 Street NW, Edmonton, Alberta T6G 2C8, Canada*
[b]*Knowledge Utilization Studies Program, Faculty of Nursing, University of Alberta, 3rd Floor Edmonton Clinic Health Academy, Edmonton, Alberta T6G 1C9, Canada*
[c]*Clinical Epidemiology Program, Ottawa Hospital Research Institute, Center for Practice Changing Research Building, 501 Smyth Road, PO Box 201B, Ottawa, Ontario K1H 8L6, Canada*
[d]*Department of Library Services, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada*
[e]*Alberta Research Centre for Health Evidence, Department of Pediatrics, University of Alberta, 4-472 Edmonton Clinic Health Academy, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada*
[f]*Information & Evaluation Services for Addiction & Mental Health, Addiction and Mental Health, Alberta Health Services-Edmonton Zone, 9942 108 Street, Edmonton, Alberta T5K 2J5, Canada*
[g]*Complementary and Alternative Research and Education Program (CARE), Department of Pediatrics, University of Alberta*

Accepted 22 March 2016; Published online 11 April 2016

Abstract

Objectives: To summarize the methods of design, analysis, and meta-analysis used in N-of-1 trials.

Study Design and Setting: Electronic search for English language articles published from 1950 to 2013. N-of-1 trials were selected if they followed an ABAB design and if they assessed a health intervention for a medical condition. Elements of design, analysis, and meta-analysis were extracted.

Results: We included 100 reports representing 1,995 participants. N-of-1 trials have been conducted in over 50 health conditions. Most reports incorporated the use of elements that maintain methodological rigor, including randomization, blinding, and formal outcome assessment; however, many failed to address trial registration, funding source, and adverse events. Most reports statistically analyzed individual N-of-1 trials; however, only a small proportion of included series meta-analyzed their results.

Conclusions: N-of-1 trials have the ability to assess treatment response in individual participants and can be used for a variety of health interventions for a wide range of medical conditions in both clinical and research settings. Considerable heterogeneity exists in the methods used in N-of-1 trials. © 2016 Elsevier Inc. All rights reserved.

Keywords: N-of-1 trial; Clinical trial; Evidence-based medicine; Systematic review; Analysis; Meta-analysis

1. Introduction

N-of-1 trials are prospective, multiple crossover evaluations conducted in a single subject (i.e., ABAB) and are often randomized and blinded [1]. They have a long tradition in psychological research [2] and have been used in medicine to generate treatment information when evidence from randomized controlled trials (RCTs) is not available or feasible. Three conditions should be fulfilled before beginning an N-of-1 trial [3]. First, the condition under study should be chronic and relatively stable (e.g., autism, irritable bowel syndrome, attention deficit/hyperactivity disorder, diabetes, chronic pain). If a condition is characterized by the possibility of rapid or spontaneous improvement, such an improvement may be mistakenly attributed to the treatment under study. Second, the intervention being studied should be quick in both onset and termination of effect, therefore, mitigating the need for long treatment periods and for lengthy washout periods between interventions. Third, ideally, outcomes will be relevant to both patient and the health care provider. Disease- and patient-specific questionnaires may be used to gather data

Conflict of interest: L.H. is supported by a CIHR New Investigator Salary Award.

Funding: Funding support was provided in part by the Lotte and John Hecht Memorial Foundation.

* Corresponding author. 1702 College Plaza, 8215—112 Street NW, Edmonton, Alberta T6G 2C8, Canada. Tel.: 780-492-6445; fax: 780-492-5883.

E-mail address: svohra@ualberta.ca (S. Vohra).

http://dx.doi.org/10.1016/j.jclinepi.2016.03.023
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What is new?

Key findings

- There has been a fourfold increase in the number of published N-of-1 trials over the last 20 years.
- N-of-1 trials have been used to yield treatment response in both individual and groups of participants.

What this adds to what was known?

- N-of-1 trials have been used to assess a variety of health interventions for a wide range of medical conditions in both clinical and research settings.

What is the implication and what should change now?

- There is a need for consistent and rigorous methods and transparent reporting among N-of-1 trials.

for this purpose. Standardized outcome measures can also be used when they have been validated for the condition and population under study.

Potential advantages of N-of-1 trials include: (1) the approach is individualized; (2) the cost is low compared to conventional RCTs; (3) therapies can be evaluated at initiation and periodically re-evaluated (to ensure ongoing effectiveness); (4) off-label or unproven therapies can be evaluated; (5) participants will have an opportunity to experience active therapy, not just placebo; (6) participants will know their results more quickly than in an RCT (e.g., months instead of years); and (7) the results will be relevant and applicable to the participants themselves. Overall, N-of-1 study design maintains methodological safeguards provided by RCTs (blinding, randomization, controls) yet avoids many of the pitfalls of large trials, such as recruitment issues, prohibitive expense, and lack of external validity (i.e., applicability to patients not fitting stringent trial eligibility criteria). Evidence-based medicine experts have suggested that the N-of-1 trial design has the potential to provide the strongest evidence for individual treatment decisions and have been listed as level 1 evidence in the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence [4]. Preliminary reviews reveal a range of N-of-1 designs and statistical methods in the literature [4−6]. To optimally apply the N-of-1 methodology, all the current knowledge regarding N-of-1 trials should be synthesized. To this end, we conducted a systematic review with the objective of describing the methods, analysis, and meta-analysis in published N-of-1 trials. This review will provide a comprehensive understanding about the methodology and reporting of N-of-1 trials. Preliminary findings from this review have been used to inform, in part, the development of the CONSORT Extension for N-of-1 Trials (CENT), a guideline for reporting individual and series of N-of-1 trials [7].

2. Methods

2.1. Search strategy

MEDLINE (1946−July week 1, 2013), EMBASE (1974−2013 week 28), PsycInfo (1806−July week 2 2013), and AMED (1985−July 2013) were searched through the Ovid interface. CINAHL (from 1982, with end date unstated) was searched initially through the Ovid interface, but later through the EBSCOHost interface. Cochrane CENTRAL (Issue 6 of 12, June 2013) and the NHS Economic Evaluation Database (coverage dates unstated) were searched through the Wiley interface. Searches were first conducted in November 2005, and updated at intervals, most recently July 15−17, 2013. Reference lists of eligible studies were examined to identify additional potentially relevant studies.

2.2. Selection criteria

Published, English language N-of-1 trials were selected if they met the following criteria: (1) a primary study; (2) the trial had an ABAB design [i.e., at least two interventions are compared, in which one arm is the treatment (A) and the other may be a treatment, control, usual care, or no treatment (B)]; and (3) the study assessed a health intervention for a particular medical condition. Single-phase studies, biphasic studies (e.g., A−B), pre−post studies, ABA studies, and case description studies were excluded because they do not use multiple crossovers of at least two treatments [8].

2.3. Selection of studies

Selection of studies was based on a screening of titles and abstracts independently by two authors (S.P. and C.B.). Both reviewers independently assessed the full-text articles using the selection criteria described above. Any disagreements were resolved by a third party (S.V.).

2.4. Data extraction

The data extraction form was piloted on 10 studies by two reviewers. After necessary revisions, one reviewer used the form to extract data from included studies, and a second reviewer verified the accuracy of extracted data for all studies. Extractions were done using the DistillerSR software (Evidence Partners Inc., Ottawa, Ontario, Canada). Extracted data included patient characteristics, treatment characteristics, design elements, methods of analysis, and meta-analysis. Any disagreements were resolved through discussion.

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