Virtual Mentor
American Medical Association Journal of Ethics
January 2013, Volume 15, Number 1: 42-45.

STATE OF THE ART AND SCIENCE

N-of-1 Trials: Individualized Medication Effectiveness Tests

Sunita Vohra, MD, MSc, and Salima Punja, BSc

Evidence-based management of chronic diseases presents a unique set of challenges. Results from randomized controlled trials (RCTs), often considered the "gold standard" of research evidence, are often not well suited to the realities of clinical practice given patient heterogeneity, comorbidities, and the use of multiple concurrent therapies. In fact, RCTs may exclude the majority of patients seen in routine clinical practice [1]. In addition, evidence is lacking on the long-term effectiveness, comparative effectiveness, and additive effectiveness of many therapies for chronic conditions. This lack of relevant evidence can limit a clinician's ability to make evidence-based decisions.

In the absence of relevant research evidence to inform clinical care, routine clinical decisions are often made based on informal "trials of therapy" during which a patient tries various therapies over the course of multiple visits with a physician and continues with the one that seems to help the most. These so-called trials are unblinded, have no control, and involve no formal assessment of effectiveness, making them vulnerable to invalid conclusions about treatment response. N-of-1 trials straddle the divide between RCTs and trials of therapy by providing scientific rigor and an individualized approach to patient care simultaneously.

N-of-1 trials are multiple crossover trials conducted on single individuals [2]. They entail making *a priori* decisions about when and how outcomes will be measured. They have been widely used in psychology and other social sciences. Research on adopting them in clinical medicine was first introduced in 1986 by Gordon Guyatt and David Sackett [3]. Advantages of n-of-1 trials are that they:

1. Offer direct evidence about treatment benefit to a particular patient rather than the population-level outcomes yielded by RCTs, which may or may not be applicable to a specific individual;
2. Allow assessment of long-term therapy in chronic conditions to determine if treatment effectiveness is continuing to be achieved;
3. Can be used to establish comparative and additive treatment effectiveness for patients with various comorbid conditions and using concurrent therapies; and
4. Help reduce ineffective polypharmacy and thus promote patient safety by limiting therapies to those with demonstrated effectiveness.

N-of-1 trials allow for treatment evaluation in understudied populations, such as those with comorbid conditions and rare diseases, and in difficult-to-study fields

such as pediatrics or palliative care. Researchers and clinicians have used n-of-1 trials to evaluate interventions for a range of clinical conditions, including those in the neurological [4], behavioral [5], rheumatologic [6], pulmonary [7], and gastrointestinal [8] domains.

The success of an n-of-1 trial depends largely on the collaboration and commitment of the patient and his or her doctor. Clinicians must explain the process to their patients and collaborate with them to develop individualized outcome measures. Clinicians must also monitor them at regular intervals throughout the trial period, then evaluate and interpret what the results of the trial mean to that individual.

Generally, an n-of-1 trial involves multiple repetitions of 2 treatment options. These options often consist of: (a) active treatment and placebo, (b) low-dose and high-dose active treatment, or (c) active treatment A and active treatment B. The sequence of treatments can be randomized. The number of treatment pairs a patient undergoes does not necessarily have to be predetermined; however, conclusions of treatment effectiveness (or lack thereof) are less subject to bias if the number is specified in advance. Alternatively, treatment pairs can be replicated until the physician and patient are convinced that the treatment is effective, harmful, or has no effect. The length of treatment period depends on the amount of time it takes for a treatment to reach full effect and to cease effect after discontinuation; therefore, interventions with a quick onset and offset are most efficient for n-of-1 evaluation. Responses to treatment must be measured at least once during each period.

Clinicians and patients should determine which symptoms are most relevant prior to commencing the trial. Target outcomes form the basis of disease- and patient-specific questionnaires. A useful questionnaire, known as the Measure Yourself Medical Outcome Profile (MYMOP), allows patients to identify the most troubling symptoms or problems they would like alleviated with the treatment and score how they are feeling daily on a 7-point scale [9]. Analysis of the data can be visual (i.e., presented in a graph) or statistical (such as making comparisons using a paired-t test).

Imagine, for example, the parents of a 12-year-old boy diagnosed with attention deficit/hyperactivity disorder come into his physician's office concerned about his behavior. The patient has been taking 10 mg of methylphenidate daily for 2 years, and the physician suspects that the child may no longer be responsive to this dose or, perhaps, the drug at all. The physician decides the best course of action is to conduct a head-to-head comparison n-of-1 trial (listed above as option 3), in which the patient undergoes randomly alternating weeks of 20 mg/day methylphenidate and 10 mg/day dexamphetamine for 6 weeks. The physician tells the parents that neither he nor they will be aware of which treatment the child will be on each week. The parents and the child discuss and decide that symptoms of hyperactivity and irritability have been the most troublesome over the past few months. The parents are instructed to monitor these target symptoms, rate their severity each day using the MYMOP, and, if the child complains of any side effects throughout the 6-week trial,

to bring him into the office immediately. After the 6 weeks, the physician graphs the results of the MYMOP, explains the results to the parents, and together they decide how to proceed.

Despite the numerous advantages offered by n-of-1 trials and their potential to provide the strongest evidence for individual treatment decisions, it is reasonable to ask whether the use of randomization, blinding, and placebos requires that n-of-1 trials be considered research and therefore necessitates the various processes that this title would imply. An ethical assessment to the use of n-of-1 trials should be based on the trial's purpose: Is the trial intended to be research or clinical care? In research, the goal is to find an answer for a particular condition with the hope of having some generalizable result, and therefore any benefit gained by individual participants is secondary. In clinical care, however, the primary goal is to find an answer about treatment effectiveness for the individual patient. The two activities are fundamentally different in their intent, and therefore require different ethical considerations. In the above example, the n-of-1 trial is being used strictly for clinical reasons; the patient's health and well-being are of primary interest.

N-of-1 trials provide a structured, objective, and evidence-based framework for evaluating treatment effect on an individual. They can provide patients with *optimal* clinical care—care that is personalized and evidence-based—and reduce the potential for bias seen in routine clinical care.

References

1. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365(9453):82-93.
2. Guyatt G, Keller J, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience. *Ann Intern Med.* 1990;112(4):293-299.
3. Guyatt G, Sackett D, Taylor D, Chong J, Roberts R, Pugsley S. Determining optimal therapy. Randomized trials in individual patients. *N Engl J Med*. 1986;314(14):889-892.
4. Forman AC, Vasey PA, Lincoln NB. Effectiveness of an adjustment group for brain injury patients: a pilot evaluation. *Int J Ther Rehabil*. 2006;13(5):223-228.
5. Nikles JN, Mitchell GK, Del Mar CB, Clavarino A, McNairn N. An n-of-1 trial service in clinical practice: Testing the effectiveness of stimulants for attention deficit/hyperactivity disorder. *Pediatrics*. 2006;117(6):2040-2046.
6. Nikles CJ, Yelland M, Glasziou PP, Del Mar C. Do individualized medication effectiveness tests (N-of-1 trials) change clinical decisions about which drugs to use for osteoarthritis and chronic pain? *Am J Ther.* 2005;12(1):92-97.
7. Smith BJ, Appleton SL, Veale AJ, McElroy HJ, Veljkovic D, Saccoia L. Eformoterol n-of-1 trials in chronic obstructive pulmonary disease poorly reversible to salbutamol. *Chron Respir Dis*. 2004;1(2):63-69.

8. Lashner BA, Hanauer SB, Silverstein MD. Testing nicotine gum for ulcerative colitis patients: Experience with single-patient trials. *Dig Dis Sci*.1990;35(7):827-832.
9. Paterson C. Measuring outcome in primary care: a patient-generated measure, MYMOP, compared to the SF-36 health survey. *BMJ*. 1996;312(7037):1016-1020.

Further Reading

Guyatt G, Sackett D, Adachi J, et al. A clinician's guide for conducting randomized trials in individual patients. *CMAJ*. 1988;139(6):497-503.

Guyatt G, Heyting A, Jaeschke R, Keller J, Adachi JD, Roberts RS. N-of-1 randomized trials for investigating new drugs. *Control Clin Trials*. 1990;11(2):88-100.

Larson EB. N-of-1 trials: A technique for improving medical therapeutics. *West J Med*. 1990;152(1):52-56.

Sunita Vohra, MD, MSc, a pediatrician and clinician scientist with a master's degree in clinical epidemiology and fellowship training in clinical pharmacology, is the leader of a Canadian Institutes of Health Research project investigating n-of-1 trials. A professor in the Faculty of Medicine and School of Public Health at the University of Alberta in Edmonton, Dr. Vohra is the founding director of Canada's first academic pediatric integrative medicine program, the Complementary and Alternative Research and Education (CARE) program at the Stollery Children's Hospital. Dr. Vohra is also the program director for Canada's first fellowship program in pediatric integrative medicine and the founding director of the Canadian Pediatric CAM Network (PedCAM).

Salima Punja, BSc, is a PhD candidate in the Department of Medicine at the University of Alberta in Edmonton.