JIM
JIM 2025; 2 (4): e1046
DOI: 10.61012_202511_1046
Category: *Editorial*

ONE SWALLOW MAKES A SUMMER: CLINICAL TRIALS THAT ENROLL ONLY ONE PARTICIPANT (N-OF-1 TRIALS)

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Keywords: N-of-1 trial, Clinical trials, Rare diseases, Chronic diseases.

"One swallow does not make a summer, neither does one fine day; similarly, one day or brief time of happiness does not make a person entirely happy."

Aristotle
Nicomachean Ethics, Book I, 1098a

Randomized controlled trials (RCTs) are widely acknowledged as the methodological gold standard in clinical research for demonstrating the efficacy and safety of treatments in large populations, due to their ability to minimize bias and establish robust causal relationships. However, while they remain essential, this approach is not always applicable or sufficient to answer all clinical questions – particularly when attention shifts from the general population to the individual patient. In such contexts, where treatment responses may vary considerably between individuals due to genetic, environmental or lifestyle factors, the relevance of n-of-1 studies becomes evident.

These studies apply the experimental logic of clinical trials to a single participant, offering a rigorous, scientifically grounded method for evaluating the effectiveness of highly personalized therapeutic interventions. They make it possible to determine whether a specific treatment is effective for a specific patient, thus providing valuable data for precision medicine and individualized care.

UNDERSTANDING THE N-OF-1 TRIAL

In clinical research methodology, an n-of-1 trial – where "n" refers to the number of participants, in this case, only one – is defined as a rigorously designed clinical study aimed at assessing the comparative effectiveness of different therapeutic interventions in a single patient[1].

This approach is methodologically sophisticated because the patient serves as both the treatment and the *control group*. The study design typically involves a structured and systematic alternation between treatment conditions (for example, an active drug *vs.* a placebo, or two different drugs). These alternations follow *predefined*, *randomized*, and *repeated sequences* – often using a *crossover* model – designed to eliminate bias related to the order of administration. A key element for the study's validity is the inclusion of washout periods (treatment suspension intervals), which help ensure that the residual effects of one intervention do not influence the assessment of the next[1].

The goal is not to generate results generalizable to a broader population, as in conventional randomized clinical trials (RCTs), but to identify the most effective treatment for that specific individual. In this sense, n-of-1 trials are powerful and pragmatic tools to advance controlled clinical research and support clinical decision-making in the era of precision medicine and therapy personalization.

The methodology of n-of-1 trials was first formalized in the second half of the 1980s by a group of researchers at McMaster University in Hamilton, Ontario, Canada, led by Gordon Guyatt, a prominent figure in the field of evidence-based medicine[2]. Despite their methodological soundness and clear potential, the practical use of n-of-1 trials in clinical settings and research has remained quite limited. This limited adoption can be attributed to several factors, including the logistical and statistical complexity of designing such studies, the essential need for close collaboration between physician and patient, and, above all, the lack of familiarity among many clinicians and researchers with this specific study design.

N-of-1 trials offer several significant advantages that make them particularly valuable in specific clinical and research settings – especially in areas such as rare diseases and chronic conditions:

1. **Cost Reduction**
   Unlike traditional RCTs, which require enrolling hundreds or thousands of participants and incur high costs, n-of-1 trials are inherently more economical. While they do require careful and thorough initial planning, conducting the trial on a single patient substantially reduces operational and logistical costs. This makes them a sustainable option for evaluating costly or resource-intensive interventions.
2. **Personalized Treatment**
   The main strength, and indeed the very essence, of n-of-1 trials lies in their ability to provide concrete, individualized evidence to guide therapeutic decisions. This approach is particularly useful in situations where treatment responses vary significantly from one patient to another, as often seen in chronic conditions, such as autoimmune diseases or chronic pain.
3. **A tool for Rare Diseases**
   N-of-1 trials are especially powerful, and at times essential, for research on rare diseases. By definition, these conditions affect very small numbers of individuals, often making it impractical to recruit a sufficiently large sample for a traditional RCT. In such cases, n-of-1 trials represent a valid methodological alternative for generating high-quality clinical evidence.

CHALLENGES TO BROADER ADOPTION

Despite their potential, the wider adoption of n-of-1 trials is hindered by several practical and methodological barriers that must be carefully addressed during the study design phase:

1. **Bias and Blinding Difficulties**
   Blinding – keeping the patient and/or clinician unaware of which treatment is being administered at a given time – is essential for ensuring the validity of the results. However, effective blinding is particularly challenging in non-pharmacological interventions such as nutritional, physiotherapy, or rehabilitation treatments, where the nature of the intervention is evident to the patient. This awareness increases the risk of bias in patient-reported outcomes.
2. **Logistical Feasibility and Operational Burden**
   Setting up an n-of-1 trial requires meticulous planning and execution. Elements such as randomization of treatment sequences, proper implementation of washout periods, and maintenance of blinding must be managed with consistent accuracy. These requirements pose significant logistical and operational challenges for clinicians and researchers, especially in resource-limited settings
3. **Ethical and Regulatory Issues**
   The approval process for n-of-1 trial protocols by Ethics Committees can be complex, as existing regulations are primarily designed for population-based RCTs. In some countries, this type of study falls into a regulatory grey area, particularly regarding informed consent, and requires proactive dialogue with regulatory authorities.
4. **Limited Generalizability**
   A fundamental limitation of the n-of-1 design lies in the nature of its results. Since the data are specific to the individual patient involved, their applicability to a broader population is inherently limited. The findings are “valid for me,” not necessarily “valid for us.”

CLINICAL APPLICATIONS

N-of-1 trials can be applied in a variety of clinical settings where individual variability in treatment response is high, and where personalization plays a decisive role:

- Chronic diseases: These trials are widely used in conditions such as asthma, arthritis, migraine, or neuropathic pain, where patients may respond unpredictably to different drug classes.
- Rare diseases: In ultra-rare conditions, n-of-1 trials can serve as a valuable alternative to generate the only possible clinical evidence when recruiting a standard study sample is unfeasible.
- Managing side effects and tolerability: This approach enables precise identification of treatment-related side effects or benefits, focusing on the patient's specific experience and improving treatment adherence.
- Behavioral and nutritional interventions: N-of-1 trials are increasingly used to evaluate individualized lifestyle changes, such as specific diets, physical activity programs or psychological therapies, where outcomes are highly subjective and depend on the patient's personal response.

THE ROAD AHEAD

Despite the current challenges, the future of n-of-1 trials appears highly promising. International initiatives, such as the DIAMOND Project[3], are actively developing standardized guidelines and practical tools to promote and facilitate the adoption of this methodology, helping overcome existing logistical and regulatory barriers.

Digital technologies are expected to play a crucial role. Mobile applications and wearable devices can greatly simplify the real-time collection of clinical data and patient-reported outcomes, significantly reducing the logistical burden for both patients and research teams.

In addition, statistical research is exploring advanced methods, such as aggregate synthesis, through prospective meta-analyses of multiple n-of-1 trials conducted in patients with similar profiles. This innovative approach could enhance the generalizability of findings while maintaining a strong focus on the personalized nature of interventions in precision medicine.

CONCLUSIONS

N-of-1 trials remain an underutilized tool in clinical research. By merging methodological rigor with individualized patient needs, this form of controlled experimentation offers a valuable opportunity to accelerate the development of treatments tailored to precision medicine. While barriers remain, it is our responsibility to raise awareness and foster broader use of this approach in the near future.

Conflict of Interest:
The author declares no conflicts of interest.

Ethics Approval and Informed Consent:
Not required due to the nature of the article.

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