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# Clinician-trialist rounds: 4. Why not do an N-of-1 RCT?

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*Are you frustrated in your attempts to help individual patients with chronic illnesses whose symptoms (despite high compliance with your evidence-based prescriptions) remain poorly controlled with their current arrays of medications? Do you wish there was some way to reliably sort out which drugs and doses are helping them, which are useless or even making them worse, and which additional drugs might help? And if you asked around, would you find that your clinical colleagues were facing similar dilemmas with individual patients in their practices? Would you like to be able to solve your individual patients' problems, and help your colleagues solve theirs? Finally, wouldn't it put the frosting on the cake if, by doing so, you generated a higher profile at your institution, and found your clinician-trialist ways of thinking become more widely accepted and appreciated by your clinical colleagues?*

The foregoing scenario isn't made up. It accurately describes my situation as I completed my second residency in internal medicine (switching from nephrologist to hospitalist) and began seeing patients in my new referral clinic in 1985. Even when my new diagnoses were confirmed and I was convinced that my patients were taking their new medicines, I frequently failed to relieve – or even improve – the disabling symptoms of their chronic illnesses; sometimes I even made them worse. Often there were no RCTs to guide their therapy; other times they presented as 'non-responders' to treatments that had been validated in RCTs. Worst of all, even when a patient improved during one of my uncontrolled 'therapeutic trials' of starting a new treatment or stopping an old one, I couldn't tell whether their illness had simply improved on its own, whether their symptoms had 'regressed toward the mean,' whether it was simply a placebo effect, whether I was minimizing their on-going symptoms through hope, or whether they were minimizing them through charity. I simply had no way to objectively determine whether my uncontrolled 'therapeutic trials' were really helping individual patients in my practice.

When I described my dilemma to a psychologist-statistician colleague, she pointed me to the psychology literature on 'single-subject' experimental designs where the units of randomization were times, not persons [1]. Fascinated by this potential solution to my therapeutic dilemmas, I presented what I'd learned at a 'Continuing Education Round' in my other department at McMaster, Clinical Epidemiology and Biostatistics. A brilliant mentee of mine, Gordon Guyatt, shared my enthusiasm and we soon embarked on the following N-of-1 RCT:

> A 65-year-old man had uncontrolled asthma despite the 'best' regimen of that era: albuterol (2 puffs qid), prednisone (25 and 10 mg on alternate days), oral theophylline (300 mg tid), and ipratropium bromide (2 puffs qid). He suffered severe bouts of shortness of breath that awakened him at night, interfered with bathing and getting dressed, and occasionally appeared suddenly at rest. Neither he nor his physician was convinced that the latter two drugs were helping him (both suspected that the theophylline was helping, but that the ipratropium wasn't). By mutual agreement, and in collaboration with statistician-colleagues, a double-blind N-of-1 trial of theophylline was set up, designed to determine its effect on his treatment targets of sleep disturbance, shortness of breath, and need for his rescue inhaler, over treatment periods lasting 10 days. These 10-day periods were paired and then randomized to provide him either active theophylline or an

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**Table 1** Guidelines for performing an N-of-1 RCT

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| Is an N-of-1 RCT *really indicated* for your patient? |
| (1) Is the effectiveness of the treatment really in doubt? |
| (2) Will the treatment, if effective, be long-term? |
| (3) Is your patient eager to collaborate in designing and carrying out an N-of-1 RCT? |
| Is an N-of-1 RCT *feasible in your patient*? |
| (4) Does the treatment have a rapid onset? |
| (5) Does the treatment stop acting soon after it is discontinued? |
| (6) Is an optimal duration for a treatment period feasible? |
| (7) Can outcomes that are relevant and important to your patient be measured? |
| (8) Can sensible criteria for stopping the trial be established? |
| (9) Is an unblinded run-in period necessary? |
| Is this N-of-1 RCT *feasible in your practice setting*? |
| (10) Is there a pharmacist who could help you? |
| (11) Is help available for interpreting the data? |
| Is this N-of-1 RCT *ethical*? |
| (12) Is there free, informed consent? |
| (13) Can your patient withdraw from the trial without loss of care? |
| (14) Will the same degree of confidentiality apply as in other clinical situations? |

identical-appearing placebo during the first period, with the alternative treatment during the second period of each pair. At the end of each period, he reported his symptom severity on a 7-point Likert scale; the higher the score, the better he felt.

After 2 pairs of treatment periods it was clear to both of them that he was very much better during some periods than others, and they stopped the trial. Breaking the code revealed that their earlier hunches were wrong; he was much better when he was NOT taking theophylline. They then collaborated in a second N-of-1 trial, this time of the ipratropium bromide inhaler that neither he nor his physician thought was helping. He again quit after 2 pairs of treatment periods because he felt so much better during 2 of them. Breaking the second code revealed that he and his clinician were wrong again; he was much better when he WAS taking ipratropium. Six months later he was much less symptomatic, no longer taking theophylline, but taking ipratropium (and albuterol), and with his prednisone dose lowered to 20 mg every other day.

The dramatic, unexpected results from this pair of N-of-1 RCTs generated considerable interest among our clinical colleagues, and by the time that we reported their results in the *New England Journal of Medicine* [2], we had set up an N-of-1 RCT Service for our town. Gordon Guyatt took command of the service, and with our research assistant and statistical collaborators, we helped clinical colleagues and their patients sort out patient-important treatment targets, generate forms for reporting them, and set period durations. One of our hospital pharmacies packaged active treatments and placebos in identical appearing opaque capsules. Patients and clinicians repeated blinded pairs of treatment periods until they became convinced that there was either a clear difference between them or none at all, at which time we broke the codes and helped them interpret the results. Over our first 50 N-of-1 RCTs, we generated the guidelines in Table 1 [3]. Taking stock after 3 years, 39% of completed trials led to changing prior treatment plans, and 29% led to discontinuing prior 'permanent' treatments [4].

Statistical analyses of N-of-1 RCTs can range all the way from 'eye-ball' tests applied by the patient–clinician collaborators to the Bayesian analyses that much more closely match the way we think as clinicians. If your design permits patients who find their treatment in a given period intolerable to skip the rest of it and start immediately on the next period, the total time spent in the two treatments provides a continuous measure of preference. I never began an N-of-1 (or any other!) RCT without a statistician co-investigator, and I urge you to do the same.

Since we began, thousands of N-of-1 RCTs have been carried out by other clinicians and patients on treatments ranging from stimulants for children with ADHD to gabapentin for chronic neuropathic pain [5]. Along the way, other and extended uses for them have been reported. For example, and because a series of N-of-1 RCTs of the same treatment for the same symptoms of the same condition sums to a conventional multiple crossover trial, some clinicians have – without the fuss and muss of a formal, full-scale RCT – gradually

accumulated, over months or years, sufficient identical N-of-1 RCTs to be able to draw more generalizable conclusions about the efficacy of that treatment [6]. Even senior members of our Society are encouraging us to incorporate N-of-1 RCTs into clinical practice [7].

And some teams of N-of-1 trialists have employed them to ask broader health care questions. For examples, Jeff Mahon's team in London, Ontario reckoned that his series of 34 N-of-1 RCTs of theophylline didn't do better than routine care for patients with irreversible chronic airflow limitation back in 1999 [8], but in 2010, Paul Scuffham's team in Brisbane, Australia reported that their series of 91 N-of-1 RCTs in osteoarthritis, neuropathic pain, and ADHD wound up saving money (partly through taking fewer expensive drugs but mostly through requesting fewer subsequent consultations) [9]. And I can't resist reporting that Deborah Zucker and some Boston colleagues recently asked whether dialysis centers and N-of-1 RCTs aren't 'made for each other' [10].

But for now, my suggestion is that you team up with your statistical colleague(s) and have a go by collaborating with individual patients in using this powerful strategy for determining the best treatments for their worst symptoms.

You'd also better check with any friends you have at your REB before you begin, to see whether they regard clinicians collaborating with patients in order to identify their best treatments as mainstream high-quality care (and none of their business) or as an ethically risky undertaking requiring their prior permission*.

By the way, an increasing number of journals are receptive to N-of-1 RCT submissions, either as case-reports or as more methodologically-oriented articles. In recognition of the importance of their publication, the CONSORT gang are developing guides for reporting them; stay tuned.

And as usual, this Clinician-Trialist Round isn't over yet. Rounders are invited to write letters to the journal (with an email copy to me at sackett@bmts.com) about their own experiences with N-of-1 RCTs, plus any suggestions or questions they have about them. I'll summarize this correspondence and report back to the group. Again as usual, my thanks to all the patients, students, and colleagues who have helped me understand and write about N-of-1 RCTs.

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*''The clinician who is convinced that a certain treatment works will almost never find an ethicist in his path, whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them.'' [11]