

Are Individual Patient Trials (n-of-1 Trials) in Rheumatology Worth the Extra Effort?



What are individual patient (n-of-1) trials?

Individual patient trials inject some methodological rigor into usual clinical decision-making. They mimic usual clinical practice in their ability to allow flexibility of dosing and followup, as well as individual tailoring of outcome measures. In usual clinical practice, patients present with abnormal signs or symptoms, and after assessment the health-care provider recommends a course of action. Therapy is considered efficacious if benefits outweigh side effects, patients appear improved over baseline, and both patients and treaters agree that the therapy ought to be continued. This “open assessment” is prone to numerous biases^{1,2}, all of which tend to exaggerate the benefits of therapy, and thereby prolong potentially ineffective or harmful therapy. Individual patient trials (n-of-1 trials) differ from usual clinical practice by offering some protection from these numerous biases: such trials can be randomized, they can have treaters and patients blinded to treatment and use uniform outcome measures that are both qualitatively and statistically evaluated. In the n-of-1 trial, the unit of randomization is the treatment sequence for an individual patient, in contrast to randomized, parallel design trials, where the individual is randomized to one group or another. A single treatment cycle includes an exposure to the innovator therapy and the comparator therapy. Comparators could be placebos or another competing therapy. This treatment cycle is repeated as often as necessary to determine a clear winner: a preference for innovator therapy or for standard therapy, or no preference. Figure 1 provides a schema of the n-of-1 design. Randomization is usually performed at the beginning of each new treatment cycle, but could be at each point where treatment was to change³. Table 1 shows the n-of-1 trial in contrast to usual patient care, the cross-over trial, and the parallel, randomized trial. In brief, the n-of-1 trial answers the question: “Is this therapy helpful in this individual patient?” while the parallel, randomized trial answers the question: “In a defined population, is treatment x better than treatment y?”

This is not an absolute, however, as responder criteria, such as the American College of Rheumatology response criteria for rheumatoid arthritis⁴ do identify response at an individual level in large, parallel randomized trials, while advances in the analysis of multiple n-of-1 trials allow estimates of population treatment responses⁵. Importantly, only a crossover design allows patients to judge which treatment they prefer.

When should n-of-1 trials be considered?

There should be legitimate doubt about whether therapy is effective, or whether it is responsible for the patient’s side effects^{1,2,6,7}. The condition should be chronic and mostly stable. It is optimal if treatment results in a rapid onset of effect that disappears quickly with treatment withdrawal. While this latter feature is not essential, delayed onset or persistent treatment effects will require a longer treatment period or a longer washout between cycles, with a longer experimental time overall. Guidelines for the conduct of n-of-1 patient trials were published in 1986¹, and followup articles document the feasibility of their conduct in clinical practice^{2,6}. These articles^{1,2,6} and some standard textbooks more fully discuss randomization, outcome measures, and statistical analysis^{3,8}.

What rheumatic conditions might be amenable to the n-of-1 design?

Common, stable, quickly reversible symptoms and signs in rheumatology practice could readily be studied using the n-of-1 approach. The design can assess treatment response^{1,2,6} and adverse effects of disease or medications⁷. Such entities might include pain, fatigue, dyspepsia, nausea, function (i.e., walking distance), Raynaud’s phenomenon, synovitis, range of motion or joint/muscle tenderness to palpation, or rash, to name a few. This design could also be used to understand clinically meaningful changes following therapy, as well as assess the time to reach these levels, in many commonly used metrics, such as the WOMAC, Health

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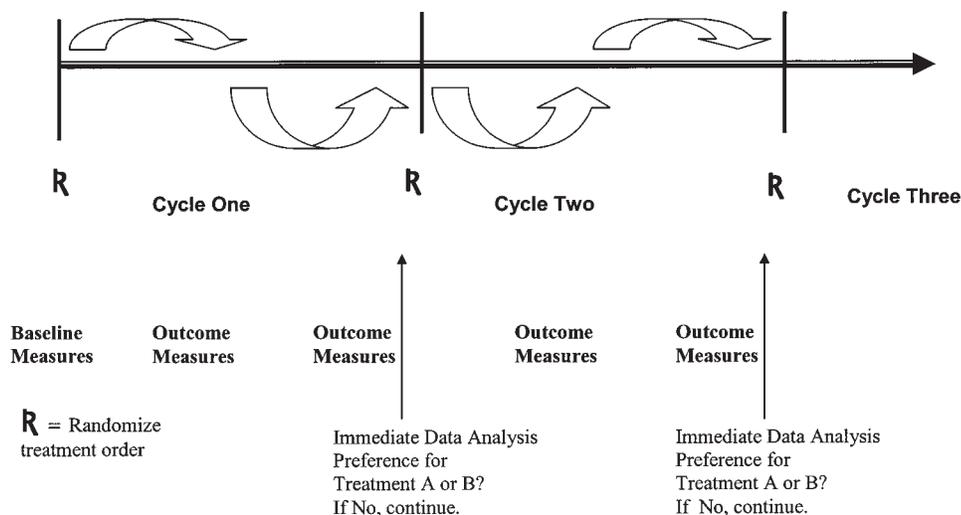


Figure 1. Schema for individual (n-of-1) trial design.

Assessment Questionnaire, Fibromyalgia Impact Questionnaire, joint counts, pain scales, etc.

How have n-of-1 trials been used in rheumatology?

Given the chronic nature of most rheumatic conditions, and the methodological rigor of n-of-1 trials, one might expect their widespread use in rheumatology. A Medline search from August 2003 back to 1966 found only 2 n-of-1 trials in rheumatology. Jaeschke and colleagues examined the role of amitriptyline in fibromyalgia⁹, while March, *et al*¹⁰ examined the preference for paracetamol or diclofenac in patients with osteoarthritis (OA). Amitriptyline for fibromyalgia was of uncertain benefit, as 2 large parallel randomized trials suggested 25 mg a day was no better than placebo, and did not identify predictors or response^{11,12}. Yet Jaeschke's study showed that doses as low as 10 mg a day could be effective in some patients, and that this improvement was apparent at 2 weeks⁹. There was also drug discontinuation in 8/23 (35%) patients who previously considered its longterm use. Thus amitriptyline is effective for some people and not for others, and this is often contrary to their pretrial opinions.

In the March study, OA patients received paracetamol 1 g BID or diclofenac 50 mg BID. Twenty of 25 who began the double-blinded, randomized n-of-1 trials had evaluable data. Eight of 20 did not express a preference, with both agents helpful: 5 preferred diclofenac, and another 5 who preferred diclofenac reported both treatments to be insufficient for their pain. A recent randomized parallel controlled trial raised controversy, when it found acetaminophen 1 g QID to be no more effective than placebo in populations of OA patients, while also declaring diclofenac 75 mg BID to be superior to placebo¹³. Pincus's crossover trial of diclofenac 75 mg + misoprostol 200 µg BID in OA showed that it was preferred by 57% (99/174), with 20% expressing preference for acetaminophen 1 g QID¹⁴. Those with lower

pain scores were less likely to express a preference for nonsteroidal antiinflammatory drugs (NSAID). Thus the parallel randomized controlled trial¹³ raises concerns about acetaminophen's efficacy in the population of OA patients, whereas Pincus's¹⁴ crossover trial supports March's findings that some people indeed prefer it.

What did we learn from the Pope trial?

The trial reported by Pope, *et al* in this issue of *The Journal* has several unique features¹⁵. The authors performed a controlled trial that randomized people to usual medical care or to n-of-1 care to judge whether n-of-1 care was superior. The assessment of "superiority" was robust and included measures of efficacy and side effects, as well as direct and indirect costs. Twenty-four of the 51 patients with OA were randomized to the n-of-1 care, which was methodologically rigorous and included randomization of treatment order and double blinding of study drug. The goal of the n-of-1 trial arm was to determine whether diclofenac + misoprostol was preferred over placebo, in patients who were not sure whether NSAID were helpful. Outcomes were assessed at 3 and 6 months. What was found? At 6 months, an equal proportion were using NSAID in both groups (71% in n-of-1 vs 67% usual care), in spite of an imbalance at baseline, with more NSAID users in the usual clinical care group. All outcome measures favored better health in the n-of-1 group, including pain scores, Medical Outcome Study SF-36, patient global scores, etc. The difference in Health Assessment Questionnaire scores between groups was clinically meaningful¹⁶. There were more side effects in the n-of-1 group, predictably related to the use of misoprostol. There were also higher costs for the n-of-1 group, from US\$60 to \$160 more per patient. This was related to higher costs of drugs, nursing and physician time, and travel costs. However, we do not know if physicians or patients were

Table 1. The n-of-1 trial in contrast to other study models.

Trial Design/ Trial Feature	Parallel Randomized Trial	Crossover Trial	N-of-1 Individual Patient Trial	Usual Patient Care
Main Focus	Is this therapy more effective than the comparator in a population of patients?	Is one therapy more effective and preferred over the other, in a population?	Is therapy effective for this patient? Is one therapy more effective in this patient?	Is this therapy effective for this patient?
Population	Strict inclusion and exclusion. Not always generalizable.	Strict inclusion and exclusion. Not always generalizable.	Very flexible. Represents usual clinic patients.	Usual clinic patients.
Randomization	Yes. Assignment to treatment group is random.	Yes. Treatment order random. Subjects get both treatments.	Yes. Treatment order random. Get both treatments.	No. Treatment not random.
Treatment	Doses specified in advance, not usually adjusted through trial.	Doses specified in advance, not usually adjusted during trial.	Can vary dose through trial, based on ongoing experience.	Dose adjustments common.
Outcome measures	Disease-specific and generic instruments. Patient and physician global scores.	Disease-specific and generic standard instruments. Treatment preferences.	Patient-specific 7-item instrument, patient global. Standard health indices may also be used.	Non-standard patient and physician global assessments the norm.
Blinded outcome assessment	Yes.	Yes.	Yes.	No.
Followup duration	Specified in advance.	Specified in advance.	Variable, depending on whether preference can be determined.	Variable.
Statistical analysis	Prespecified sample size. Emphasis on group differences.	Prespecified sample size. Group differences as well as treatment preference. Efficiency with paired design.	Single patient qualitative and quantitative tests of preference (plots and t tests) can be used to judge population effects.	No formal analyses. Qualitative assessment of effects.
Costs	\$\$\$\$\$	\$\$\$	\$	\$
Advantages	Most common design, with well-developed methodologic standards. Usual design for approval.	Get patient preference for comparator products.	Can judge if therapy is effective, or preferred over others. Methodologically more rigorous than usual care. Flexibility in dose and followup to effect can inform future trials.	Standard, familiar method of assessing clinical effectiveness.
Disadvantages	May not generalize to other populations or other doses. May not know optimal dose or followup in advance, and trial can be inefficient. Requires large sample sizes.	Dropouts can negate value of treatment preferences. Carry-over effects can influence second phase of trial.	Not common. Not readily understood. Takes more time and is more expensive than usual care.	Can overestimate treatment efficacy. Weak design to judge effect in populations. Outcomes may not be recorded or extractable.

more satisfied or confident with their treatment plans in the n-of-1 group, as this was unmeasured.

While the n-of-1 strategy is arguably less subject to bias, in this OA model, it does not provide convincingly superior outcomes, and costs more. Further study is needed to firmly establish the value, and need, of the n-of-1 approach to patient care.

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