

What follows is my last email from him about a year before he passed and an article he sent me.
From Dr Meyers.

The approach you use to evaluate the treatments you are trying involves starting a test compound and then using the PSA change to evaluate effectiveness. This is basically an informal clinical trial with an N=1. I just came upon a nice review of the history and statistical issues involved in such trials. As you read it, you will see that this approach has been widely used to optimize the treatment of individual patients. They discuss many interesting issues. For example, they review the difference between informal use by clinicians to optimize the management of individual patients and a formal approach with publication as a goal."

Paper follows that Dr.Meyers sent attached to his email of N=1 clinical trials.

From the James Lind Library

The history and development of N-of-1 trials
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Introduction

‘Trials of therapy’, in which physicians ‘try out’ treatments and assess patients’ responses, are long-established, common elements of routine medical practice.

Because ‘trials of therapy’ are usually informal, they may only be reported if treatments are associated with dramatic changes in a patient’s condition – whether by improvement or deterioration.

Our understanding of bias suggests that informal

‘trials of therapy’ – comparisons of patients’ condition before and after treatment – do not provide a

trustworthy basis for inferring treatment effects.

More sophisticated comparisons are usually needed: for example, comparing a patient’s responses when

treatments are given or withheld ('crossed over') and conducting formal assessment of outcomes. In 1676, Richard Wiseman (a surgeon to King Charles II) reported an unplanned experiment. He had prescribed a pair of laced stockings for a patient suffering from leg oedema. The stockings had reduced the oedema to the extent that the patient 'was able to walk to his closet, and take the air in his coach, and

was well pleased with them'.¹ However, someone suggested to the patient that the stockings might do him

harm and persuaded him to remove them. His legs swelled up, he became confined to bed again and developed leg ulcers. Dr Wiseman waited six weeks for the ulcers to heal, restored the laced stockings, with the result that the patient recovered.

A century after Wiseman's crude crossover trial of laced stockings, Caleb Parry,^{2,3} a doctor in Bath, England, published a more formal, planned use of between two and six crossover periods of variable duration in 13 patients, to compare the purgative effects of three varieties of rhubarb. Parry was unable to find any advantage of the more costly Turkish rhubarb compared with English rhubarb. Parry's 'trials of therapy' were important in having used at least two crossovers, but he took no steps to

ensure that his and his patients' assessments of the treatment effects were not influenced by his or the patients'

knowledge of the type of rhubarb being given. Fourteen years later, also in Bath, John Haygarth⁴ compared the

effects on rheumatism of a metal 'tractor' with a matched wooden (placebo) tractor. This demonstrated that the assumed treatment effects of the metal tractor resulted from patients' imagination.⁵

Haygarth's study made clear that informal 'trials of

therapy' can be plagued by false positives (due to placebo effects, physicians' and patients' desires to please,

the pre-existing expectations of both parties and natural history). And they can also result in false negatives

(patients destined to deteriorate and the intervention resulting in them remaining stable). Although more than a century passed after Haygarth before Paul Martini set out principles for designing unbiased crossover trials in his 69-page book,^{6,7} it appears that

it was not until 1953 that serious scientific consideration was given to how controlled trials in individual

patients could complement traditional parallel group trials. Hogben and Sim⁸ recognised that:

The now current recipe for a clinical trial based on group comparison sets out a balance sheet in which individual variability with respect both to nature and to previous nurture does not appear as an explicit item

in the final statement of the account; but such variability of response to treatment may be of paramount

interest in practice.

Trialists conducting parallel group trials using alternate or random allocation had been trying for half a

century to deal with the challenge of deducing how to treat individual patients by using estimates of effects

in subgroups of participants, but this was only a partial way of addressing the fundamental underlying

issue – ascertaining individual responses.⁹

The experiment reported by Hogben and Sim is a methodological landmark (see Appendix 1 for a list of N-of-1 trials completed to date), celebrated more than half a century later by republication and commentaries in the International Journal of Epidemiology.

10–12 One

of the commentaries¹² summarises the features of the study:

Because they used patient's self-reported symptoms, they put a particular emphasis on careful blinding:

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the use of a placebo and keeping both clinical and patient unaware of the sequence of treatments. They were also concerned about the non-specific response

to prostigmine so they used two comparators: dex-amphetamine (a stimulant) and lactose (as an inert

placebo). Their weighted analysis, based on concerns about wash-out and wash-in effects, also appears to be novel. Finally, with a minimum of eight periods for each treatment, they seemed to have set a new record for the number of crossovers in any crossover trial in an individual patient.

Hogben's and Sim's paper does not appear to have had an impact – possibly because it was published in a non-clinical journal. Glasziou¹² identified only 12 citations, and only one of those reported a replication of their methods (in 30 patients in a neurosis unit).¹³ Thereafter, these two studies and developments in the application of single subject design methodology in the social sciences¹⁴ appear to have gone unnoticed in the medical community until 1986.

Baskerville et al.¹⁵ were the first to apply principles of adaptive design to the N-of-1 model. Instead of fixed treatment periods, length was determined by adverse events, clinical deterioration, and patient preference. Their model was further expanded to account for typical crossover features, including carry-over effects.¹⁶

N-of-1 trials come of age

In 1986, in the *New England Journal of Medicine*, a group of clinical investigators at McMaster University, Canada, published a paper entitled 'Determining optimal therapy – randomized trials in individual patients', in which they labelled such studies 'N of 1 randomized control trials'.¹⁷ Their interest had been prompted by a poorly controlled asthmatic patient treated with inhaled beta agonists, theophylline and prednisone. The N-of-1 trial they designed addressed the utility of the theophylline the patient

was using. After the second paired block of theophylline and placebo, the patient ended the trial early: the

results were clear to him, and, from the symptom diary he had been keeping, to the clinician who instituted the trial. When the blind was broken, it was clear that during the periods when the patient had been using theophylline his symptoms were much worse. Improvement was sustained when theophylline was withheld after the trial ended, with much better asthma control despite a reduced dose of steroids.

The trial proved spectacularly helpful: improved symptom control, reduced drug burden and decreased costs.

Among the class of single patient/person study designs, 18–20 N-of-1 trials are unique as rigorously

controlled intervention studies that can provide a basis for inferring cause and effect. Though many variations exist, the work that originated at McMaster University focused on single patient trials with two or more pairs of treatment periods, one for the intervention and one for the comparator, ideally with blinding of both patients and healthcare providers (Figure 1). The outcome measures in such trials are the experiences of the patients, recorded using individualised, patient-reported outcomes.

Clinicians have now formally reported on hundreds, if not thousands, of N-of-1 trials, exploring

their utility in avoiding unnecessary treatment and improving patient outcomes, and also in facilitating drug development (See Appendix 1). Despite these

reports, and the enormous potential that the originators saw for use of N-of-1 trials, their uptake has

remained limited in the decades since 1986, although there have been recent signs of renewed interest.^{22–25}

The N-of-1 niche

The N-of-1 trial identifies whether an intervention is

likely to benefit or cause unwanted effects in an individual patient. The design is most suited to assessing

interventions that act and cease to act quickly.

It is particularly useful in clinical contexts in which

variability in patient responses is large, when the evidence is limited, and/or when the patient differs in

important ways from the people who have participated in conventional randomised controlled trials.

Examples include conditions with quickly acting symptomatic treatment, in which variability in response is large (e.g. chronic pain, obstructive lung disease); conditions with a prevalence too low for large, parallel group randomised controlled trials; medically complex patients who differ substantially from patients who have participated in existing Figure 1. Depiction of N-of-trial. Modified from Shamseer et al.²¹

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trials; and patients who have been treated over a long time when there is uncertainty about ongoing need

for treatment (e.g. proton pump inhibitors in longstanding dyspepsia). Indeed, the applicability of the

results of parallel group randomised clinical trials to

individual patients (i.e. external validity) may sometimes be limited by narrow inclusion criteria and the

exclusion of patients with co-morbidities and/or concurrent treatment Reviews of randomised controlled

trials have found average exclusion rates of 73% and

recruitment of less than 10% of patients with the primary diagnosis.²⁶ These concerns, however, should

be tempered by knowledge that true subgroup effects are very unusual.²⁷ The real issue of importance to N-of-1 trials is the likelihood, in many instances, of large variability in responses among patients.²⁸

N-of-1 trial services

The result of their first N-of-1 trial inspired the team at McMaster to develop a full N-of-1 referral service to

address patient dilemmas that met criteria for our N-of-1 designs: therapeutic impact was uncertain, the

treatment target was to reduce daily or otherwise frequent symptoms, the intervention (typically a drug)

worked quickly, and it quickly ceased acting. Within two years, the group had completed 57 N-of-1 trials. Results had provided a definite therapeutic answer in 88% of the patients studied and these results prompted

39% of physicians to change their prior-to-trial treatment plan. This experience led the McMaster team to

offer guides for clinicians wishing to apply the N-of-1 concept in their own practice.²⁹ Ultimately, however, the clinical communities interest in conducting N-of-1 trials diminished and the service was terminated.

Eric Larson was in the audience at a presentation of the McMaster work at the American Federation for Clinical Research.³⁰ Appreciating the utility of the design, Larson developed an N-of-1 clinical service at the University of Washington. Over two years,

Larson's group completed 34 trials, again demonstrating that N-of-1 trials could provide physicians with

useful treatment guidance in uncertain cases and improve patient satisfaction.³¹ Unfortunately, funding for the service ran dry and it was discontinued.

In 1999, the University of Queensland in Australia created the first national N-of-1 research service,

referred to as a 'single patient trial service'.³² The service was designed to acquaint general practitioners

with research methodology and to introduce research-derived data into clinical decision-making for conditions where treatment effectiveness was uncertain.

Physicians could refer their patients to the service,

which was centrally located, and so used mail and telephone communication only. The service managed all

major components of trial management: randomisa-

tion, preparing tablets, sending all materials to patients, following up, and relaying results to clinicians. Of the N-of-1 trials carried out by this service and which had available data, post-trial management decisions were consistent with trial results at 12 months in approximately 70% of attention deficit hyperactivity disorder trials³³ 45% of osteoarthritis trials,³⁴ and 32% of neuropathic pain trials.³⁵ This is a successful example of how

N-of-1 trials can be implemented at a national level, though, again, only as a temporary research initiative. Another example of the versatility of N-of-1 trials began when the Complementary and Alternative Research and Education (CARE) programme at the University of Alberta established the first academic paediatric integrative medicine programme in

Canada. In 2006, as part of this programme, a paediatric N-of-1 service responded to the increased use of

complementary therapies in children with chronic conditions. The goal of this service is to offer an objective, evidence-based approach to assessing whether a given complementary therapy is effective for a specific patient. The service is designed to assist patients, their parents and referring physicians throughout all stages of the N-of-1 trial, including the design and implementation of the N-of-1 evaluation. For example, this service has assessed natural health products (e.g. melatonin, probiotics, micronutrients) and acupuncture for conditions including attention

deficit hyperactivity disorder, eczema, sleep disturbances, chemo-induced nausea and vomiting, irritable

bowel syndrome and autism.

N-of-1 in drug development

The McMaster group speculated that drug development might also benefit from use of the N-of-1 methodology. The reasoning was that pre-approval drug

development costs are high (average \$479–936 million USD^{36,37} and rising³⁸). Conducting N-of-1 trials before a costly large-scale randomised controlled trial could (a) help to assess early efficacy, (b) be less expensive than traditional approaches, and (c) identify predictors of response.³⁹

The idea of applying the N-of-1 approach to early

drug development arose from experience with multiple N-of-1 trials in specific conditions. For instance,

when what is now termed myofascial pain syndrome

was labelled fibrositis and there had been one apparently positive randomised controlled trial of amitriptyline, the condition provided a framework for N-of-1 trials in early drug development. The McMaster

team conducted 14 N-of-1 trials which demonstrated substantial benefit from amitriptyline at doses far lower than had been used for the primary indication³³² *Journal of the Royal Society of Medicine* 110(8)

for the drug, depression.³⁹ The McMaster team also demonstrated the utility of multiple N-of-1 trials in Alzheimer's disease⁴⁰ and in the use of home oxygen

in patients with chronic obstructive pulmonary disease.⁴¹ In each of these situations the process

appeared to be efficient, requiring limited cost and time investment. Nevertheless, subsequent attempts to apply the reasoning in drug development have been sporadic and unsuccessful.

Failure to revolutionise clinical practice:

were N-of-1 trials ahead of their time?

Early experience was disappointing, shattering the initial optimism that N-of-1 trials would quickly revolutionise clinical practice. There had been some tantalising results,⁴² but randomised controlled trials in which patients were randomised to conventional

care or to N-of-1 trials generally failed to show dramatically convincing benefits of participation in the

N-of-1 trials.^{43,44}

At McMaster University, despite educating local

clinicians, playing cheerleader, succeeding in conducting 73 N-of-1 trials over three years,⁴⁵ and inspiring other 'N of 1 services', interest still faded. An

attempt to use venture capital to create an efficient, marketable service went nowhere. Thirty years after our initial publication, few clinicians have even heard of N-of-1 trials.

Sporadic reports of success with N-of-1 continue. For instance, Joy et al.⁴⁶ reported findings consistent with 'the nocebo phenomenon' – patients sometimes report side effects to placebo:⁴⁷ in seven patients with

suspected but uncertain statin-associated myalgia, N-of-1 trials failed to detect any statin-related symptoms in any of the patients, allowing patients to continue the drugs. Despite such isolated reports of

successes, clinicians seldom use N-of-1 trials and most remain unaware of the design.

Renewed interest in N-of-1 trials

At the University of Alberta, recent efforts have focused on methodological issues related to N-of-1 trial design and reporting. For example, N-of-1

trials have been criticised for their lack of generalisability. The Alberta group recently partnered with the

Journal of Clinical Epidemiology to publish a series dedicated to N-of-1 trials and included papers to address this concern. A comprehensive systematic review of the design, analysis and meta-analysis of

N-of-1 trials found that the majority (60%) of published N-of-1 trials are published as a series (i.e. one

report publishing N-of-1 trial data about more than one participant for the same condition-intervention

pair), suggesting their value beyond assessing individual treatment effects and their potential to provide

more generalisable treatment effects. Indeed, the Oxford Centre for Evidence-Based Medicine⁴⁸ has

classified N-of-1 trials as Level 1 evidence, comparable to systematic reviews of randomised controlled trials.

By virtue of their methods (i.e. use of randomisation, blinding, formal outcome assessment), the

meta-analysis of N-of-1 trials may provide a valuable source of population data for conditions that

have little to no randomised controlled evidence,

and to help refine evidence when parallel group randomised controlled trials may exist.

Given the large number of published N-of-1 trials

in attention deficit hyperactivity disorder, the condition may serve as a clinical model to explore the

applicability of N-of-1 trials beyond the individual patient.⁴⁹ Investigators at the University of Alberta conducted a systematic review and meta-analysis of N-of-1 trials and demonstrated the use of traditional randomised controlled trial meta-analysis methods in N-of-1 trials.⁴⁹ In another study, Punja et al.⁵⁰

demonstrated the value of N-of-1 trials in meta-analyses by conducting a combined meta-analysis of

N-of-1 trial data with randomised controlled trial data. The inclusion of N-of-1 data in randomised controlled trial meta-analyses improved the precision of population treatment effects, suggesting their potential to provide a rich source of data allowing

for more powerful and reliable assessments of treatment effects.⁵⁰ This example also highlights the relevance of N-of-1 trials in conditions for which there is

also traditional randomised controlled evidence.

Range of conditions assessed in N-of-1 literature n
Diseases of the nervous system 27
Diseases of the musculoskeletal system and
connective tissue

20

Mental and behavioural disorders 17
Diseases of the digestive system 11
Diseases of the respiratory system 09
Diseases of the circulatory system 04
Endocrine, nutritional, metabolic diseases 02
Infections and parasitic diseases 02
Other (non-specific) 08

N1/4100; number of published N-of-1 studies that have assessed treatments for the respective condition category (adapted from Punja et al.⁵¹).

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Challenges and future directions

Methodological considerations for N-of-1 trials differ from those for standard, parallel group randomised controlled trials. When considering N-of-1 trials as a

research endeavour, investigators have proposed solutions to three major limitations among reported N-of-1 trials: incomplete reporting, marked variability in

quality, and unacceptably high rates of prospective protocol registration.

First, as is the case with parallel group randomised controlled trials, lack of complete and transparent reporting is a problem in the N-of-1 trial literature. The Alberta group⁵¹ found that authors of N-of-1 trials failed to report on a number of critical design and conduct elements: trial registration (97%), whether individuals with co-morbid conditions (77%) or on concurrent therapies (69%) were included, and whether adverse events were assessed (64%). Another review confirmed that the quality of

reporting of published N-of-1 trials was highly variable.⁵² The Alberta group led the development of the

CONSORT Extension for N of 1 Trials (CENT) in response to the limitations and heterogeneity in reporting,^{53,54} serving as a minimum checklist for reporting N-of-1 trials.

Second, careful development and reporting of N-of-1 protocols is necessary for researchers, ethics

review boards and funders. The Alberta group is currently developing a SPIRIT Extension for N of 1

Trials (SPENT). This will recommend essential elements in N-of-1 trial protocols, in the expectation that

this will help to improve the quality of published reports of N-of-1 trials and promote the inclusion of N-of-1 trial protocols in trial registries.

Third, only 3% of published N-of-1 trials are reported as having registered protocols prospectively. It is certain that not all N-of-1 trials are published and readily available (nor, for those conducted as part of optimal routine clinical practice, should they be) – unpublished trials begun as part of the research endeavour may create a risk of bias for future systematic reviews and meta-analyses. One way of capturing these trials would be to establish an electronic repository (as is done for conventional randomised controlled trials with clinicaltrials.gov) and encourage authors to register their N-of-1 trial protocols. This would help reviewers to identify selective outcome reporting and publication biases. Beyond these challenges, emerging methodologies may facilitate optimal use of N-of-1 principles.

Bayesian and adaptive designs have potential applicability to N-of-1 trials. Trials can be designed with

preset points based on adverse effects or patient preferences to crossover, change dose or discontinuation.

These methods can be used both to analyse and to

meta-analyse N-of-1 trials.^{55,56} The strength of Bayesian approaches lies in their ability to maximise the use of reliable available information from each

participant, as well as the use of reliable prior information for incorporation in the statistical model so

that each N-of-1 trial can inform the next. Zucker

et al.⁵⁶ have demonstrated the use of Bayesian methods to aggregate N-of-1 trials to yield estimates of

population treatment effects. Combining Bayesian approaches with adaptive designs may prove to be a useful combination for future N-of-1 trials.

Discussion

What explains the failure to adopt and sustain N-of-1 trials? The obstacles to conducting N-of-1 trials as an element of routine clinical practice have been too great. For many pharmacists, preparing identical

drug and placebo combinations proved too labour-intensive. For clinicians, N-of-1 trials take too much

time, even with easy-to-use guidance:²⁹ preparing questionnaires, instructing patients and examining the results all require clinician commitment.

By comparison, the simple question, ‘did the treatment help’ is too easy, and has too much face validity, compared to the more onerous substitution of a

formal N-of-1 trial. The late Professor Charles

Bridge-Webb proposed a workaround to the expensive, time-consuming process of arranging placebo.⁵⁷

He suggested a simplified N-of-1, The Single Patient Open Trials (SPOTs), substituting the blinded trial for an open one. This trial trades pragmatism for

rigour, particularly useful for independent practitioners without access to N-of-1 services.

The advent of technological advances may help to overcome the operational complexity and costs that have hindered the uptake of the N-of-1 methodology. The emergence of mobile electronic health devices makes it easier than ever for patients to engage

in their own healthcare. The creation of an IT-based N-of-1 trial platform would help clinicians and

patients to collaborate in designing their own N-of-1 trials, track health outcomes and produce a report of results for patients and clinicians to discuss.

Researchers from the University of California, Davis, have developed a mobile application called the ‘Trialist’

specifically to facilitate the conduct of N-of-1 trials in clinical settings. They are testing the feasibility and efficacy of this application in a randomised controlled trial comparing the effects on patient outcomes of participating in a mobile N-of-1 trial versus usual care.⁵⁸

This potential for N-of-1 trials as a way of providing clinical care differs from its use as a research endeavour. The distinction comes down to the intent behind conducting an N-of-1 trial. If the objective is to

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inform treatment decisions for an individual patient, the trial is optimal clinical care and should therefore not require formal ethics approval⁵⁹ nor regulatory oversight from agencies monitoring clinical research. When choices from among two or more alternative treatments are being considered, patients should be

informed about genuine uncertainties about their relative merits and how treatment should be selected in

these circumstances.⁶⁰ Random allocation within formal treatment comparisons is one of the options that should be offered to patients.

If the primary purpose of N-of-1 trials is to produce generalisable knowledge to inform treatment

decisions for future patients, these N-of-1 trials are more properly regarded as research. In these circumstances, compliance with methodological and ethics

standards will be expected. In 2014, the Agency for Healthcare Research and Quality commissioned a user's guide to N-of-1 trials, which clarifies this distinction.²⁴

N-of-1 trials may have a future, both as a research endeavour complementing standard trials and as a strategy for improving clinical care outside of the research setting. Unlike conventional parallel group randomised controlled trials, which assess what is

best on average for a given population, N-of-1 trials assess what is best for an individual patient.⁶¹ They are thus particularly well suited to emerging interests

in patient-centred research and ‘precision’ or ‘personalised’ medicine. N-of-1 trials support the evolution

of patient-centred research by offering an evidence-based approach for personalising care. They help to

answer, for example, which treatment options are most effective through a process that strengthens the clinician–patient relationship and ultimately empowers the patient to be more engaged with their healthcare. Furthermore, with the advent of ‘big

data’, and its hoped-for potential to inform care, N-of-1 trials can provide opportunities to learn how to

improve care. The potential exists. The extent to which it will be realised remains uncertain.

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Godbee K, Togher L, et al. Revision of a method quality rating scale for single-case experimental designs and

n-of-1 trials: The 15-item Risk of Bias in N -of-1 Trials (RoBiNT) Scale. *Neuropsychol Rehabil* 2013; 23: 619–638.

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Appendix 1

N-of-1 timeline

Author, year Citation Description/significance
Hogben and Sim,
1953

Hogben L, Sim M (1953). The self-controlled and self-recorded clinical trial for

low-grade morbidity. *Br J Prev Soc Med* 7:163–179.

Hare, 1955 Hare EH (1955). Comparative efficacy of

hypnotics: a self-controlled, self-recorded clinical trial in neurotic

patients. *British Journal of Preventive and Social Medicine* 9:140–146.

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Continued.

Author, year Citation Description/significance
Guyatt, 1986 Guyatt G, Sackett D, Taylor DW, Ghong J,

Roberts R, Pugsley S (1986).
Determining Optimal Therapy – –
Randomized Trials in Individual Patients.
N Engl J Med 314:889-892.

N-of-1 trials are first brought to the
attention of a wide medical readership

Guyatt, 1988 Guyatt G, Sackett D, Adachi J, Roberts R,
Chong J (1988). A clinician's guide for

conducting randomized trials in indivi-
dual patients. CMAJ 139: 497–503.

The practical approach presented
encourages clinicians to conduct N-of-1
trials

Guyatt, 1990 Guyatt GH, Keller JL, Jaeschke R,
Rosenbloom D, Adachi JD, Newhouse
MT (1990b). The n-of-1 randomized
controlled trial: clinical usefulness. Our
three-year experience. Ann Intern
112:293–299.

Results of the first N-of-1 trial clinical
service

Guyatt, 1990 Guyatt GGH, Heyting A, Jaeschke R, Keller
J, Adachi JD, Roberts RS (1990a). N of 1
randomized trials for investigating new
drugs. Control Clin Trials 11:88–100.

A proposal that individual N-of-1 rando-
mised controlled trials could be used to

elucidate drug effects at an early stage of
development

Molloy, 1991 Molloy DW, Guyatt GH, Wilson DB, Duke

R, Rees L, Singer J (1991). Effect of tet-
rahydroaminoacridine on cognition,

function and behaviour in Alzheimer's
disease. CMAJ 144:29–34.

Early use of multiple N-of-1 trials in a particular condition to address drug effectiveness

Zucker, 1997 Zucker DR, Schmid CH, McIntosh MW, D'Agostino RB, Selker HP, Lau J (1997). Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. *J Clin Epidemiol* 50:401–410.

Using Bayesian technique to combine N-of-1 trials

Guyatt et al., 2000 Guyatt G, Haynes RB, Jaeschke RZ, Cook DJ, Naylor CD, Wilson MC, Richardson WS (2000). Users; guide to the medical

literature: XXV. Evidence-based medicine: principles for applying the users'

guides to patient care. Evidence-Based Medicine Working Group. *JAMA* 284:1290–96.

N-of-1 trial described as top of methodological hierarchy for informing treatment decisions

Guyatt, 2002 Guyatt G, Zhang Y, Jaeschke R, McGinn T (2002). Therapy and Validity: N of 1 Randomized Controlled Trials. Users' Guides to the Medical Literature: A manual for Evidence-Based Clinical Practice. Chicago, IL: American Medical Association 275–290.

Users' guide to N-of-1 trials

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Continued.
Author, year Citation Description/significance

Nikles, 2006 Nikles C, Mitchell G, Mar C Del, Clavarino A, McNairn N (2006). An N of 1 trial service in clinical practice: Testing the

effectiveness of stimulants for attention-deficit/ hyperactivity disorder. *Pediatrics*

2006;117:2040–2046.

One of the largest series of N-of-1 trials carried out in children with ADHD - carried out by a National Service to support the conduct of N-of-1 trials (the first ever) in Australia

Zucker, 2006 Zucker DR, Ruthazer R, Schmid CH, Feuer JM, Fischer PA, Kieval RI, Mogavero N, Rapoport RJ, Selker HP, Stotsky SA, Winston E, Goldenberg DL (2006). Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. *J Rheumatol* 33:2069–2077.

Using Bayesian technique to combine N-of-1 trials

Tate, 2008 Tate RL, McDonald S, Perdices M, Togher L, Schultz R, Savage S (2008). Rating the methodological quality of single-subject designs and N of 1 trials: Introducing the single-case experimental design (SCED) scale. *Neuropsychol Rehabil* 18:385–401.

Single-Case Experimental Design (SCED) Scale

Zucker, 2010 Zucker DR, Ruthazer R, Schmid CH (2010). Individual (N of 1) trials can be

combined to give population comparative treatment effect estimates: methodological considerations. *Journal of*

Clinical Epidemiology 63:1312–1323.

Using Bayesian technique to combine
N-of-1 trials

Gabler, 2011 Gabler NB, Duan N, Vohra S, Kravitz RL
(2011). N-of-1 Trials in the Medical
Literature: a systematic review. Med
Care 49:761–768.

Systematic overview of the N-of-1
literature

OCEBM, 2011 OCEBM Levels of Evidence Working
Group*. “The Oxford Levels of
Evidence 2”. Oxford Centre for
Evidence-Based Medicine. [http://www.
cebm.net/index.aspx?o1/45653](http://www.cebm.net/index.aspx?o1/45653)

N-of-1 trials are considered level 1 evi-
dence by the Oxford Centre for

Evidence-Based Medicine

Tate, 2013 Tate RL, Perdices M, Rosenkoetter U,
Wakim D, Godbee K, Togher L,
McDonald S (2013). Revision of a

method quality rating scale for single-
case experimental designs and N of 1

trials: The 15-item Risk of Bias in N of 1
Trials (RoBiNT) Scale.
Neuropsychological Rehabilitation
23:619–38.

15-item Risk of Bias in N-of-1 Trials
(RoBiNT) Scale

DEcIDE Methods
Center N of 1
Guidance Panel,
2014

Kravitz RL, Duan N, eds, and the DEcIDE
Methods Center N of 1 Guidance Panel
(Duan N, Eslick I, Gabler NB, Kaplan
HC, Kravitz RL, Larson EB, Pace WD,

Schmid CH, Sim I, Vohra S) (2014).
Design and Implementation of N of 1
Trials: A User's Guide. AHRQ

N-of-1 AHRQ Publication

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Continued.
Author, year Citation Description/significance

Publication No. 13(14)-EHC122-EF.
Rockville, MD: Agency for Healthcare
Research and Quality; February 2014.
[www.effectivehealthcare.ahrq.gov/N-1-
Trials.cfm](http://www.effectivehealthcare.ahrq.gov/N-1-Trials.cfm).

Tate, 2014 Tate RL, Perdices M, McDonald S, Togher
L, Rosenkoetter U (2014). The design,
conduct and report of single-case
research: Resources to improve the

quality of the neurorehabilitation litera-
ture. Neuropsychological Rehabilitation

2014;24:315–31.

Reporting guidelines: Risk of Bias in N of 1
Trials (RoBiNT) Scale; Single-Case
Reporting guideline In BEhavioural
interventions (SCRIBE)

Shamseer, 2015 Shamseer L, Sampson M, Bukutu C, et al.
CONSORT extension for reporting N
of 1 trials (CENT) 2015: Explanation
and elaboration. BMJ 2015;350:18–46

CENT explanation and elaboration

Vohra, 2015 Vohra S, Shamseer L, Sampson M, Bukutu
C, Schmid CH, Tate R, Nikles J, Zucker
DR, Kravitz R, Guyatt G, Altman DG,
Moher D, CENT group (2015).
CONSORT extension for reporting
N-of-1 trials (CENT) 2015 Statement.

BMJ 350:h1738

CENT checklist

Punja, 2016 Punja S, Bukutu C, Shamseer L, Sampson M, Hartling L, Urichuk L, Vohra S (2016c). N-of-1 trials are a tapestry of heterogeneity. *J Clin Epidemiol* 76:47–56

A systematic review of the methods of design, analysis, and meta-analysis used in published N-of-1 trials

Punja, 2016 Punja S, Schmid CH, Hartling L, Urichuk L,

Nikles CJ, Vohra S (2016). To meta-analyze or not to meta-analyze? A

combined meta-analysis of N of 1 trial data with RCT data on amphetamines and methylphenidate for pediatric ADHD. *J Clin Epidemiol* 76:76–81.

Combined meta-analysis of N-of-1 trials with randomised controlled trial data

Punja, 2016 Punja S, Xu D, Schmid CH, Hartling L, Urichuk L, Nikles CJ, Vohra S (2016a).

N of 1 trials can be aggregated to generate group mean treatment effects: A

systematic review and meta-analysis. *J Clin Epidemiol* 76:65–75.

Meta-analysis of N-of-1 trials

Tate, 2016 Tate RL, Perdices M, Rosenkoetter U, Shadish W, Vohra S, Barlow DH, Horner R, Kazdin A, Kratochwill T, McDonald S, Sampson M, Shamseer L, Togher L, Albin R, Backman C, Douglas J, Evans JJ, Gast D, Manolov R, Mitchell G, Nickels L, Nikles J, Ownsworth T, Rose M, Schmid

CH and Wilson B (2016). The Single-Case Reporting Guideline In

BEhavioural Interventions (SCRIBE) 2016 Statement. *J Clin Epidemiol* 73:142–152.

Provides authors, readers and reviewers of single case design studies with a tool to maximise clarity, transparency and completeness in reports of such trials