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ISCRR
Institute for Safety, Compensation and Recovery Research

Investigation of N-of-1 trial models

Evidence review

A review of the literature on the utility and methodology of N-of-1 trials

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A joint initiative of WorkSafe VICTORIA and MONASH University

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Disclaimer

Please note: This Evidence Review has been produced by the Institute for Safety, Compensation and Recovery Research (ISCRR) in response to specific questions from WorkSafe Victoria. The content of this report does not involve an exhaustive analysis of all existing evidence in the relevant field, nor does it provide definitive answers to the issues it addresses. The review findings were current at the time of publication, March 2021. Significant new research evidence may become available at any time. ISCRR is a joint initiative of WorkSafe Victoria and Monash University. The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of WorkSafe Victoria or ISCRR.

EXECUTIVE SUMMARY

Introduction

Evidence-based medicine is the cornerstone of clinical practice. However, in many cases, the evidence is lacking or inconsistent; or the individual patient has unique characteristics that raise questions about the suitability of conventional treatments.

WorkSafe Victoria (WSV) requested ISCRR to examine the utility and methodology of N-of-1 trials to determine whether a treatment with insufficient evidence of effectiveness may be of benefit to an individual in specific circumstances.

Research questions

1. What models currently exist for N-of-1 studies?
2. What are the essential criteria for conducting N-of-1 studies?
3. In what areas have N-of-1 studies been used?

Methods

An Evidence Review was undertaken in January-March 2021, involving a desktop scan of the published and grey literature.

Findings

Eighty-nine articles informed this review, including systematic reviews, individual N-of-1 trials, series of N-of-1 trials and articles related to the design and conduct of N-of-1 trials.

What models currently exist for N-of-1 studies?

There were four categories of N-of-1 trial designs, with options in each category:

1. **Phase design**: Measurements are taken in consecutive phases where different treatments, or levels of treatment, are implemented. The data are examined as one continuous time-series. This design is best suited to interventions that can be withdrawn or switched, without long carryover effects.
2. **Alternation design**: Treatments are implemented alternately and can be randomised in blocks. Each treatment block is examined as its own time series. This design is best suited to interventions that can be withdrawn, without harm to the patient.
3. **Multiple baseline design**: Several baseline measures are taken and then interventions are applied sequentially to one behaviour, without affecting the others. This design is best suited to interventions that cannot be reversed (e.g. behavioural or learning interventions).
4. **Changing criterion design**: Treatment is adjusted according to changes in a patient's response. This design is best suited to treatments that are irreversible and involve gradual change.

N-of-1 trial

- Patient-centred
- Prospective
- Controlled
- Multiple measures
- Rigorous approach
  - Blinding
  - Randomised sequence of treatment

What are the essential criteria for conducting N-of-1 studies?

One of the key advantages of the N-of-1 trial design is its flexibility to be tailored to the individual. Thus, there was a high degree of variability in criteria across published studies. Overall, there were some **essential** criteria and some **preferred**, but not essential criteria.

- Essential criteria:

- Determine whether the N-of-1 trial design is suitable for the patient, condition and circumstances
- Identify relevant and repeatable measures of effect, in collaboration with the patient
- Include multiple crossovers in treatments.

- Preferred, but not essential criteria:

- Randomise sequence of treatments (e.g. random block design)
- Blinded assessment of outcomes (single or double-blinded)
- Washout period to avoid carryover effects.

Guidelines for conducting N-of-1 trials and standards for reporting on them have also been developed. These are a useful tool to guide design and implementation of the trial.

In what areas have N-of-1 studies been used?

N-of-1 trials have been implemented in a wide range of areas across all physiological systems as well as for behavioural and psychological interventions. These include:

- Chronic pain
- Chronic diseases
- Neurodegenerative diseases
- Mental health and sleep disorders
- Lifestyle and behavioural interventions
- Complementary and alternative medicines and therapies
- Prescribing and de-prescribing.

Resources for N-of-1 trials

Advances in mobile technologies provide convenient and easy-to-use tools for monitoring patients' symptoms, collecting data and prompting patients to act (e.g. take medications, do exercises). N-of-1 trial services can assist with trial design as well as some of the time- and resource-intensive requirements, such as treatment sequence allocation and access to compounding pharmacies.

Other considerations

The key advantages of the N-of-1 trial design are: scientific rigour; patient-centredness; flexibility; granularity of treatment effects; direct benefit to the patient; cost-effectiveness; and efficiency in determining the most appropriate treatment.

The main disadvantages of the N-of-1 trial design are: findings are not generalisable to the broader population (unless combined with other trials); they are best suited to chronic stable conditions; potential for carryover effects need to be considered; and interpretation of results can be challenging.

Other design challenges include: identifying appropriate randomisation of treatments; getting the right balance between collecting enough data and not placing too much burden on patients; statistical analyses (calculating power, managing autocorrelation); addressing carryover and slow-onset effects; feasibility of blinding, withdrawal or washout periods; and limiting potential biases (Type I error, Hawthorne effect).

Summary and conclusions

The N-of-1 trial design is best suited where there is a need to tailor treatment to the individual patient's circumstances. While the flexibility of the design is one of its greatest strengths, there are some critical design elements needed to ensure scientific rigour and study validity. These include: appropriateness of the design, relevant and repeatable measurements and multiple crossover treatment periods.

The implementation of N-of-1 trials, while not onerous compared with randomised controlled trials (RCTs), requires a commitment from health care providers and patients. Embarking on an N-of-1 trial could be facilitated by having access to adequate resources and trial support services.

Although not every N-of-1 trial is guaranteed to deliver clear guidance on optimal treatment for a patient, the rigour of the model may avoid wasting time on ineffective treatments that delay recovery.

INTRODUCTION

According to the Non-established, New or Emerging Treatment and services (NeNET) policy, WorkSafe Victoria (WSV) will not fund a NeNET that is not supported by high-level evidence; nor will they fund treatment experiments on patients. This policy safeguards workers against exposure to unproven treatments that may be ineffective or harmful. However, in some cases, inexpensive but unproven treatments are started prior to WSV approval; and the worker or health care provider believes that the treatment has improved the patient's health or function.

Currently, there is no procedure for WSV to review requests to fund an unproven treatment (i.e. insufficient evidence of effectiveness) that the patient or health care provider reports is beneficial. In this situation, an independently-conducted N-of-1 trial could determine whether the benefit is real or due to a placebo effect.

WSV have requested ISCRR to examine the methodology for conducting N-of-1 trials and the healthcare areas where they have been applied.

Background

Although randomised controlled trials (RCTs) are the gold standard for determining the effectiveness of interventions, even the most rigorous RCT cannot predict how an individual may respond to an intervention that has demonstrated significant effectiveness in the study population. An individual's genes, environment and lifestyle may influence how well they respond to the clinical management of their disease/condition.[1] Although the overall risk is relatively low, treatments that have demonstrated safety and effectiveness on average may be ineffective or harmful to an individual patient. In particular, the impact of evidence-based interventions (based on RCTs) may be unknown for patients with comorbidities or complex medical conditions (generally excluded from RCTs), rare diseases (insufficient numbers for a robust RCT) or sub-groups of patients who may be resistant to usual drug treatment due to individual factors or genetic abnormalities. Many other minorities or marginalised groups are under-represented in clinical trials. A review on the representativeness of RCTs showed that participants were not always representative of those treated in routine clinical practice.[2]

Evidence-based medicine is expected in clinical practice, yet studies have estimated that less than 50 per cent of clinicians base clinical decisions on evidence-based guidelines.[3] Clinicians often find that the patient in front of them differs markedly from the participants in the RCTs that formed the basis of clinical guidelines; and they decide to choose a more pragmatic and targeted approach for patients with complex conditions or comorbidities.[4]

A single-case experimental design, or N-of-1 trial, may be appropriate in certain circumstances, including: 1) when a physician is uncertain about the best treatment approach for a patient (clinical equipoise); 2) when the patient differs substantially from the study population in existing RCTs; or 3) when there is insufficient or inconsistent evidence relevant to the patient and their condition. Box 1 (Appendix) briefly describes the original N-of-1 trial conducted in 1985.[5]

N-of-1 trials represent the intersection of research and clinical care in real-world circumstances. Rather than extrapolating inferences from group data (RCTs) to the individual, the N-of-1 study design evaluates treatment responses at the individual level.[6]

OBJECTIVES

Aims

The main aim of this Evidence Review was to examine the methodology used in N-of-1 trials, including identifying the key criteria.

Research questions

1. What models currently exist for N-of-1 studies?
2. What are the essential criteria for conducting N-of-1 studies?
3. In what areas have N-of-1 studies been used?

METHODS

An Evidence Review was undertaken in January-March 2021 to examine and synthesise the evidence related to the methodology used for N-of-1 trials. This involved a desktop scan to identify relevant articles in the published and grey literature.

Literature search

Four academic databases (PubMed, Embase, Cochrane, Scopus) were searched to identify relevant articles or reviews that were published in English, through peer-reviewed academic literature between January 2010 and January 2021. A Google search was also undertaken to identify reports, guidelines and other documents in the grey literature.

Following discussions with WSV about areas in which N-of-1 trials were conducted since 2010, a list of studies were included that had been conducted before 2010 and published in one of the systematic reviews.

Search terms contained in key words, titles and abstracts included:

> **Line 1:** N-of-1 OR N=1 OR (single patient) OR (single case) OR (precision medicine) OR (personalised medicine) OR (personalized medicine)
>
> AND
>
> **Line 2:** study OR trial

The focus of this Evidence Review was on details of the methodology for N-of-1 trials, including the essential criteria. The review was not concerned with the effectiveness of the therapies of interest or the quality of the studies. Therefore, no formal quality assessment of studies was undertaken.

Figure 1 shows the search process and how relevant articles were selected.

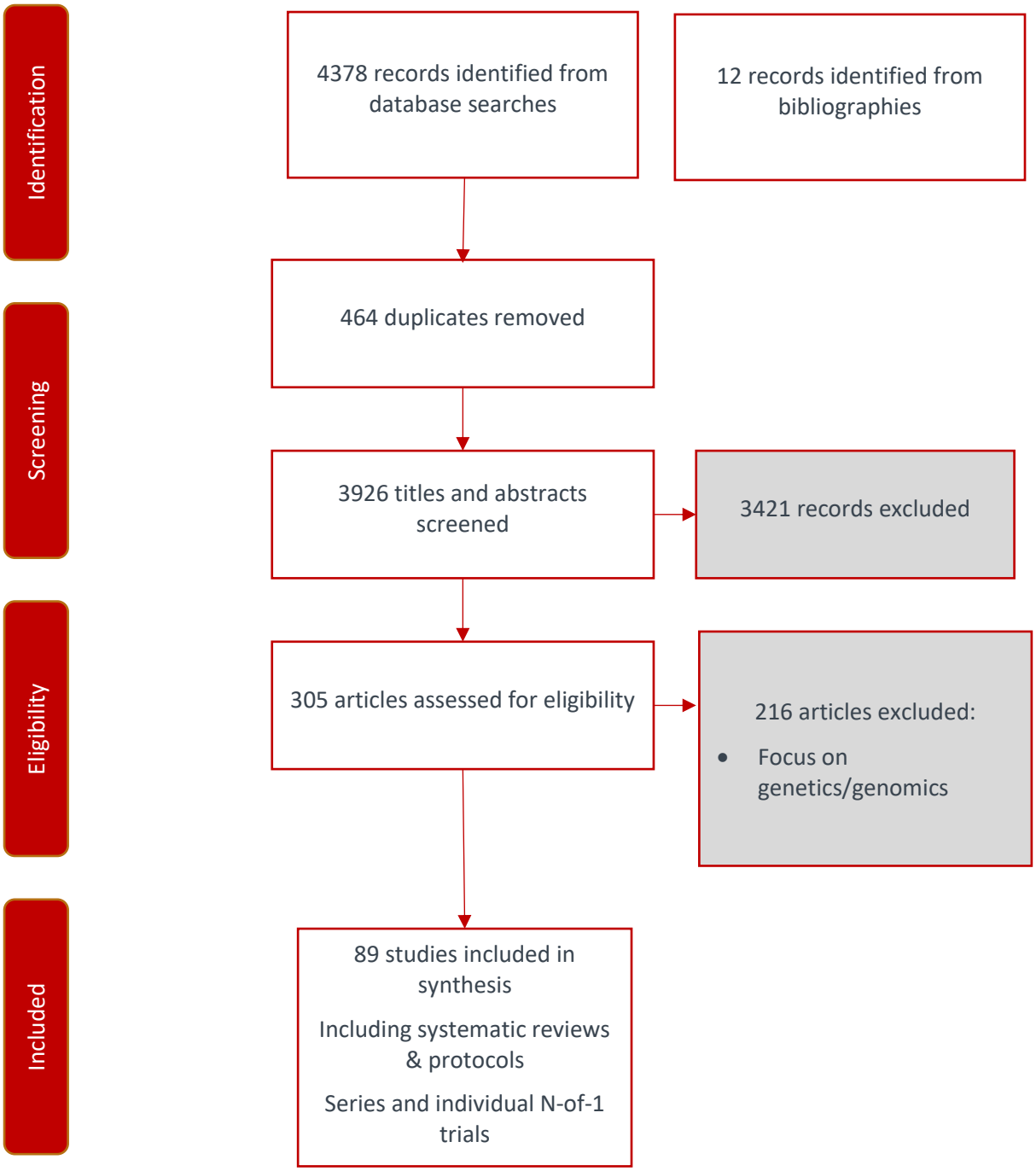


Figure 1. PRISMA flow diagram depicting search process for identifying relevant articles related to N-of-1 trials

FINDINGS

Searches identified over 4,000 articles related to N-of-1 trials and personalised medicine that had been published since 2010. After removing duplicates and screening by title and abstract, 305 articles were assessed for eligibility. Of these, 216 articles that focused primarily on the genetics and genomics of precision medicine were excluded as this area was out of scope for this review. The remaining 89 articles were used to inform the findings.

Single-case experimental studies

N-of-1 trials are one of several types of single-patient study (Table 1). Most common are case studies, which are usually retrospective reports on a single patient, and Trial by Therapy, which is used frequently in clinical practice.

A typical single-case experimental design involves a comparison between two experimental time periods (phases), including a representative baseline phase.[7] The main purpose of a single-case experimental study is to determine whether an intervention works for an individual (compared with placebo, no intervention); or which of several interventions works best for an individual.

Table 1. Comparison of single-patient studies

Study design	Time orientation	No. of measurements	Randomised	Blinded	Control	Bias
Case study	Often retrospective	Limited; based on clinical need	No	No	Possibly	Yes
Trial by therapy	Prospective	Limited; based on clinical need	No	No	No	Yes
N-of-1 trial	Prospective	Many	Yes	Yes	Yes	Likely

Source: Margolis and Giuliano, 2019[8]

Trial by therapy

Individualised patient-centred care is an inherent part of clinical decision-making. However, patient-centred care is not practised in a systematic way across every patient. For the most part, clinicians have used a Trial by Therapy approach to determine the appropriate treatment regimen (medication, dose), adjusting the regimen according to a patient's responses. However, the Trial by Therapy approach has a number of problems, including:

- *Stability of the condition*: The treatment may be initiated during a natural remission phase of a chronic illness; or the patient may recover spontaneously and outcomes may be unrelated to the treatment
- *Placebo effect*: The expectation and desire for improvement may account for approximately 30 per cent of the effect, overriding the actual effects of the treatment
- *Series of trial-and-error treatments*: Only one treatment is tested at a time, which prolongs the time to achieve an optimal response.[2]

N-of-1 trials

N-of-1 trials explore the variability in efficacy that is seen in most clinical trials, using a systematic and objective approach. Heterogeneous effects across participants are common in RCTs. That is, some individuals in the treatment group may have worse effects compared with the average for the control group and others may have much better responses compared with the average for the control group. In this case, it is impossible to determine whether a treatment is appropriate for an individual patient and an N-of-1 trial may be useful.[4]

In contrast, if there is a homogeneous treatment effect, where all of the treatment group have a larger response compared with the control group and there are no large differences in the magnitude of effect, there is no need to conduct an N-of-1 trial to understand how an individual patient is likely to respond.

The N-of-1 trial study design avoids confounding and biases inherent in Trial by Therapy by using the patient as the study subject; and determining the best course of treatment objectively and empirically using the rigorous tools of an RCT (randomisation, blinding, formal assessments). This approach also addresses the problem of generalisability of RCTs when there are heterogeneous treatment effects.[2] In contrast to RCTs, N-of-1 trials focus exclusively on the empirically-determined optimal intervention for a single patient and, while results are not easily generalisable, the endpoint for patient-centred care is achieved.

N-of-1 trials may also follow a RCT, where the RCT demonstrates effectiveness (on average) for a population; and the N-of-1 trial may determine whether the intervention works for an individual.[8]

WHAT MODELS CURRENTLY EXIST FOR N-OF-1 STUDIES

One of the key advantages of conducting an N-of-1 trial is that it can be tailored to the patient's unique characteristics, including their clinical condition, comorbidities, lifestyle and preferences. The intrinsic variability in this approach makes it more difficult to establish standardised design protocols. Figure 2 illustrates a prototypical balanced sequence design with repetition, blinding and systematic outcomes assessment. However, there is room for flexibility in this approach.

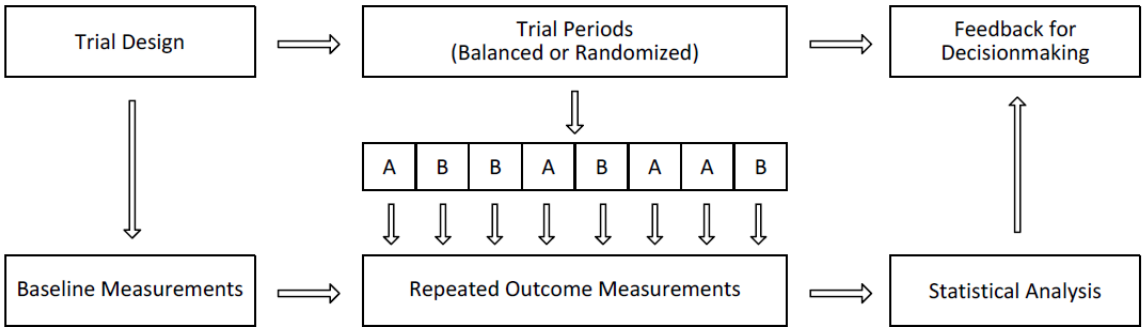


Figure 2. Prototypical N-of-1 trial design

Source: Kravitz et al., 2014[9]

In Figure 2, A and B refer to two different treatments (or treatment and placebo). By convention, the baseline or control (e.g. placebo) is designated 'A' and the treatment or intervention is designated 'B'.[10]

Ultimately, the choice of study design will depend on:

1. The condition of interest
2. The ease of collecting data on patient responses and outcomes
3. The most appropriate time for collecting data and availability of appropriate measurement devices (e.g. smartphone app)
4. The half-life of pharmacological treatments
5. The patient's unique characteristics and preferences.

Example of double-blind, crossover comparison N-of-1 trial: Celecoxib vs paracetamol[11]

2 treatments for osteoarthritis were compared in a series of N-of-1 trials

- 3 pairs of 2-week periods
- Randomised order for each pair
- Blinded patients and physicians

Table 2 provides an overview of the most common types of single-case experimental designs and further details on these designs are provided below.

Table 2. Overview of single-case experimental designs and examples

Type of single-case experimental design	Design examples
Phase designs	AB
	ABA
	ABAB
	ABAC
	ABACA
Alternation designs	Completely randomised
	Randomised block
	Alternating treatments
Multiple baseline design	Across participants
	Across outcomes
	Across settings
Changing criterion design	Single-point criterion
	Range-bound criterion

Source: Tanious and Onghena, 2019[12]

Phase designs

Phase designs include designs involving multiple measurements taken in consecutive phases where different treatments, or levels of treatment, are implemented.[12] The data are examined as one continuous time series to identify changes over time.

Simple AB designs involve a series of measures taken at baseline (A) followed by a series of measures taken after an intervention (B). However, if the study concludes at this point and the patient shows benefit after phase B, this may be due to the intervention, but it may also be a result of spontaneous recovery. According to the What Works Clearinghouse standards,[7] the AB design does not fulfil the necessary requirements for an N-of-1 trial as at least three phase changes (ABAB) are needed to demonstrate treatment effect; and five phase changes are recommended.[10]

The ABA design (introduction and withdrawal) consists of two phase changes, which is considered acceptable, but would be strengthened by use of multiple sessions where an intervention is applied for a period of time (or in a number of sessions) and then withdrawn.[10]

The ABAB design shows at least three phase changes; and can be continued in multiple crossovers as needed. For example, a drug to improve sleep (vs placebo) may be tested on patients with a sleeping disorder (placebo – drug – placebo - drug).

Where there are insufficient phase changes, any observed effects may coincide with factors unrelated to the intervention and an ABAB design provides an additional phase change to improve quality. More than one intervention may also be evaluated in the ABAC or ABACA designs. These comparative designs have the potential to assess the effectiveness of several different interventions in one trial.[4] Putative treatments can be tested sequentially and a longer timeframe is required to gather sufficient data for each treatment.

Alternating (AB) or introduction/withdrawal (ABA or ABAB) designs have both been used in behavioural intervention trials for smoking cessation, physical activity, drug use, eating behaviour

and sleep behaviour.[13] Replications of the sequence are needed to avoid temporal confounders and enable valid conclusions to be drawn.

Other variations include dosing trials and observational design. An N-of-1 dosing trial assesses a patient's responses to different doses of a single intervention over time.[4] This model can be blinded and randomised, using placebo or usual care in a crossover design.

An observational N-of-1 trial for health behaviours involves repeated measures over time, without implementing an intervention. The aim is to characterise relationships between behaviours and predictors, such as levels of pain, cognitions or attitudes related to physical activity.[13] Information can then be used to design an intervention (e.g. frequency, intensity, duration) that is tailored to the individual.

Alternating treatment designs

Alternating treatment designs involve rapid alternation between different treatments, whereby A is the first treatment (or baseline) and B is the second treatment. This design allows the clinician to determine the relative impact of two (or more) different treatments on the patient's response. The main differences compared with the phase design are that each treatment condition is its own time series; and there is no minimum number of measures required in the same condition.

For example, three types of ankle-foot orthosis were compared during physiotherapy sessions to determine which was most effective for improving the walking capacity of a hemiparetic patient.[10] Over five days of physiotherapy, the patient tried each treatment in random order: ACB, BCA, BAC, ACB, CAB.

A completely randomised design has strong internal validity, but may result in an undesirable order of treatments (e.g. AAAABBBB).[12] In contrast, the randomised block design avoids that problem by grouping treatments into blocks and randomising the order of treatment administration within the block. For example, each block may contain two time periods (e.g. weeks 1 and 2) and the treatments are randomised (AB or BA) in each block.

In another alternating design, treatments are randomised but constraints are put in place to ensure that the same treatment is not administered more than twice in a row.

Multiple baseline design

The multiple AB baseline design involves taking measures for several baseline behaviours and then sequentially applying interventions to one behaviour, without affecting the others.[10, 13] That is, stability in the control behaviours after the intervention shows that improvements in the target behaviour are unlikely to be due to spontaneous recovery, or practice effects. This design is suitable for interventions with slow onset, delayed changes or where the behaviour is not reversible or reversing it is not desirable; and where a washout period is not feasible. The multiple baseline approach is most suited to interventions promoting permanent change, or where the intervention is not easily withdrawn. However, there is a trade-off in using the multiple baseline design. The sequence cannot be blinded or fully randomised, resulting in a lower level of evidence.

Multiple baseline designs are commonly used in a small group of patients (at least 3) whereby measures are taken at regular intervals and implementation of the intervention is staggered temporally across patients.[10] The main disadvantage of this design is that some patients have to wait before treatment commences.

Multiple baseline design is also suitable for an individual patient with a rare condition or unusual recovery goal. Complementary and alternative medicines (CAMs), which may have a long metabolic half-life may also be suited to the multiple baseline design to avoid long withdrawal or washout periods.[3]

Changing criterion design

The changing criterion design involves phase changes once an outcome variable meets pre-determined criteria and can be adjusted as the study progresses.[7, 13] In this design, the patient must meet a specified criterion before a change in treatment occurs (e.g. frequency, intensity, dosage).[12] This design is useful in circumstances where a gradual change in behaviour is preferred. A strength of this approach is that the treatment is never withdrawn, making it particularly suited to interventions where a slow or stepwise change is appropriate.

Although there are no clear guidelines on the minimum number of data points, Tanious et al.[12] recommended that at least three, and preferably five, data points should be collected.

The range-bound version of the criterion design involves a predetermined range of acceptable outcomes, rather than a single criterion. For example, an upper and lower limit to the amount of exercise may be set so that the individual does not overdo exercise, potentially resulting in injury, but maintains a minimum level.

Other designs

Mixed designs may include a combination of designs, such as an introduction/withdrawal embedded in a multiple baseline design.[7]

WHAT ARE THE ESSENTIAL CRITERIA FOR CONDUCTING N-OF-1 STUDIES?

The definitions of N-of-1 studies and the characteristics of interventions, measurements, implementation protocols, outcomes and analyses vary widely across the different fields in which they have been used. The flexibility of this approach adds to its appeal and practical application to each individual, but also makes it more challenging to tease out the essential criteria.

The specific design of the trial depends on the question of interest. However, the first critical question is to determine **whether** an N-of-1 trial is suitable. If the criteria for suitability are met, there are several **critical** design elements and others that are **preferable**, but not essential.

Is an N-of-1 trial suitable for the patient?

The N-of-1 trial design is suitable only in situations where:

- There is substantial uncertainty about the optimal treatment path for a patient:
  - Lack of evidence to support clinical decision (e.g. rare condition)
  - Evidence of heterogeneity in the effectiveness of a treatment (e.g. contradictory or mixed effects reported)
  - Patient characteristics are not represented in existing clinical trials or guidelines for their condition (e.g. comorbidities, age, concurrent medication)
- The clinical condition is chronic or frequently recurs
- The treatment being considered demonstrates measurable outcomes within a short period
- Both patient and clinician are committed to the effort required to undertake a trial.

In contrast, the N-of-1 trial design is NOT suitable for acute conditions or ones that progress rapidly; and are more challenging for treatments that have a slow onset and long carryover effects once treatment ceases.

Determining the suitability of the N-of-1 trial for the patient and condition is **essential**

Balanced sequence assignment and randomisation

A key aim of N-of-1 trials is to achieve balance in assigning treatments, thereby ensuring that the treatment effects are not biased by time-dependent cofounders.[9] This can be achieved by randomisation of treatment periods, or using a paired or counterbalanced design.

The paired ABABABAB crossover design and counterbalanced ABBAABBA are the simplest and most common methods used for balanced assignment in N-of-1 trials.

While randomisation in RCTs refers to allocation of participants to intervention groups, different elements of the single-case experiment can be randomised, including the number of measures in each phase and the order of introducing interventions.[10]

Randomisation of sequences minimises the patient's ability to predict cross-over points in a trial, adding scientific rigour; but is not essential as it is not always feasible or ethical (e.g. withholding treatment from patient with chronic pain).[12] Differential (i.e. random) block sizes may also reduce predictability.[14] Similarly, it may not be practical or ethical to delay treatment to establish a baseline.[11]

In some cases, randomisation may raise problems in interpreting outcomes in an individual patient if the sequence does not alternate or if the order of treatment effects influences findings.[11]

Examples of balanced sequence assignment are:

1. Randomised treatment assignment
    a. Counterbalanced: randomised block design ABA or BAB; ABAB or BABA
    b. Ascending dose design, with random sham between doses: A1, sham, A2, A3, A4, A5
2. Non-randomised, balanced sequence design.[15]

Randomisation is **preferable**, but not essential

Duration and frequency of treatment

Duration of each intervention period should take into account the time required for a drug or intervention to take effect as well as the time for the effect to disappear.[2]

A pre-specified number of crossovers is preferred; however, it may not always accommodate the patient's needs.[16] A more flexible approach is to employ a sequential stopping rule once an acceptable level of uncertainty has been reached. For example, where a dramatic difference between two treatments is clear, early stopping may be indicated; whereas wider fluctuations in responses may indicate a need for more crossovers.

Multiple exposures and crossovers increase the statistical power and reduce the effect of confounders, but also incur more costs. The longer the trial continues, the greater the burden placed on the patient and the higher the likelihood of withdrawal from the trial.[10, 16, 17]

Similarly, shorter blocks of treatment may be preferred to longer blocks, but rapid switching may obscure differences due to carryover effects. Therefore, the duration of the treatment periods and the overall duration of the trial need careful consideration.

In one example, a probiotic supplement was introduced to reduce pain associated with fibromyalgia.[3] Since the supplement took time to take effect, each intervention block lasted one month, with a 2-week washout between blocks and multiple blocks (total 26 weeks).

The length of crossover periods is determined by: 1) the nature of the outcome; 2) nature of the intervention; and 3) the number of data collection points.[10] Table 3 provides examples of how the duration of a trial can be calculated.

Table 3. Examples of methods to determine an appropriate duration for N-of-1 trials

Proportional	Having in mind the time constraints for the study (e.g. 12 weeks) and the number of phases, duration of each phase is calculated to be same length (e.g. 3-week phase in 12-week study).
Response-guided	The phase length depends on the emerging data. For example, when an intervention is applied only after baseline data have stabilised; or an intervention is applied only after a participant reaches a certain level of performance in the first setting before intervening in the second setting.
Randomised	Phase length is determined at random, by a randomisation procedure.
Restricted randomisation	Due to clinical or financial constraints, trials may need to be completed within a specified timeframe. Design will depend on the frequency of intervention sessions and the total time required for the intervention. Phase length may then be randomised within pre-specified requirements (e.g. at least 5 measures per phase) and constraints (e.g. total duration of the study less than 16 weeks).
Mixed response-guided and randomised	Increases the study validity of response-guided designs that are prone to bias if the intervention is introduced when the experimenter thinks it has the best chance of success. This mixed design uses random assignment of intervention times and a data analyst who is blind to when the participant receives treatment.

Source: Krasny-Pacini and Evans, 2018[10]

Washout periods and carryover effects

Some drugs linger for a period after the treatment has ceased and may carry over into the next phase of a trial.[11] Similarly, many types of behavioural or psychological interventions have a continuing impact, even when the intervention is withdrawn, thereby influencing patients' responses in the 'no treatment' period.[14]

A washout period may be used to separate active treatment periods and limit any lingering or carryover effects that could influence outcomes measured in the following block of treatment.[9] There is ongoing debate in the literature about the costs and benefits of including a washout period. Although a washout period is not essential, the risk of carryover effects needs to be considered in either the design (e.g. longer treatment blocks) or the analysis.

One way to manage carryover effects in the design is to include longer periods of control, where measures taken early in the control period are not included in the analyses.[14]

Washout periods may be useful to combat potential carryover effects, but it may not be practical or ethical to withhold treatment in some conditions.[11] For example, the lack of treatment during washout period may not be optimal for the patient (e.g. pain increases).

In the absence of a washout, alternative methods may address carryover effects:[16]

- Taking daily measurements in each 3-day time period, with down-weighting of earlier measures that are more susceptible to carryover effects
- Taking a single measurement at the end of each treatment period.

A washout period is **preferable**, but not essential

Blinding

Although blinding of patients, clinicians and outcome assessors is considered good practice in conducting RCTs, it is preferred, but not always feasible or essential in N-of-1 trials.[9]

Blinding is **preferable**, but not essential

Outcome measures and data collection

Determining the outcome domains is critical to designing an N-of-1 trial.[9] Clinicians and patients need to identify the specific symptoms or behaviours targeted for change; and then select the appropriate measures that are practical and repeatable (e.g. intensity or frequency of back pain; walking distance). Relevant outcome measures should be quick and easy to assess; and simple tools, such as daily diaries, smartphone apps or similar digital devices that require minimal effort and enhance the user's experience are recommended. Patients' goals and preferences need to be incorporated into the selection of outcomes to be assessed.

The statistical power of an N-of-1 trial lies in the number of repeated observations.[14] More than one exposure to A and B is necessary to ensure that outcomes are not affected by extraneous factors that have not been measured (e.g. diet, fatigue). Repeated measures in an N-of-1 trial are equivalent to sample size in an RCT.[9]

Identifying the most appropriate outcome measures, including the frequency and method of data collection, is **essential**

Analysis and feedback

Visual representation of data

The most common and simplest way to present and interpret data is through visual analysis of graphs that demonstrate the strength of a functional relationship between the intervention and the patient's responses. Graphical presentations that depict trajectories of treatment responses over time are both informative and easily understood.[16] Clear interpretation of data for the patient is critical to informed decision-making. Figure 3 illustrates how a change in symptoms during an ABBA trial may be presented visually.

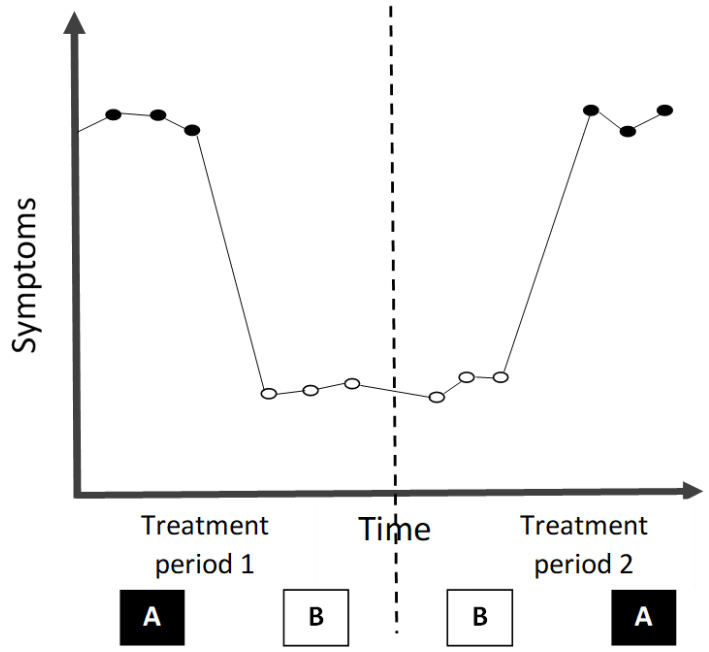


Figure 3. Graph illustrates changes in symptoms across an ABBA treatment sequence

Clear visual representation and feedback to the patient is **essential**

Statistical representation of data

Increasingly, there has been an upward trend towards the use of statistical analyses using measures of effect size to allow for pooling data from N-of-1 trials. However, there is little consensus on the most suitable methods of statistical analysis of data from N-of-1 trials;[18] and statistical analyses are not essential for clinical decision-making.[9]

In contrast to data analyses from RCTs, which are concerned with inter-individual variation over a small number of observations, the unit of analysis in N-of-1 trials is at the level of the individual participant and data analysis requires a larger number of observations collected from a single patient.[11]

Following an evaluation of the different statistical models for N-of-1 trials, Xie et al.[19] recommended the use of paired t-tests (for normally distributed data) or mixed effects model of difference (where there are carryover effects).

Time-series analyses may be needed to account for serial correlations where there are short time periods between measures. That is, observations collected in close time points are more likely to demonstrate strong correlations.[11] For example, high stress levels recorded on one day may be closely associated with stress levels recorded on the previous day. A detailed examination of statistical analyses is beyond the scope of this report and Kravitz et al.[9] provide a summary of statistical techniques to account for autocorrelations and carryover effects of N-of-1 trials.

The three main issues related to analysis and feedback are:

1. Present data item-by-item or as a composite measure. Item-by-item provides more clinical granularity, but may be confusing if the direction of multiple outcomes varies
2. Present data as graphics, statistics or both: simple graphs are easy to understand, so long as the results are unambiguous

3. Use only results of an N-of-1 trial for clinical decision-making or combine with results from previous similar patients, where data are available.

Follow-up after a trial is also recommended to monitor adverse effects, maintenance of response and to adjust intensity or frequency of intervention if needed.[20]

Statistical analysis of the data is **preferred**, but not essential

Guidelines and standards

In contrast to the well-accepted standards for conducting and reporting randomised and non-randomised clinical trials (e.g. CONSORT statement), there is less consensus on what constitutes a high quality single-case experimental design.[7] This may partially be due to the flexibility and diversity in methodology.

Recently the N-of-1 trial design has been elevated to Level 1 in the hierarchy of evidence, particularly "for treatment decision purposes in individual patients".[10]

The Oxford Centre for Evidence-Based Medicine[21] included N-of-1 trials at Level 1 in the hierarchy of evidence, under the following categories:

- Treatment benefits: Systematic review of randomised trials or **N-of-1 trials**
- Treatment harms: Systematic review of randomised trials, systematic review of nested case-control studies, **N-of-1 trial** with the patient you are raising the question about, or observational study with dramatic effect.

In line with this recognition, a CONSORT statement (Consolidated Standards of Reporting Trials) extension for reporting N-of-1 trials (CENT) was developed.[22]

The CENT statement provides a 14-item checklist, including a requirement for 'N-of-1' to be used in the title of articles and recommends more than five measurement points in each period and more than two repeated blocks. The CENT checklist aims to improve the quality of published N-of-1 trials, promote evidence-based decision-making and help researchers and clinicians to design good quality N-of-1 trials. Similarly, the SPIRIT (standard protocol items: recommendations for interventional trials) guideline has been developed to improve the transparency and quality of N-of-1 trials;[23] and the SCRIBE statement outlines the key steps and reporting requirements in single-case experimental studies involving **behavioural** interventions.[24]

Checklists to improve the quality of N-of-1 trial methodology have also been developed. Two examples are: the Comparative Single-Case Experimental Design Appraisal Rating System (CSCEDARS) to assess the internal validity of individual studies that aim to determine the effectiveness of two or more **instructional** interventions for non-reversible behaviours;[25] and the Risk of Bias in N-of-1 Trials (RoBiNT) scale.[26] Applying these tools to a study can identify whether the findings are trustworthy.

Reporting and quality guidelines provide a useful check before commencing a trial to determine the following elements:[10]

- Type of design (e.g. alternating; introduction/withdrawal)
- Number of phases required (including baseline, experimental, and follow-up)
- Order of sequences (e.g. randomised, counterbalanced)
- Number of sessions in each phase
- Duration of sessions

- Time interval between sessions
- Duration of each phase.

Six different standards for single-case experimental studies have been published and compared.[7] Each provides some variation on design requirements. The What Works Clearinghouse provides the most detail (Table 4).

Table 4. What Works Clearinghouse research design standards

	What Works Clearinghouse
Experimental manipulation	The intervention must be systematically manipulated by the researcher/clinician
Research designs	
General guidelines	At least 3 attempts to demonstrate an effect at 3 different time points or with 3 different phase repetitions
Introduction/withdrawal (ABAB)	Minimum of 4 x A and B phases
Alternating treatment or simultaneous treatment	At least 3 alternating treatments compared with a baseline condition or two alternating treatments compared with each other
Multiple baseline/combined series	At least 3 baseline conditions
Changing criterion	At least 3 different criteria
Baseline	Minimum of 3 data points; more preferred 1-2 data points can be sufficient in alternating treatment designs
Measures	
Assessors	>1 independent assessors if possible
Interrater reliability	On at least 20% of data in each phase and in each condition
Interval of assessment	Must be measured repeatedly over time (no minimum specified) within and across different conditions and levels of the intervention
Visual analysis	4-step, 6-variable procedure
Statistical analyses	Estimate effect sizes where number of data points warrant statistical procedures
Demonstrate effect	• Document consistency of level, trend and variability within each phase • Document immediacy of effect, proportion or overlap and consistency of data across phases • Identify for whom intervention is and is not effective • Examine external factors and anomalies

Source: Smith, 2012[7]

Guidance and key steps for conducting N-of-1 trials

A checklist by Kravitz et al.[9] provides guidance on the key considerations for conducting an N-of-1 trial (Table 5); and Table 6 lists the steps to designing and implementing an N-of-1 trial.[10]

Table 5. Checklist for N-of-1 trials

Guidance	Key considerations
Determine whether N-of-1 methodology is applicable to the clinical question of interest	**Indications include:** • Substantial clinical uncertainty • Chronic or frequently recurring symptomatic condition • Treatment with rapid onset and minimal carryover effects **Contraindications include:** • Rapidly progressive condition • Treatment with slow onset or prolonged carryover effects • Patient or clinical insufficiently interested in reducing therapeutic uncertainty to justify effort
Select trial duration, treatment period length, and sequencing scheme	• Longer trial duration delivers greater precision, but completion can be difficult or tedious, with the potential for extended exposure to inferior treatment during trial • Treatment period length should be adjusted to fit the therapeutic half-life (of drug treatments) or treatment onset and duration (of non-drug treatments) • Simple randomisation (e.g. AABABBBA) optimises blinding (more difficult to guess treatment), while balanced sequencing (E.g. ABBABAAB) is a more reliable guarantor of validity
Invoke a suitable washout period, if indicated	• Washout is not necessary if treatment duration of action is short relative to treatment period • Washout is contraindicated if patient could be harmed by cessation of active treatment
Decide whether or not to invoke blinding	• Blinding is feasible for some drug treatments but not feasible for most non-drug treatments (behavioural, lifestyle) • Adequate blinding allows investigators to distinguish between specific and non-specific treatment effects • In some circumstances, this distinction may not matter to patient and clinician; in others, participants may be primarily interested in the combined treatment effect (specific and non-specific)
Select suitable outcomes domains and measures	• Patient preferences are preeminent, but clinicians' goals and external factors should be accounted for and may occasionally supervene • Valid and reliable measures are preferred when available, but patient-centeredness should not be sacrificed to psychometric imperatives

Analyse and present data to support clinical decision-making by patients and clinicians	• There is a natural tension between identifying a single, primary outcome for decision-making and coming to a full understanding of the data • A reasonable approach is to select one or two primary outcome measures but present or use a variety of statistical and graphical methods to fully explicate the data

Source: Kravitz et al., 2014[9]

Table 6. Steps to designing and implementing an N-of-1 trial

1	Identify appropriate, repeatable outcome measures that are relevant to the intervention target, easy to administer and important to the patient. Outcomes should be specific, observable and replicable
2	Identify any other outcome measures that may be useful – e.g. control measures, implementation measures, other standardised measures
3	Select an appropriate study design – e.g. alternating, introduction/withdrawal, multiple baseline
4	Plan the design details: • randomisation or treatment order • blinding of patients and clinician • washout periods • consider carryover effects
5	Adapt intervention details and consider a measure of procedural fidelity
6	Check protocol against standards – e.g. SCRIBE
7	Commence experiment • monitor unexpected events • record any deviation or adaptation from the original study design/intervention
8	Data collection and analysis: • Remote wireless devices to monitor responses and collect data maintain transparency and may reduce costs and demands on time • Statistical power is derived from the number of repeated measures • Consider analyses that account for serial correlation (e.g. time-series analysis) • Present data visually, where possible • Pooling data from multiple N-of-1 trials may provide insights that could benefit a wider group of patients

Source: Krasny-Pacini and Evans, 2018[10]

IN WHAT AREAS HAVE N-OF-1 STUDIES BEEN USED?

The N-of-1 trial design has been used widely in a variety of health-related areas including physical, mental and behavioural disorders.[2]

N-of-1 trials are particularly relevant in the following circumstances:

- *Rare diseases:* RCTs are not feasible as it is difficult to achieve adequate sample size
- *Co-morbid conditions and concurrent therapies:* RCTs typically exclude these populations
- *Chronic diseases:* To monitor long-term therapies
- *Patient safety:* To reduce polypharmacy and cease ineffective therapies
- *Complementary and alternative medicines:* RCT evidence is not available; personalised treatment is the cornerstone of many CAMs
- *Clinical equipoise:* Current evidence is inadequate or evidence shows that several treatments may be equally effective
- *Clinician or patient uncertainty about current treatment regimen:* Suspected side effects or lack of effect; or to refine the optimal dose.

Davidson et al.[27] suggested that the clinical areas that are most likely to benefit from N-of-1 trials may involve management of "high burden, high prevalence, high cost disorders or symptoms, such as chronic pain, diabetes, arthritis, depression, obesity, smoking, dementia, mild hypothyroidism, hypertension, generic versus trade name medication use, asthma, hyperlipidemia and insomnia".

Table 7 lists examples from 44 systematic reviews, N-of-1 series and individual studies (published since 2010) that have used N-of-1 trials to assess the efficacy of specific treatment regimens or the feasibility of the trial design. Table 8 lists examples of N-of-1 trials that were undertaken before 2010.

Table 7. Examples of clinical areas of application for N-of-1 studies

Area of application	Trial details	Protocol
Chronic pain	**PREEMPT study on use of smartphone Apps for chronic pain** Part of an RCT – 244 patients randomised to PREEMPT or usual care PREEMPT: 122 patients in N-of-1 trials compared 2 pain regimens selected from flexible menu of options (e.g. any NSAID vs opioid medication or CAMS, such as massage, meditation, exercise) 'Trialist' app provided treatment reminders and collected data daily[28]	Trial duration: 4-12 weeks, depending on option selected Each treatment period: 7 or 14 days No. or treatment cycles: 2,3 or 4 Randomised treatment sequence
	Smartphone app to support treatment for musculoskeletal pain Individualised mHealth-supported pain management was compared with usual care pain management in a series of 215 N-of-1 trials The mHealth app (Trialist) provided reminders for individualised treatments (e.g. NSAIDS or opioids or CAMS); and uploaded responses	Trial duration: 4, 6, 8 or 12 weeks Treatments were single or combined The Trialist app randomly selected a balanced sequence (e.g. ABAB)[29, 30]
	Muscle stiffness: Mexiletine treatment for patient with non-dystrophic myotonia Double-blinded, randomised, placebo-controlled series of N-of-1 trials in 30 patients[31]	Multiple blocks of 4-week treatment periods
	Transcutaneous electrical nerve stimulation (TENS) for chronic pain TENS treatment compared with no treatment phases. Daily pain scales and sleep monitoring over 2-month period showed reduced pain levels and increased hours of continuous sleep. Due to the clear benefit of the device and rapid return of pain during the 'no treatment' phase, the trial was discontinued early.[32]	Alternating study design (ABAB)
	Ultra-micronized palmitoylethanolamide in older patients with chronic pain Series of N-of-1 trials (10 patients) compared um-PEA with placebo Daily self-reported pain measures[33]	Randomised, blinded interventions 2 x 3-week blocks, separated by 2-week washout periods

Area of application	Trial details	Protocol
	Neuropathic pain N-of-1 trial comparing topical analgesic creams for patient with symmetrical polyneuropathy in the feet. Analgesic response occurs within 30 minutes of treatment	Single or double-blinded, randomised, placebo-controlled Step 1: Identify whether there is a response: • 1 analgesic cream applied to one foot and a different or no cream applied to the other foot Step 2: If there is an initial response, the patient goes to an extended response test: • Cream A applied in Week 1 and Cream B in Week 2[34]
	Whiplash injury Series of N-of-1 trials comparing different combinations of analgesics for whiplash injury Daily self-reported neck pain	Multi-cycle, double-blinded, randomised, with multiple baseline design 3 x cycles of 10-day treatment triplets (paracetamol, naproxen, or combined paracetamol/naproxen) 3 baselines of 5, 8 or 11 days[35]
	Arthritic pain A hand-held personal digital assistant (PDA) was used to assess pain, activity, perceived behavioural control and intention to move in 6 patients with arthritic pain[36] Overall, findings highlighted the individual differences in what influences activity - importance of patients' behaviour, rather than physical impairment	Patients entered data twice daily and data were analysed to determine whether impairment, perceived behavioural control or intention to move predicted activity

Area of application	Trial details	Protocol
	Use of probiotics for osteoarthritic pain Active intervention: 2 x daily capsules of Lactobacillus rhamnosus (LGG), Saccharomyces cerevisiae (boulardii) and Bifidobacterium animalis ssp lactis; placebo was identical capsule without probiotics. Measures were daily pain scores Probiotics reduced pain scores	3 blocks of 10 weeks. Each block of one pair of randomised, blinded interventions, separated by a washout period of 2 weeks[37]
	Topical ibuprofen gel or capsaicin cream for painful knee osteoarthritis Series of 22 N-of-1 trials of randomised ibuprofen or capsaicin cream	3 treatment cycles, comprising 1 x treatment for 4 weeks[38]
Chronic disease	**Diabeloop for highly unstable Type 1 diabetes** Sereis of N-of-1 trials comparing Diabeloop with predictive low glucose suspend (PLGS)[39]	2 cycles with 2 crossover 4-week periods of randomised treatment
	Specific Cough Technique to clear airways in cystic fibrosis Series of 6 x N-of-1 trials compared Specific Cough Technique with forced expiration technique 3/6 patients produced significantly higher sputum using Specific Cough Technique compared with forced expiration Specific Cough Technique was well-tolerated, easier to use and non-inferior to forced expiration technique[40]	8 weeks treatment with 2 interventions each week Blinded assessor measured wet weight of sputum after each session
	Ivacaftor for patients with cystic fibrosis Series of N-of-1 trials to assess effects of Ivacaftor compared with placebo[41]	Patients randomised to 1 of 4 treatment sequences for 2 x 4-week, randomised, double-blinded trials, followed by 8 weeks of open-label Ivacaftor treatment

Area of application	Trial details	Protocol
	Irritable bowel syndrome – treatment improvement and satisfaction with therapy Aggregated analysis of N-of-1 trials of 81 patients with irritable bowel or chronic constipation to determine patients' satisfaction after 1 month of therapy[42]	Measures of satisfaction with treatment
	Elasticated orthotic garment compared with use of cane to improve gait and function in chronic stroke survivors Series of 2 N-of-1 trials compared cane-walking (usual care) with use of an orthotic garment worn through the day[43]	9-12 weeks baseline cane walking; 9-16 weeks orthotic garment wearing 9-10 weeks follow-up to assess need for walking aid
Neurodegenerative disorders	**Coffee to treat daytime drowsiness in Parkinson's disease** Series of N-of-1 trials assessed espresso coffee compared with decaffeinated coffee in Parkinson's disease patients[44]	Each trial involved a sequence of 3 crossovers (2 x treatment periods, separated by 2 days washout period) 2/4 patients benefitted from espresso coffee
	Nicotine to manage Levodopa-induced dyskinesia in Parkinson's patient 2 identical e-cigarettes (with nicotine and without nicotine) were compared and the patient recorded how they felt immediately afterwards[45]	Randomised and blinded in 5 tests (ABBBA) 2 identical e-cigarettes (with nicotine and without nicotine) were used in random order (blinded) in 5 tests (ABBBA)
	Deep brain stimulation for neurodegenerative disorders Deep brain stimulation in an N-of-1 trial has the potential to assess the efficacy of the device as well as potential harms and personal experiences of the individual[46]	Measures of efficacy and potential harms
	Off-label use of ephedrine as add-on treatment for myasthenia gravis Study assessed the feasibility of using data from N-of-1 trials to inform decisions about reimbursement for prescribing inexpensive medications for off-label use[47]	Feasibility study of N-of-1 trials to inform decisions related to reimbursement of costs

Area of application	Trial details	Protocol
Rare diseases	**On-demand use of Sildenafil for Raynaud phenomenon** Series of 38 N-of-1 trials to assess Sildenafil compared with placebo Aggregated data showed that Sildenafil was more effective than placebo; but responses were heterogeneous, which indicated that individual patient response in N-of-1 trials was useful for clinical decision-making[48]	Randomised, double-blinded trials, with multiple crossover periods Repeated blocks of 3 periods of on-demand treatment: 1 week placebo, 1 week Sildenafil Patients completed 2-5 treatment blocks;
Mental health: depression, schizophrenia, chronic stress, cognitive functioning, sleep disorders	**Systematic review of health psychology treatments** 54 N-of-1 trials in 1,193 participants Areas included: pain, sleep/fatigue, ADHD, wellbeing, mood/depressive symptoms, nausea, cognitive function[49] Interventions: pharmacologic, behavioural, physical (e.g. nerve stimulation for pain)	Randomisation and blinding varied across studies High variability in method: paired design, counterbalanced (single or double)
	Systematic review of N-of-1 trials for depression 5 studies on 47 depressed patients evaluated pharmacological treatments for depression[50] 3 studies: off-label treatment vs placebo 1 study compared 2 off-label treatments 1 study compared escalating doses of off-label treatment with placebo N-of-1 trials were feasible for treatment-resistant patients or patients with comorbidities not represented in RCTs	4 studies were counterbalanced, randomised block design; 1-5 blocks; washout periods 1-14 days; duration 2 days to 28 weeks 1 study was ascending dose, block design, with random assignment of sham doses, 1-day washout period over 6 weeks duration

Area of application	Trial details	Protocol
	Systematic review of N-of-1 trials for schizophrenia 6 studies, 9 patients stabilised on antipsychotic medication, with various presenting problems and interventions (pharmacological, psychological, behavioural, physical)[51] Comparators: placebo, no treatment, usual care Assessments: psychological functioning, frequency of exercise	Duration ranged from 8-30 weeks 2 studies: ABAB crossover design; 2 studies used ABA reversal design; 1 study used ABAC design; and 1 study used BAB design 2 studies used blinding measures (single or double)
	Measuring chronic stress in police officer Perceived stress and mood assessed via smartphone app 4 x per day (at waking, 2 x during day, before bed) and after police incidents while on duty[52]	Duration: 3 weeks, 90 data points
	Measuring chronic stress in professional ballroom dancer Measures of perceived stress and cortisol in saliva samples[53]	Daily measures collected over 8-month period
	Brain Boost smartphone app to improve cognitive function (study protocol) Series of N-of-1 trials 640 participants to be recruited and 97 must complete for feasibility study Study will compare effects of caffeine and L-theanine on cognitive performance[54]	Interventions randomised to different study durations (5, 15, 27 days) and notification levels (light, moderate)
	Smartphone app for treating insomnia Assess the potential of N-of-1 trials, awareness of the trial design and likelihood of treating physicians using the design for patients with insomnia[55]	Feasibility study to assess acceptability of N-of-1 trial design
Lifestyle and behavioural interventions: nutrition, exercise, alcohol use	**WESTLAKE N-of-1 trials to determine benefit of macronutrient diet** 6-day isocaloric dietary intervention: high-fat - low-carbohydrate compared with low-fat - high carbohydrate diet[56]	3 x 12-day dietary intervention pairs including a 6-day washout period before each intervention

Area of application	Trial details	Protocol
	Inactivity alerts (fitness trackers) to reduce sedentary behaviour in obese adults 10 x N-of-1 trials compared intervention (inactivity alerts) with baseline (no alert), followed by no intervention (reversal phase)[57]	Phase design (ABA)
	Smartphone technology used to increase physical activity using a personalised 'activity fingerprint' Series of 79 N-of-1 trials with personalised activity 'fingerprint' sent via email to intervention patients.[58] Data were collected on number of days exercised occurred	Randomised intervention or control
	Use of smartphone technology to reduce alcohol intake in adults who drink in excess Series of N-of-1 studies to determine individual predictors of alcohol reduction strategies[59]	Observational phase design
Prescribing and de-prescribing	**Statin-related myalgia** 8 x N-of-1 trials Weekly visual analog scale for myalgia and pain severity scores NS difference in pain scores between statin treatment and placebo[60]	3 x double-blind, crossover comparisons with placebo separated by 3-week washout periods
	Statin-related adverse effects 3 arms of N-of-1 studies (90 patients) • Unblinded behavioural intervention (education about statins) • Blinded behavioural intervention (education about statins) • Usual care statin therapy[61]	3 arms of N-of-1 trials within a RCT

Area of application	Trial details	Protocol
	SAMSON study Smartphone app was used to report daily symptom intensity Patients received 4 x bottles of atorvastatin, 4 x bottles of placebo, and 4 x empty bottles Findings showed NS difference in side effects between statin and placebo 6 months after the trial, 50% of patients restarted statins[62]	Double-blinded, randomised, 3 group N-of-1 trial Each bottle was for 1 month period according to a randomised sequence
	SR on de-prescribing medications in older adults 6 studies assessed efficacy of pharmacological and non-pharmacological therapies for treating various disorders. 4 trials showed non-significant benefits of treatment, leading to discontinuation of medications in some cases; and where treatments demonstrated benefit, all participants complied with the regimen at follow-up[63]	Various protocols
Complementary and alternative medicines: Traditional Chinese medicine, homeopathic medicine	**Sijunzi decoction for treatment of ulcerative colitis** Series of 10 N-of-1 trials compared modified Sijunzi decoction with mesalazine for treating ulcerative colitis in patients in remission[64]	3 cycles of N-of-1 trials with 2 treatment periods in each cycle over 8 weeks, with no washout period
	Chinese medicine herbal decoction for patients with stable bronchiectasis Series of N-of-1 trials in 17 patients Individualised interventions compared with fixed decoction (control)[65]	3 cycles of 2 x 4-week interventions
	Chinese medicine for chemotherapy-induced leukopenia in gastric cancer patient Series of N-of-1 trials compared a decoction with Astragalus mongholicus and Semen Cuscutae vs placebo between chemotherapy cycles over 20-30 weeks[66]	Randomised, blinded 3-day treatment periods

Area of application	Trial details	Protocol
	Gingko biloba extract for treating patients with coronary heart disease and impaired glucose regulation Series of 12 N-of-1 trials compared Gingko biloba with placebo	Randomised, double-blinded, placebo-controlled; 3 x crossover periods over 48 weeks; and 10 week follow-up period[67]
	Homeopathic treatment for cancer-related fatigue Homeopathic treatment (verum) or placebo was administered between 6 cycles of chemotherapy sessions NS difference between placebo and homeopathic treatment[68]	Randomised, double-blinded, matched pairs of treatment
	Cannabidiol to reduce frequency of seizures for treatment of epilepsy in paediatric patients N-of 1 trial investigated Cannabidiol for treatment of epilespsy[69]	Randomised, double-blind, placebo-controlled
	Shiatsu to improve health-related quality of life in patient with multiple sclerosis Shiatsu compared with standard care Reported improvements in spasticity, bowel function, fatigue, pain, sleep and relaxation[70]	6 periods of paired 2-week blocks of standard care followed by standard care plus 2 shiatsu sessions/week (AB – BA – AB); counterbalanced mixed-methods trial over 12 weeks
	Bright light therapy for depressive symptoms in cancer patients 2 putative sham treatments (dim red light, dim white light) were compared to determine which condition is the ideal sham to judge the efficacy of bright light therapy 5 N-of-1 trials of cancer survivors with depressive symptoms Smartphone app was used to report daily symptoms Findings demonstrated lower symptoms with DR vs DW light, suggesting that DR may be as effective for some patients as bright light therapy[71]	Multiple crossover conditions Randomised, balanced treatment sequence with one repetition (DR-DW/DW-DR or DW-DR/DR-DW) Each treatment was for 30 mins/day for 3 weeks over period of 12 weeks

Area of application	Trial details	Protocol
Other conditions	**Removal of diethylhexyl phthalate (DEHP) by handwashing techniques** N-of-1 trials assessed effectiveness of handwashing with soap-and-water compared with water-only to remove DEHP[72]	2 x 3-day crossover periods

Table 8. Examples of N-of-1 trials undertaken prior to 2010

Condition	No. of trials	Intervention	Results
Pain and discomfort			
Chronic pain	34	Cannabis extracts	28/34 patients achieved benefit
	116	Paracetamol/ibuprofen	N-of-1 trials led to many changes in treatment
	21	Ketamine	Small subgroup responded
Chronic neuropathic pain	73	Gabapentin	N-of-1 trials impacted use of Gabapentin
Osteoarthritic pain	56	Paracetamol/celecoxib	Paracetamol more effective
	13	NSAIDS	Heterogeneity in response to NSAIDS
	51	NSAIDS	N-of-1 trials slightly better than standard
	25	NSAIDS	NSAIDS are useful in pain management
Childhood arthritic pain	6	Amitriptyline	No benefit of Amitriptyline
Refractory neuralgia	1	Spinal cord stimulation	Study led to effective use of stimulation
Migraine	32	Dextroamphetamine	Improvements with Dextroamphetamine
Skeletal muscle cramps	13	Quinine	Heterogeneity in Quinine response
Other conditions			
Sleep disturbances	15	Temazepam	Temazepam is beneficial
	42	Valerian	Valerian did not improve sleep
Nausea from chemotherapy	12	Metopimazine	Metopimazine is beneficial
Depression	5	Methylphenidate	2/5 patients improved with Methylphenidate
Chronic obstructive pulmonary disease	26	Ambulatory oxygen	Reported use of oxygen is biased
	27	Eformoteral	No effect of Eformoterol

Condition	No. of trials	Intervention	Results
Chronic airflow limitation	68	Theophylline	N-of-1 trials no better than standard treatment
Cystic fibrosis	52	Recombinant DNase	Marked improvements with Recombinant DNase
	48	Recombinant DNase	Marginal improvements with Recombinant DNase
Anticoagulation	7	Generic/brand warfarin	No difference between generic/brand
Attention deficit hyperactivity disorder	86	Stimulants	28/64 trials led to change of treatment
	43	Methylphenidate	Improvement with Methylphenidate
Brain injury	Not reported	Methylphenidate	No benefit of Methylphenidate

Source: Lillie et al., 2011[11]

Pain management

Clinical equipoise is common in the area of pain management as the health care provider may be uncertain about the best course of treatment when there are many different approaches and differential responses across patients.

The PREEMPT study evaluated smartphone assisted N-of-1 trials for patients with chronic pain.[28, 29] Two pain management interventions were compared in a series of N-of-1 trials in 108 patients. Another group of 107 control patients received care as usual. Patients and clinicians jointly decided on the trial parameters and the treatment regimens. The smartphone app provided reminders to patients to take treatments on specific days and to upload daily responses to questions about pain through a Patient-Reported Outcomes Measurement Information System (PROMIS). Although there was overall satisfaction and acceptability of using the smartphone app to manage pain, there was no significant improvement in pain outcomes compared with usual care.

In another study, a number of compounded topical medications, which contained known analgesics (ketamine, baclofen, amitriptyline, phenytoin), were developed to treat neuropathic pain in treatment-resistant patients.[34] Using a single- or double-blinded design, patients with bilateral pain were given the active cream to one foot and a placebo cream to the other over two weeks of testing.

Complementary and alternative medicines (CAMs)

CAMs and therapies, including traditional Chinese medicine, are popular healthcare options amongst the general public, but typically excluded from mainstream clinical care due to the lack of evidence of efficacy.[3]

Patient-centred care is the cornerstone of CAMs. The N-of-1 trial design fits well with the principles of holistic medicine that play a key role in traditional Chinese medicine, homeopathy, naturopathy, acupuncture and other fields of CAMs.[73] Due to its rigorous design, the N-of-1 trial approach has the potential to demonstrate true clinical effect (or lack of effect) of CAM therapies (compared with conventional treatments) in an individual; identify optimal dosing regimens and avoid adverse effects; and investigate the placebo effect in patients who are convinced of the efficacy of a particular formulation.

N-of-1 trials are more accessible to CAM practitioners compared with RCTs. In contrast to RCTs, which focus primarily on a single treatment or condition, the N-of-1 trial may adopt a biopsychosocial approach that aligns more closely to CAM practice.[3]

For example, traditional Chinese medicine for bronchiectasis was evaluated in a series of N-of-1 trials.[65] Results showed more improvement of symptoms from individualised herbal decoctions compared with standard decoctions.

A published study protocol described a series of N-of-1 trials for 10 patients that aims to evaluate the effectiveness of modified Sijunzi decoction with mesalazine for treating ulcerative colitis in remission.[64] Modified Sijunzi decoction combined with mesalazine placebo or mesalazine combined with modified Sijunzi decoction placebo will be randomised during three 8-week treatment cycles.

Mental health and sleep disorders

A systematic review of N-of-1 trials for tailoring pharmacologic treatments for depression (5 studies; 47 patients) demonstrated that data could be used to select optimal treatment for patients, particularly for those with treatment-resistant depression who would most likely have been excluded from conventional clinical trials.[15]

Evidence also suggested that the N-of-1 trial design was acceptable to treating physicians. For example, of 45 healthcare professionals treating patients with insomnia, 64 per cent reported that they were likely to use an App-based N-of-1 trial to identify the best treatments for their patients if the service was free and easy to use.[55]

Prescribing and de-prescribing

A systematic review of N-of-1 trials showed that the trials successfully distinguished between patients who could discontinue medications that provided no significant benefit and those who benefited from maintaining their medication regimen.[63]

For example, N-of-1 trials that assessed theophylline prescribed for irreversible chronic airflow limitation led to less theophylline use without adverse effects; and authors concluded that "there was a clinically important bias towards unnecessary treatment".[11]

The SAMSON series of trials to investigate the reported side effects of statins for high cholesterol provided clear evidence to patients that the muscle aches they were experiencing were not related to the prescribed statins.[74] Importantly, this series of trials led to increased compliance with the prescribed medication.

Lifestyle and behaviour change interventions

Intractable health problems, such as obesity, smoking and lack of exercise are targets for lifestyle interventions that often have limited long-term benefits. Unlike physiological responses to pharmacological treatments, which typically occur within a known timeframe, behaviour changes related to an intervention may follow a wide variety of patterns with considerable variability across individuals.

Diverse behavioural interventions have been implemented in N-of-1 trials related to physical activity, drug/alcohol use, sleep disorders, smoking and nutrition.[13] The N-of-1 trial design is also useful for assessing how an individual's health behaviours change over time.[13] This can be used to identify an individual's responses to treatment and for monitoring changes and refining interventions to optimise outcomes.

A key benefit of the N-of-1 trial approach is that the intervention can be tailored to the individual from the start. For example, in interventions to increase exercise, participant engagement is likely to be higher if they identify their preferred physical activity and the intervention is tailored to that activity.[14]

Key challenges for N-of-1 trials targeting behaviour change include: slow onset effects; carryover effects; and difficulties with blinding, identifying suitable repeatable measures and optimal sequence allocation techniques.[14] Since the main aim is to achieve long-lasting change, they are not suited to designs that include a reversal phase.

Measuring target behaviours repeatedly may be challenging and the timing may be important (e.g. independent of the intervention, during the intervention, randomly during an intervention), particularly if the behaviour changes occur slowly over time or the intervention itself is time-consuming and intensive.[10] Highly variable behaviours may require more frequent measures over a longer duration compared with those that are more stable. Patterns or trends also need to be considered, such as differential engagement in activities on weekdays versus weekends.

RESOURCES FOR N-OF-1 TRIALS

Advances in mobile health technologies, electronic health records and genetics/genomics has created new interest in N-of-1 trials to implement more targeted, personalised care.

Broader acceptance and utilisation of the N-of-1 trial approach is likely where there is support available to administer the intervention, with user-friendly and accessible interfaces for both the clinician and the patient.[75]

Kravitz et al.[9] provide a comprehensive list of desirable capabilities for an N-of-1 trial platform, with requirements for automating tasks, access to support and IT infrastructure (Table 9). While not all elements will be needed for every trial, accessibility to an N-of-1 trial platform may reduce the costs and burden of running N-of-1 trials.

Table 9. Recommendations for N-of-1 trial platform

Features supporting N-of-1 trials

- Record clinician goals and patient goals
- Document the experimental hypothesis
- Protocol implementation support
  - Library of characterised treatments (e.g. details of onset, carryover)
  - Library of characterised measures (e.g. precision and variance)
  - Support for randomisation
  - Web service connections to acquire/share libraries of standard measures
- Trial protocol specification
  - Choice of characterised treatments
  - Choice of measures
  - Choice of duration and number of treatment periods
  - Decision on important covariates to track
  - Analytical design
- Connection to electronic medical records, personal health records, pharmacy records
- Data collection and user engagement support
  - Data capture modules (e.g. choice lists, visual analog scales)
  - Applications programming interfaces to third-party data services such as sensors, Apps (e.g. symptom tracking)
  - Direct email or SMS submission of patient-reported outcomes
  - Trial progress review screens for patients and clinicians and other user engagement modules
- Data analysis and review
  - Data pre-processing modules
  - Statistical analysis modules
  - Visualisation modules
  - Data review and decision-support modules

Institutional support for N-of-1 trials

- Integration with electronic health records for recruiting and screening
- Configure eligibility requirements

- Support for external informed consent processes and documentation requirements
- Population review
- Summary reports (e.g. participation, utilisation)

Aggregation of N-of-1 trial results

- De-identification of patient record (for real-time *in situ* analysis, or for download to external systems for secondary analysis
- Statistical analysis and aggregation of raw individual patient-level data
- Statistical analysis and aggregation of summary results data
- Statistical analysis and modelling of aggregated outcomes
- Models for using aggregated group outcomes to facilitate "borrow from strength" for individual treatment effects and to estimate individual-level heterogeneity of treatment effect

IT infrastructure

- Secure data storage
- Data transmission security
- Data downloading in multiple formats
- Authorisation controls (who can do what)
- De-identified views of data

Source: Kravitz et al., 2014[9]

N-of-1 trial services

Dedicated N-of-1 trial referral services, which manage the key components of trials, have been established in Canada, US and Australia. The first referral service, which was established in Canada, supported 57 N-of-1 trials, which provided clear clinical guidance for 88 per cent of patients and led to 30 per cent of clinicians changing patient care plans.[76, 77]

Similarly, a pilot N-of-1 trial service was established at the University of Washington Medical Center; but despite reported success in improving "therapeutic precision" in 34 trials, the service did not continue beyond the 2-year pilot phase.[75] The lack of funding led to both of these services closing, despite positive outcomes.[77]

In Australia, Nikles et al. established a nationwide N-of-1 trial (single patient trial) service for patients with attention deficit and hyperactivity disorder, which commonly manifests substantial variation in intervention responses.[11, 78] The trial service was evaluated to determine its value and utility for undertaking N-of-1 trials. Nikles et al. reported that 45 doctors across Australia used the service to conduct 108 N-of-1 trials (86 completed). Overall, findings showed that it was feasible to implement N-of-1 trials via mail and telephone communication; and post-trial management was consistent with trial results in over 60 per cent of cases.[78]

Although the service is not currently running (personal communication, Jane Nikles), the International Collaborative Network for N-of-1 Clinical Trials and Single-Case Designs provides resources on conducting, reporting and analysing data from N-of-1 trials, including a helpline.[79]

Early studies that have assessed the feasibility and utility of N-of-1 trials with standard care or Trial by Therapy approaches found that they were not only feasible, but also the cost of using the trial

service was comparable to other services.[5, 11] Moreover, the findings led many physicians to change patients' treatment plans.

Simulation studies

Simulated N-of-1 studies can assist in the design of a trial and increase the likelihood of success.[17] Percha et al.[17] developed a time-series simulation model for N-of-1 studies (GitHub) that can account for various effects such as carryover and washout effects. The simulation model can also be used to select study parameters including sampling times/frequency, treatment order, treatment period duration and total number of blocks needed to achieve statistical estimates of treatment effects. The key features of the model involve four groups of parameters: 1) study design; 2) treatment; 3) measurements; and 4) outcomes.

Devices and technologies

Monitoring and measuring a patient's responses may be time-consuming and inconvenient. Therefore, leveraging on appropriate wireless devices and smartphone Apps may facilitate outcome assessments and reduce costs to patient and physician.[11] Table 10 lists some examples of devices that can be used for monitoring and collecting data from patients.

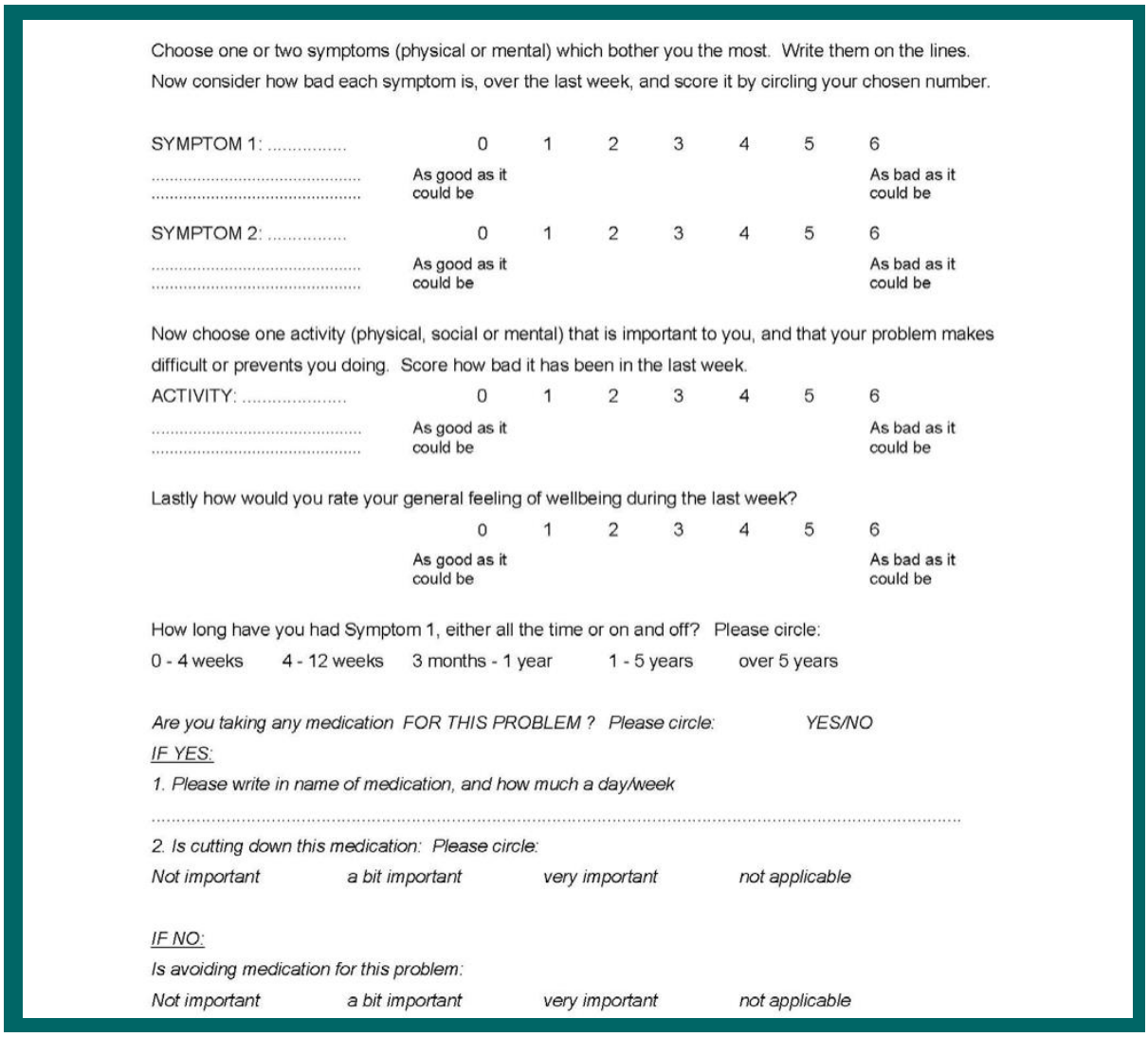
Table 10. Examples of devices for monitoring and gathering data

Device	Examples
Smartphone app or Smart watch	• Brain Boost app to improve cognitive functioning[54] • Sleep app for insomnia[55] • Mental health app for suicide prevention[80] • Track frequency/intensity of pain[28, 29] • Track caloric intake • Track physical activity/movement monitor[58] • Diary app to record events (e.g. migraines) • Reminders app – e.g. to take medications, rehabilitation exercises at appropriate times[30]
Continuous glucose monitoring	Type 2 diabetes
Blood pressure monitor	• Hypertension
Heart rate monitor	• Atrial fibrillation
Mechanical device	Sleep apnoea

The *Trialist* smartphone app has been developed to facilitate implementation of an N-of-1 trial for treatment of chronic pain.[28] The app provides treatment reminders and collects data daily from patients. The PREEMPT study implemented 122 N-of-1 trials compared with 122 patients receiving usual care. The N-of-1 trials compared two treatment regimens within a patient (NSAID, opioid medication, complementary medicine); and aimed to develop individualised treatment plans. The app randomised the treatment sequence, sent the participant daily reminders and questionnaires on pain levels.

Ecological Momentary Assessment (EMA), which is available on a smartphone App, is a common method of collecting data in real time, particularly for behavioural interventions.[14] The EMA prompts the patient to input data at regular intervals. The key advantage of this tool is that it avoids recall bias that may occur when using a diary. While it also poses a greater burden in terms of effort, acceptability and compliance rates are reported to be higher than with paper diaries.[9]

MYMOP (Measure Yourself Medical Outcome Profile) is another example of a patient-generated outcome measure that has been used in N-of-1 trials.[76] The MYMOP tool identifies outcomes that are important to the patient and problem-specific (Figure 4).



Choose one or two symptoms (physical or mental) which bother you the most. Write them on the lines.
Now consider how bad each symptom is, over the last week, and score it by circling your chosen number.

SYMPTOM 1:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be
SYMPTOM 2:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be

Now choose one activity (physical, social or mental) that is important to you, and that your problem makes difficult or prevents you doing. Score how bad it has been in the last week.

ACTIVITY:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be

Lastly how would you rate your general feeling of wellbeing during the last week?

0	1	2	3	4	5	6
As good as it could be						As bad as it could be

How long have you had Symptom 1, either all the time or on and off? Please circle:

0 - 4 weeks 4 - 12 weeks 3 months - 1 year 1 - 5 years over 5 years

Are you taking any medication FOR THIS PROBLEM ? Please circle: *YES/NO*

IF YES:

1. Please write in name of medication, and how much a day/week

.....

2. Is cutting down this medication: Please circle:

Not important a bit important very important not applicable

IF NO:

Is avoiding medication for this problem:

Not important a bit important very important not applicable

Figure 4. Sample of questions form MYMOP[76]

A wide spectrum of data collection modalities can be used in N-of-1 trials, from traditional formats (e.g. surveys, diaries, medical records) to more advance technologies (e.g. EMA, smartphone Apps, remote physiological monitoring devices).[9] Technologies equipped with GPS or movement detection (actigraphy) can track patients' activities with little effort; and additional monitoring devices (e.g. heart rate, blood pressure, blood glucose, galvanic skin response, vocal stress) can also connect with these devices.

Overall, these technological advances provide flexibility and increase accuracy and compliance.[27]

OTHER CONSIDERATIONS

Advantages of N-of-1 studies

- ***Scientific rigour***: The N-of-1 design offers the rigor of an RCT while allowing treatments, protocol and assessment of measures to be tailored to the individual[6]
- ***Patient-centred***: Achieves individualised medicine despite lack of generalisability. Patients learn more about their condition and treatment compared with patients who receive usual care or those who participate in RCTs; and participation enhances communication with their health care provider[9]
- ***Flexibility***: Allows flexibility in the trial design (e.g. number and length of crossover periods), so long as there is rigor and objectivity in outcomes assessed. Departure from the initial protocol is also acceptable so long as this is reported and treatment fidelity is monitored – i.e. treatment is delivered as intended; and/or the extent to which treatment varies from the original. Flexibility in the N-of-1 study design also allows for modifications in lifestyle as well as treatment parameters to optimise outcomes
- ***Granularity of effects***: Repeated measures allow insights into differential responses within a patient (e.g. fatigue, pain or other factors that may influence response at the time of measure)
- ***Benefit to patient***: Patients draw immediate benefit from the trial, or can withdraw at any point (low risk of participation); limits exposure to therapies of little or unknown benefit to the individual
- ***Cost-effective***: Timing and costs of conducting a series of trials can be shared across participating clinics.[11]
- ***Efficient***: Reduce inefficiencies in clinical care by eliminating ineffective treatments (e.g. de-prescribing) and identifying side effects.

Situations where N-of-1 trials may be useful:[10]

- Evaluating the efficacy of a current intervention for one particular patient in daily clinical practice to provide the best treatment based on evidence, rather than clinical impressions
- Conducting research in a clinical rehabilitation setting (outside a research team) with a single or small group of patients
- Piloting a novel intervention, or application/modification of a known intervention to an atypical case or other condition/type of patients that the intervention was originally designed for (e.g. off-label use)
- Investigating which part of an intervention package is effective
- Working with rare conditions or an unusual target of intervention, for which there would never be enough patients for a group study
- Situations where it is Impossible to obtain a homogenous sample of patients for a group study
- Time limitation or limited funding for recruitment of a group.

Disadvantages of N-of-1 studies

While N-of-1 trials are useful in many situations, they are not ideal for others. The disadvantages of N-of-1 trials include:

- *Not generalisable*: Applies to individual patient only, therefore not generalisable (unless in a series of similar trials)

- *Limited conditions*: Best suited to chronic stable conditions, rather than acute conditions that progress or regress rapidly (e.g. infections)
- *Limited treatments*: Best suited to treatments with rapid onset and termination of effects
- *Potential for carryover effects*: Can be addressed with multiple random cross-over periods, and using average of all measurements within each period of analysis; or exclude the first measurements in a period from analysis (washout period)
- *Interpretation of results can be challenging*: While longer trials improve statistical power, results from earlier periods in the trial may be less relevant if the patient's condition has changed over time.[16]

Challenges of N-of-1 studies

Design challenges for N-of-1 trials:[14]

- *Randomisation*: Although randomised treatment schedules are preferred, treatment blocks can also be arranged according to a non-random schedule
- *Non-adherence to data collection and missing data*: The repetitive nature of the study design can place a burden on participants to record data; but this is counterbalanced by evidence of overall high adherence rates
  - Software solutions to manage missing data (e.g. Amelia II)
  - User-centred study design may minimise non-adherence – participant co-designs study including measures
  - Technological solutions that unobtrusively collect data via smartphone Apps or wearables
- *Calculating power/sample size*: Requires a good understanding of the multiple parameters and assumptions to determine the number of repeated measures needed
- *Autocorrelation*: Sequential data points may be associated with each other, particularly if the intervals are short, or the time-point for data collection is a confounder (e.g. lower stress level on weekends)
  - Statistical analyses may manage autocorrelation (e.g. autoregressive or dynamic regression models)
- *Carryover and slow-onset effects*: The impact of psychological and behaviour change interventions does not end immediately after withdrawal of treatment, leading to carryover effects, or irreversible change, especially if long-term behaviour change is the goal of an intervention
  - Behavioural change therapies that are most likely to have carryover effects are those that involve learning, attitudinal change, and knowledge or skill development[14]
  - Additional 'washout' periods may be included to limit carryover effects; but an N-of-1 trial may not be appropriate where there are likely to be enduring effects; a basic cross-over design (AB with long baseline and post-intervention data collection) may be more suitable
  - Slow-onset effects may also require longer periods of repeated measures – a good understanding of the health psychology underpinning behaviours and interventions is needed before embarking on a trial
- *Withdrawal or washout periods*: May not be feasible for interventions that have long-term sustained effects. In these cases, modification to the methodology is required, such as multiple baseline designs, which are suited to CAMs interventions that have a long metabolic half-life or a carryover learning effect in behavioural interventions.[3]

- *Determining* appropriateness: Not all behavioural interventions are appropriate for an N-of-1 study design. Interventions that are time-specific are more suited, due to the lower likelihood of carryover effects (e.g. prompts/cues; goal-setting). Interventions with intended long-term effects, such as those associated with learning (high carryover) are less appropriate
- *Allocation sequencing and blinding*: Flexibility is needed to account for carryover; different lengths of blocks for control days for 'washout'; blocks of varying lengths can be randomly allocated to reduce chances of predicting change between treatment and non-treatment days
- *Bias*: Type 1 error risk is common, whereby an intervention is thought to be effective when it is just as likely that the patient recovered spontaneously. Bias can be reduced through block randomisation or counterbalancing, repetitive measures, blinding of assessors and patients and accounting for carryover effects[81]
- *Hawthorne effect*: Another source of bias, whereby the high level of attention and interaction between patient and practitioner may lead to improvement with both intervention and placebo. Another condition, where the patient receives neither intervention nor placebo may allow an assessment of this effect.[3]

Administrative challenges for N-of-1 trials

Even a simple N-of-1 trial can have its challenges. Chalmers et al.[76] described the "formidable barriers and bureaucratic hurdles that led to substantial delays and expense" when attempting to implement a series of N-of-1 trials in the UK. The trials aimed to investigate the purported side effects attributed to long-term statin therapy for lowering cholesterol.

Chalmers et al.[76] suggested that N-of-1 trials could be facilitated by providing access to the following elements:

1. A research pharmacy to encapsulate, number and label two identical medications: placebo and active drug
2. A simple randomisation system for the crossover, with appropriate time periods tailored to the clinical question and to number the medication packs
3. A flexible method to collect repeated self-reports of potential beneficial and adverse effects (e.g. pain relief, gastrointestinal upsets)
4. Some 'back-end' online software to process, analyse and present the data to clinicians and patients.

This type of administrative support may also allow retrospective aggregation of data from similar trials to establish more robust estimates of treatment effects. Over time, the logistical and cost barriers may decrease and the databank of results may be sufficient to inform some clinical decisions, without the need to repeat trials in each individual.

Other challenges

The health care provider's time, patient's willingness and overall costs of running a trial are recognised barriers to conducting N-of-1 trials.[4, 16]

- *Clinician time*: Trials may require multiple appointments for transition between conditions and outcome assessment
- *Patient time*: Multiple assessments and outpatient visits can be onerous
- *Costs (not reimbursed)*:
  - Developing data collection tools
  - Developing randomised treatment plans

- Developing blinding strategies
- Designing and preparing medications/interventions
- Database preparation and analysis.

The role of genetics and genomics

There is growing recognition of the unique characteristics of individual patients, including at the genetic level, and the role of precision medicine in delivering patient-centred care. Genetics and heredity has been used to guide clinical decision-making in many conditions; and genomics, which involves the interrelationship between genes and their functions, is the cornerstone of precision medicine.[82] For example, many cancer drugs have shown greater efficacy when they are used to treat individuals with specific mutations or genetic profiles.[11, 83] This is a fast-growing area of research and, while N-of-1 trials perform a key role in this area, it is beyond the scope of this report.

Moreover, just knowing the risk or susceptibility may not change individual behaviour to prevent disease. Other factors, including environmental factors or patient preferences, may play a role in determining the optimal treatment strategy for an individual.

Pooled N-of-1 trial data

In the traditional RCT approach, a large population sample is recruited to a study to assess the average response to an intervention. Additional analyses may identify specific characteristics that distinguish responders from non-responders. In contrast, a **series** or aggregate of N-of-1 trials can achieve the same goal by recording responses for each patient and noting which ones benefited from the intervention. Identifying common characteristics in responders may be used to inform future implementation of the intervention in patients with similar characteristics or conditions.[11] That is, where it is not feasible to conduct an N-of-1 trial on an individual patient, but there are data available on many N-of-1 trials, the combined results may still be used to guide clinical decision-making in patients not involved in the trials.[84] Advances in medical record systems may allow more efficient data capture and analysis; and sharing data in a secure and safe manner may assist patients more broadly.[11]

Aggregated N-of-1 trials offer a balance of feasibility, economy and rigorous methodology for personalised medicine.[81] A comparison of aggregated N-of-1 trials with parallel group RCTs showed that well-conducted N-of-1 trials that accounted for carryover effects provided better estimates of patient-level random effects.

Costs

Given the increasing costs in medications, devices and health care services, a precise assessment of therapeutic effectiveness through an N-of-1 trial may be more cost-effective than a series of stepped care or Trial by Therapy attempts to find the most effective treatment, particularly in long-term chronic conditions.

An investigation of the costs and impact of a series of three N-of-1 trials in Australia (arthritic pain, neuropathic pain, attention deficit hyperactivity disorder) demonstrated both cost savings and overall better adherence with optimal treatment.[85] While increased costs occurred in some patients who were switched to more expensive medicines, cost reductions were achieved in over 70 per cent of patients by de-prescribing unnecessary expensive medications or reduced healthcare use post-trial. Therefore, overall costs can be offset by reducing the number of clinic visits and less time wasted on suboptimal treatment approaches.

Importantly, Scuffham et al.[85] reported significant cost-savings to the health system in the osteoarthritis and neuropathic pain trials, with most savings due to reduced consultations, rather than medication costs.

Scuffham et al.[85] also estimated that the marginal costs for each trial were approximately $600 per participant, where there was a research agenda involving a series of trials. In practice, the marginal costs may be limited to preparation and dispatch of medications, data collection and analyses and report generation (approximately $100 per patient), not including fixed costs related to design of protocols, questionnaires, and pharmaceutical packs.

An economic analysis of N-of-1 trials was beyond the scope of this report. However, Kravitz et al.[9] have dedicated a chapter of their guidelines to addressing the financing and economics of conducting N-of-1 trials.

Support

To sustain the renewed interest in single-case experimental designs and precision medicine, support is needed to promote use of N-of-1 trials through development of systems to facilitate trials; and engagement and training of health care practitioners in execution of good quality trials.[9]

Since N-of-1 trials are closely aligned with the informal Trial by Therapy that is common in clinical practice, health care providers may be receptive to incorporating the more rigorous protocols of an N-of-1 trial if some support is available.[16]

Patient-centred approach

Placing patients at the centre of their own care is widely believed to improve compliance with treatment and patient outcomes.[3]

N-of-1 trials are a useful tool to engage patients in their own health care and to incorporate their values and preferences (e.g. culture, lifestyle). It also increases their understanding of their condition and improves communication with their health care provider.

Tangible benefits for the patient include:

- Involvement in their own healthcare decisions, including design of the trial; outcomes to be assessed
- Results in a timely manner that inform immediate treatment decisions
- Long-term follow-up to ensure ongoing effects and assessment of adverse events
- Re-evaluate current treatments e.g. if a patient is using expensive supplements or services, they may want to know if it is worth the cost.[3]

Although potential candidates for N-of-1 trials are not required to meet the restrictive inclusion criteria for a RCT, the success of a trial is enhanced when patients are fully engaged, have a positive and open attitude to novel approaches, a high level of motivation, good cognitive capacity and willingness to put in the effort needed.[9] A strong and trusting relationship between the patient and clinician is also critical. Evidence suggests that patients preferred participating in N-of-1 trials compared with RCTs as they were more likely to receive at least one active treatment, rather than potentially be assigned to a control group.

Research and ethics

A large proportion of the evidence base related to N-of-1 trials focused on the research value of the design and the quality of reporting.[86] Since the key focus of this review pertains to clinical decision-making for the individual patient, a discourse on research quality is outside the scope of this report.

If the purpose of the N-of-1 trial is to determine the optimal treatment for a patient, research ethics approval is not required. However, if the practitioner intends to publish results or share findings, then the trial requires research ethics approval.[3, 34]

Health care professionals undertaking N-of-1 trials for research purposes should consult their professional association or University to ensure that they have adequate professional indemnity insurance.[3] In addition, independent oversight of a trial is good practice to monitor patient safety, quality of data and unbiased assessment of treatment effects.[3]

In brief, for research purposes, randomisation, blinding and placebos are more important for publishing results. In contrast, for clinical care, optimal patient care, informed consent and trial design are intended primarily for the patient's benefit.

An ethical framework for N-of-1 research trials has been developed and provides guidance on the research ethics requirements.[87]

Reviews in progress

A systematic review is currently underway to assess the usefulness of N-of-1 trials for achieving optimal individualised treatment strategies; and to determine the clinical conditions in which they would be beneficial.[2] The findings from this review are not yet available (personal communication with authors).

Two other systematic literature reviews on N-of-1 trials are currently underway:

- Systematic review of N-of-1 trial protocols and reporting guidelines[88]
- Systematic review of N-of-1 trials used as a decision support tool in clinical practice.[89]

SUMMARY AND CONCLUSIONS

A patient-centred care approach

The N-of-1 trial design brings the most value to a patient-centred care approach when there is uncertainty related to: 1) the comparative effectiveness of treatment options (e.g. mixed results from RCTs); 2) the absence of good quality clinical trials (e.g. rare conditions); 3) the effectiveness of new therapies that demonstrate marginal benefits compared with existing treatments; or 4) the individual patient's unique characteristics that differ substantially from existing clinical trial participants.

Flexibility of the N-of-1 trial design

The flexibility of the N-of-1 trial design allows it to be tailored to the individual. The nature of the condition, clinical goals, type of intervention and unique characteristics of the patient will inform the design of the N-of-1 trial.

To enhance the rigour and validity of the study, there are several criteria to consider:

- Appropriateness of the trial design
- Relevant and repeatable measurements
- Multiple crossover, balanced sequence of treatments
- Randomisation, blinding, washout periods and statistical analyses, where feasible.

Benefits and challenges of the N-of-1 trial

The main benefits of the N-of-1 trial are the patient-centred focus, the direct benefits to the patient, and the enhanced communication between the patient and provider. However, there are also challenges related to this approach. It takes time and effort from both patient and health care provider.

Access to resources and support services may facilitate the implementation of N-of-1 trials in practice; and reduce the costs and inconvenience of data collection. The three key areas of support are:

- Trial support services: To assist with randomisation, compounding pharmacy for medications/placebo and independent oversight to avoid bias
- Technologies (e.g. smartphone Apps): To collect data, monitor symptoms and provide prompts to patients
- Shared support networks: To enhance skills in designing and conducting trials; and counterbalance some of the challenges.

Concluding remarks

As with findings from RCTs, not every N-of-1 trial is certain to provide clear guidance on clinical decisions. It is possible that results do not favour one intervention over another, or that two interventions are equally effective. However, where no discernible difference is demonstrated, other factors may inform decision-making, such as cost, convenience, side effect profile or patient preferences. In addition, other data collected through self-tracking by the patient may reveal triggers or modifiers to consider. Thus, the rigour of the model may reduce the time wasted on ineffective treatments and identify a clearer path to recovery.

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APPENDIX

Box 1. Original N-of-1 trial in 1985

Theophylline or ipratropium bromide for asthma in 65-yr-old man[5]

Subject: 65-yr-old male with stable asthma

Trial design: multi-crossover periods of 4 x 20-day blocks:

- Theophylline or placebo for 10 days
- Ipratropium bromide or placebo for 10 days

Identical tablets compounded by pharmacist

Measures: Daily self-report on asthma symptoms

Data analysis: After 4 blocks (2 placebo; 2 theophylline), results clearly showed that symptoms were worse with theophylline

After ceasing theophylline, a subsequent drug-placebo sequence with Ipratropium bromide indicated improvement in symptoms

Data collection: Series of similar trials aggregated to identify population-level trends