N-of-1 trials & their use in neuromodulation

N-of-1 trials are a:	Carefully consider:
- personalised method for investigating treatment effects in an individual(s).	- any generalisation beyond the specific individual. - the double-blinding protocol. - carry-over effects and wash-in periods for pharmaceutical interventions.

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An older friend once said that one really starts to feel their age when you know your good knee from your bad knee. Only problem was, years of basketball had left me with *exactly* 0 good knees, and so I had much to ponder when consulting my doctor about the inflammatory pain in my legs. At this point, knee pain is not a new phenomena. There are many different treatments, for which some treatments work better for some individuals, and so how to choose amongst the options was my particular problem. Here, the N-of-1 trial has much to offer.

The N-of-1 trial folds into the philosophy of personalised medicine and takes an experimentation framework to identifying treatment efficacy for an individual patient. For example, suppose we use an N-of-1 trial to determine the efficacy of non-steroid anti-inflammatory drugs (NSAID's) for my knees. A pharmacist creates a set of placebo tablets, indistinguishable from the NSAIDs, and a regime that alternates placebo and treatment. Over weeks and blind to the drug regime, a patient would provide repeated outcome data to determine the efficacy directly, and experimentally. In this primer, we explore how the N-of-1 trial places an individual's outcomes centre stage, and highlight the design and statistical considerations in both clinical and research contexts.

1 What is a N-of-1 trial?

The N-of-1 trial is a systematic method where a patient receives repeated cycles of treatment and placebo interventions, called *crossovers* (see Figure 1). The N-of-1 trial establishes the efficacy of a treatment by administering multiple crossovers (at least two) and comparing patient outcomes during each phase over time. The benefit of this individualised method is that each patient serves as their own control, and so treatment decisions can be tailored to each patient's unique outcomes. N-of-1 trials have been used to investigate a range of treatments for chronic disorders such as osteoarthitis and cystic fibrosis, and are classified as the highest level of evidence for assessing treatment benefits, alongside systematic reviews of RCT's, by the Oxford Centre for Evidence-Based Medicine.

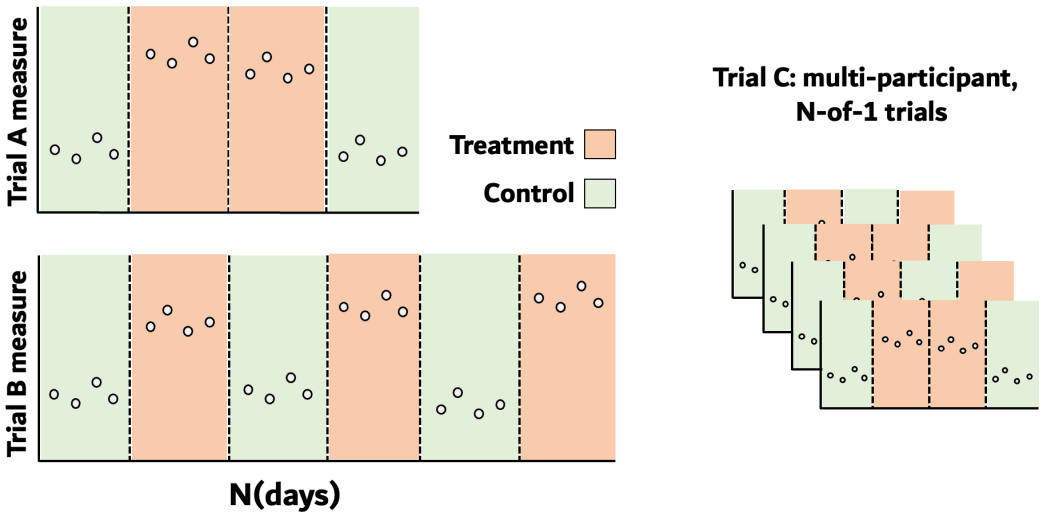

Figure 1: Hypothetical data of different N-of-1 trials. Across each plot, the blinded intervention, either treatment or control, and measurements are taken on a daily basis. For clinical examples, trial A and B show N-of-1 trial sequences for individual patients. Trial A shows 2 crossovers between treatment and control phases in the ordering ABBA. Trial B shows 3 crossovers in the ordering ABABAB. Trial C demonstrates how N-of-1 trials can be scaled in research settings to multiple participants across counter-balanced orderings in order to make inferences beyond the individual patient.

2 For whom is it for?

N-of-1 trials are well-suited for patients with stable symptoms, such as those with chronic disorders. The personalised focus makes N-of-1 trials an option for individuals that are under-served by randomised control trials (RCT's). This may include individuals, or a group of individuals, that are typically excluded from the population pool due to comorbidities, that meaningfully differ from the tested RCT population, or cases where a low prevalence rate means RCT's are not feasible. More broadly, advocates of N-of-1 trials envisioned that the design would be beneficial in drug treatments and development. Prior to large-scale testing, N-of-1 trials could serve as an alternative for identifying the range of treatment effects associated with specific patient profiles.

3 Key features of an N-of-1 trial

Across clinical and research settings, there are several key features common to an N-of-1 trial. N-of-1 trials must be double-blinded such that both patient and clinician are unaware of which phase is being administered. The personalised nature of the testing makes double-blinding essential.

Within the trial, a crossover is typically a single paired alternation between the treatment and placebo phases, and each trial should contain multiple crossovers. For an individual patient, the sequence of crossover pairings can be randomised *a priori* or counterbalanced (e.g., ABBA as in Trial A of Figure 1) to take into consideration the passage of time. In a research setting where multiple N-of-1 trials are run simultaneously, the sequences across all participants should be counterbalanced to avoid drawing inferences that are dependent upon an idiosyncratic crossover sequence.

Importantly, the trial should be designed to avoid carry-over effects between the data points. Consideration of the 'wash-in' period is necessary to avoid contamination between time points.

This might be particularly relevant for pharmacological interventions that take time to take effect. Conversely, it may also be necessary to consider a 'wash-out' period after an intervention is administered to protect against intervention carryover into control phases. These temporal precautions are necessary to ensure that data from each phase do not cross-contaminate and dilute the measurement of the intervention.

3.1 Considerations for statistical analysis

N-of-1 trials have been conducted in both clinical and research settings and the choice of statistical analysis depends on the goal of the trial. If the goal is to determine the best treatment for a specific individual, as in the case of the family doctor and a patient, then statistical analysis is not needed at all. The patient and the doctor can decide whether the effects of the treatment for that *individual* were meaningful. Written reports of N-of-1 trials can then be interpreted like a case study, and the data may involve visually interpreting trends or comparing simple means.

To extrapolate beyond individual cases to a population, however, both the analyses and the trial should be carefully constructed to ensure that the inferences are statistically warranted.

3.2 Data collection & choice of statistical model

A core issue for N-of-1 trials is the large variability of outcomes that an individual might experience. This has implications for data collection in both research and clinical contexts. For the clinical context, the patient and clinician might decide to measure multiple outcomes over the course of the trial to capture the personally important features of the treatment. In a research context where multiple participants complete trials in parallel, it is important that the choice of outcome(s) is consistent across all individuals. For data presentation, these data are often shown graphically across the phases as in Figure 1 and, where multiple individuals participated, care should be taken in aggregating outcome data across subjects but, in particular, over time.

Simple statistical tests, such as signed difference or paired samples t-tests, may collapse data across the phases (and so, time) and compare mean outcomes values. However, one should treat these statistics with caution, because of the strong degree of auto-correlation between each data point, i.e., data is collected from each person sequentially and so the data violates the assumption of independence. Ideally, the statistical model should account for auto-correlation, such as in time-series analyses, or explicitly incorporate the passage of time into the analysis.

4 Further reading

Below, are three resources that discuss N-of-1 trials in greater detail. These include:

- Recent DBS neuromodulation example using the n-of-1 trial design (Free PMC article)
  Mendonça, M., Cotovio, G., Barbosa, R., Grunho, M., & Oliveira-Maia, A. J. (2022). An Argument in Favor of Deep Brain Stimulation for Uncommon Movement Disorders: The Case for N-of-1 Trials in Holmes Tremor. *Frontiers in Human Neuroscience*, 16, 379. Click to access URL
- Review of N-of-1 trials in the medical literature:
  Gabler, N. B., Duan, N., Vohra, S., & Kravitz, R. L. (2011). N-of-1 trials in the medical literature: a systematic review. *Medical care*, 761-768. Click to access URL
- Special issue series on N-of-1 trials in the Journal of Clinical Epidemiology.
  Knottnerus, J. S., & Tugwell, P. (Eds.). (2016). Series: N of 1 Trials to Enhance Patient Outcomes [Special Issue], *Journal of Clinical Epidemiology*, 76, Click to access URL