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The Potential Role Of Single-Patient Randomized Controlled Trials (N-Of-1 RCTs) In Clinical Practice

When deciding how patients, as a group, ought to be treated, randomized controlled trials (RCTs) are usually required to establish valid evidence of drug efficacy. As shown by Nuovo and his colleagues in this issue of the *Journal*,[1] however, when deciding on optimal treatment for a given patient, the clinician often cannot rely on the results of such studies. For example, no guidance can be obtained about a treatment when no RCT has been conducted on it. Further, even when a relevant RCT has generated a definite answer, there are two reasons why its result might not apply to an individual patient. First, if the patient does not meet the study's eligibility criteria, extrapolation can be inappropriate; second, even in positive trials not every eligible patient benefits.

Under these circumstances, clinicians typically choose to conduct the time-honored "trial of therapy" in which the patient is given a treatment and the subsequent clinical course determines whether (or which) treatment is judged effective and endorsed. Nevertheless, many elements of these conventional therapeutic trials can mislead the clinicians who conduct them into drawing false-positive conclusions about efficacy. Chief among these conclusions are the placebo effect, the natural history of the illness (which, if self-limited, would have improved if left untreated), the understandably positive expectations of the patient and the clinician about the treatment effect, and the desire of the patient and the clinician not to disappoint one another.[2] Fortunately, such pitfalls can be avoided or minimized if neither the patient nor the clinician knows when active treatment (or which type of treatment) is being administered, and that is why random allocation and double-blinding are key elements of the RCT.

These methodological safeguards of the large-scale RCT now have been applied to the trial of therapy in individual patients. Borrowing from single subject or n-of-1 RCTs developed in psychological research, their therapeutic usefulness (determining the most suitable treatment for a given patient) has repeatedly been demonstrated in medical practice.

In the classical n-of-1 RCT, the patient undergoes several pairs of treatment periods. Each pair includes one period on active or experimental medication and one period on placebo or an alternative drug. The order of the treatment periods is determined by random allocation,[2,3] and both patient and clinician are kept blind. Other n-of-1 RCTs use unconstrained randomization of four or six (or more) planned treatment periods,[4] and phase 2 of the trial reported in this issue by Nuovo and his colleagues is of this sort. Whichever allocation strategy is used, treatment targets (key symptoms, physical signs, or laboratory measurements) are recorded throughout the trial. When the code is broken, treatment effects can be examined by observing the nu-

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meric data or a graph of it or by formal statistical analysis.

The main advantage of using an n-of-1 RCT is that the results of the trial are directly applicable to the patient studied. N-of-1 trials therefore overcome the problems of large-scale RCTs, which average, rather than emphasize, individual benefits and risks of therapy and thus can make it difficult for the clinician to decide about the usefulness of a given drug for a particular patient. Using the n-of-1 technique, the patient and clinician can clarify several important questions: Is the active drug superior to the placebo? Are two medications (or different doses of the same medication) comparable? Which therapy positively (or adversely) influences quality of life?

The limitations of n-of-1 trials arise from the prerequisites for their execution. First, before planning an n-of-1 RCT, both the patient and physician must agree that the effectiveness of the treatment in question is in doubt. This occurs when one of the following conditions prevail:

1. Neither the clinician nor the patient is confident that a treatment is really providing benefit.
2. The clinician is uncertain whether a treatment that has not yet been started will work in a particular patient.
3. The patient insists on taking a treatment that the clinician thinks is useless or potentially harmful.
4. The patient is experiencing symptoms that the clinician and patient suspect represent medication side effects, but neither is certain.
5. Neither the clinician nor the patient is confident of the optimal dose of a medication.

Moreover, both patient and clinician must agree that finding the answer to this therapeutic question is important enough to be worth the extra time, effort, and cost associated with conducting such a trial.

Second, the disease process must have certain characteristics: it must be relatively chronic (self-limiting disease is unsuitable for such a study) and stable (otherwise the natural history of the illness can be such that changes in the severity of the symptoms will swamp the effect of the intervention). Third, treatments with rapid onset and termination of action are most suitable for n-of-1 RCTs. If the treatment continues to act long after it is stopped, the necessarily prolonged washout periods can compromise the feasibility of the trial. Of course, treatments that can cure the underlying condition are not suitable for n-of-1 RCTs.

The fourth prerequisite for an n-of-1 study is the availability of both clinically relevant outcome measures and the means for analyzing and interpreting them. Fifth, clinicians planning an n-of-1 RCT must gain the collaboration of a pharmacy service to prepare the randomization schedule (a simple coin toss can serve), medications, and placeboes. Finally, the trial must fulfill several ethical requirements: patients should be fully informed about the nature of the study, including the use of placeboes; follow-up should be close enough to prevent any deleterious consequences of the treatment or its withdrawal; in some jurisdictions, written consent would be indicated.

Since our first n-of-1 RCT several years ago, we have learned much about their planning, conduct, and interpretation. Some elements of their execution, however, remain controversial. For example, some researchers prefer unconstrained randomization of all treatment periods, rather than randomization within pairs, on the grounds of the greater statistical power that results. Others point out that unconstrained randomization will occasionally result in extreme allocation in which, for instance, six treatment periods might be ordered so that the first three are all placebo, and the last three all active treatment; if the underlying disease is progressively improving or worsening, false-positive or false-negative conclusions about efficacy will result, despite adherence to rigorous n-of-1 methods.

Similarly, debate continues over the most appropriate means for interpreting n-of-1 RCTs. Simple visual inspection of the results, or nonparametric tests (such as the Kruskal-Wallis one-way analysis of variance used by Nuovo, et al.) are standard methods that are generally accepted. The use of parametric tests, such as the Student t-test, is more controversial. Although they offer increased power (because they consider not only the direction, but also the degree, of the effects of treatment), the day-to-day entries of key symptoms are not independent (the

patient who felt poorly yesterday is more likely to feel poorly today), which causes some methodologists to advocate caution when using them.

How useful and practical are n-of-1 RCTs in clinical practice? In many situations, physicians will continue to rely on open, unmasked, before-after studies — the trial of therapy. Although this traditional approach is fraught with the limitations that we have outlined, it has one major advantage: it is easy. On the other hand, n-of-1 RCTs require more time and effort from both clinician and patient. Are they worth it? Our experiences in more than 70 n-of-1 RCTs, as well as that of others elsewhere,[5] suggest that they are. Treatment frequently changes,[3] and both patients and physicians report increasing confidence in the ultimate management decisions.[3,6] Even though conducting n-of-1 RCTs requires additional time and effort, their execution is feasible in day-to-day practice, and guidelines for conducting them are available.[7]

The n-of-1 RCT provides physicians and their patients with a set of tools that can advance the science of the art of medicine and result in both improved and more consensual clinical care. It will be interesting for readers of the *Journal* to follow the extent to which the n-of-1 approach is integrated into family practice in the future. Studies like that of Nuovo, et al. suggest that this approach has much to offer primary care physicians and their patients.

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Teamwork And Informed Consent

The Cotsonas article[1] in this issue is a welcome addition to the literature on informed consent in primary care. It emphasizes that the essence of informed consent is meaningful communication rather than formalistic disclosure. It acknowledges that the tort law can send misleading messages to physicians (especially family physicians) about what sort of consent process is optimal. And it points out that ethical obligations to patients can suggest broader and more proactive responsibilities for education and consent than do minimal legal requirements.

Cotsonas offers many items of illuminating advice for family physicians. I wish here to draw out for further elaboration a theme that is implicit or explicit in much of her discussion — the idea of optimal informed consent as teamwork. I will ask who should be a member of this "team" and what their respective roles ought to be.

Cotsonas explicitly notes the importance of good communication and collaboration between the family physician and the specialist performing the procedure or consultation. Implicit in her analysis is the role of the patient as an essential team member — in effect, the most efficient and critical "messenger" between primary

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