ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 471−480

Journal of Clinical Epidemiology

Aggregating single patient (n-of-1) trials in populations where recruitment and retention was difficult: The case of palliative care

Jane Nikles[a], Geoffrey K. Mitchell[a,*], Philip Schluter[b,c], Phillip Good[e,f], Janet Hardy[d], Debra Rowett[g], Tania Shelby-James[h], Sunita Vohra[i], David Currow[h]

[a]*The University of Queensland, Discipline of General Practice, Queensland, Australia, South Australia*
[b]*Auckland University of Technology, School of Public Health and Psychosocial Studies, New Zealand*
[c]*The University of Queensland, School of Nursing and Midwifery, Qld 4072, Australia*
[d]*Mater Health Services, Department of Palliative Care, Queensland, Australia*
[e]*Calvary Mater Newcastle Department of Palliative Care, NSW, Australia*
[f]*University of Newcastle, NSW, Australia*
[g]*Repatriation General Hospital, Drug and Therapeutics Information Service [DATIS], South Australia, Australia*
[h]*Flinders University, Department of Palliative and Supportive Services, South Australia, Australia*
[i]*Faculty of Medicine and School of Public Health, University of Alberta, Alberta, Canada*

Accepted 28 May 2010

Abstract

Randomized controlled trials (RCTs) are the gold standard for evaluating new interventions. Different RCT designs apply depending on the patient population, clinical setting, and intervention being evaluated. A design that may help to generate evidence in some clinical areas where recruitment is a challenge is aggregated n-of-1 trials.

N-of-1 trials are randomized, double-blind, and multiple crossover comparisons of an intervention and a control treatment. Methodologically robust n-of-1 trials provide an objective means of testing the effectiveness of treatments within individual participants. Aggregation of multiple cycle identically conducted n-of-1 trials yield a population estimate of effect, which potentially commensurate with that derived from other RCT designs. Trial participants contribute data for both intervention and control treatments creating matched data sets while using generally smaller sample sizes than conventional RCT trials.

Careful choice of symptoms and medications are required for n-of-1 trials to be feasible. A validated and reliable outcome measure sensitive to change is still required.

This article reviews the utility and limitations of aggregated n-of-1 trials to gather evidence in populations where conducting formal RCTs is difficult because of the low prevalence of the underlying condition or the clinical condition making recruitment and retention difficult. The article examines a proposed palliative care trial as a test case.

Keywords: Palliative care; Hospice care; Randomized controlled trials; N-of-1 trials; Controlled clinical trials; Statistical methods

1. Populations where recruitment and retention is a specific limit in conducting controlled clinical trials

A key problem in palliative care research is recruitment and retention to controlled clinical trials [1]. Additional methodologies need evaluation. Aggregated, multiple crossover, and single patient trials (n-of-1 trials) may provide a mechanism for doing this for some interventions [2]. The "aggregated" n-of-1 trials approach—concept, design, potential benefits, limitations, applications, and a proposed analytical method for the combining—was described in an article in the *Journal of Clinical Epidemiology* in 1997 [3]. Prior and subsequent publications have described experiences with the combined n-of-1 design's implementation (including recruitment, retention, and outcomes comparisons with standard trials), extended/modified analytical methods (including alternative models), cost-effectiveness, and theoretical and actual applications [3−15]. The authors and others have since used this approach in several studies, including insomnia [16],

[1] Authors' contributions statement: Dr. J.N. was the lead author. Profs. G.M., J.H., S.V., and D.C.C. provided important direction and did substantial editing. Prof. P.J. S. contributed the section on statistical analysis and edited the rest of the article. P.G., D.R., and T.S.-J. contributed to the initial concept development and early drafts of the article.

* Corresponding author. Tel.: +61-7-3381-1361; fax: +61-7-3381-1356.

E-mail address: g.mitchell@uq.edu.au (G.K. Mitchell).

0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2010.05.009

What is new?

This article reviews the advantages of aggregated multicycle n-of-1 trials over standard randomized controlled trials (RCTs) and over crossover RCTs that include:

1. A reduction in sample size compared with standard RCTs. A series of such individual trials administered in an identical way can yield an estimate of the population effect essentially comparable to a conventional RCT but requiring smaller numbers of participants. This will allow the accumulation of a broader evidence base in populations like palliative care where providing evidence supporting clinical practice is limited by poor recruitment and retention to rigorous clinical trials.
2. That an individual participant receives a tailored recommendation about the efficacy of a particular intervention for him/her immediately following completion of his/her trial.
3. An ability to use this methodology in previously difficult to study populations or clinical situations.
4. The article also provides new statistical discussion on accounting for within-cycle deterioration in palliative care n-of-1 trials.

people with arthritic pain comparing celecoxib with long-acting paracetamol [17], chronic neuropathic pain treated with gabapentin [18], pediatric oncology [19], and in pediatric rheumatology [20].

Aggregated n-of-1 studies builds on the individual (n-of-1) trial design and crossover trial designs, the details of which have also been described elsewhere (including types of conditions, interventions, measures, and implementation) [6–8,11]. This article reviews the utility of aggregating n-of-1 trials to derive population estimates of efficacy. It uses the palliative care population as an example where n-of-1 trials may offer some methodological advantages over both parallel group and crossover RCTs.

2. Problems associated with RCTs

RCTs are the gold standard by which the quality of evidence for the assessment of new interventions is judged. There are some drawbacks however. Parallel arm and crossover trials have as their goal to measure the "group effect" of some treatment of interest and usually no individual patient results are produced. Another difficulty occasionally encountered when recruiting to parallel arm trials is the concern on the part of some patients about the possibility of drawing the control arm, which in the absence of a current — would be a placebo [21].

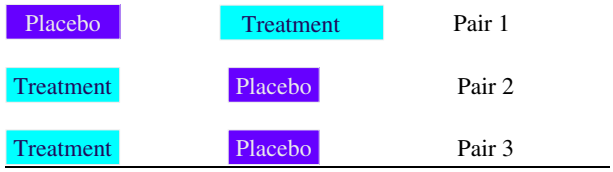

Fig. 1. Typical n-of-1 trial. The order of treatment and placebo are randomly assigned for each cycle.

3. N-of-1 studies as an alternative study design

N-of-1 trials are multicycle, double-blind, and controlled crossover trials using standardized measures of effect (Fig. 1). They were initially designed to test the effectiveness of medicines in individuals. The randomization order for each cycle is independently generated for each participant. At the end of the trial the order is revealed and the participant's objective response within each cycle is compared against the presence or absence of the test treatment. Consistent results in favor of the test treatment over multiple cycles provide the most rigorous evidence possible of efficacy of that treatment in that individual [22]. Individual participant reports are generated to facilitate rational decision making between patient and clinician.

This design was first described in the psychological literature by Sidman in 1960 [23]. Since then, n-of-1 trials have been used in a variety of disciplines. In palliative care, n-of-1 trials have been used to assess the efficacy of oxygen in people with severe dyspnea [24] and in the management of sweating [25].

Patients may have more interest in doing an n-of-1 trial rather than a standard RCT or a crossover trial as it gives them more accurate feedback on their own response. As with any crossover study, the subjects will participate in both the new and existing interventions and not in just one arm, as is the case for parallel arm studies. This might increase the acceptability to potential participants and the clinicians responsible for referring them to the study.

Not all *interventions* are suitable for such studies. N-of-1 trials are less feasible for medications with long half-lives, where a long time is required to reach steady state, or where there is a long period of time before a clinical effect is evident. Essential characteristics of medicines most suitable for the conduct of an n-of-1 trial can be defined (Box 1) [2].

Not all *clinical conditions* are suitable for study using n-of-1 trial designs. For example, progression of the disease or changes in the test symptom during the study may cloud any treatment difference within and between cycles. Furthermore, if an intervention directly modifies the course of the disease, it is unlikely that the intervention will be suited to multicycle crossover studies. This necessitates careful participant selection, relatively stable symptoms, and short cycle times.