Chapter 1
Introduction

Jane Nikles and Geoffrey Mitchell

N-of-1 trials are multi-cycle within-patient, randomized, double-blind, cross-over comparisons of a drug and placebo (or another drug) using standardized measures of effect. They provide evidence-based information on individual response to treatment and can be used to optimize the chronic disease management of the individual.

Why This Book? Why Now?

With the rising cost of patient care (including drug costs and clinic visits), N-of-1 trials have potential to minimize clinician and patient investment in time and money on suboptimal treatments. Recognition that the USA is in the midst of a healthcare crisis has prompted calls for advances in biomedical research. Potential ways forward are individualized medicine and personalized evidence-based medicine to improve treatment efficiency, by reducing individual patients' exposure to treatments that do not work and those that cause adverse side effects. In addition, moving towards a more individualized and personalized health-care system of the type built from the N-of-1 study principle and infrastructure, would allow exploration and tapping into the potential of genomics and wireless devices. In this context, a text setting out the theoretical and practical issues surrounding N-of-1 trials in the health setting is timely. This is illustrated by a quote from Lillie et al. 2011:

> Despite their obvious appeal and wide use in educational settings, N-of-1 trials have been used sparingly in medical and general clinical settings. We emphasize the great utility of

J. Nikles (✉) • G. Mitchell
School of Medicine, The University of Queensland, Ipswich, QLD, Australia
e-mail: uqjnikle@uq.edu.au; g.mitchell@uq.edu.au

J. Nikles, G. Mitchell (eds.), *The Essential Guide to N-of-1 Trials in Health*,
DOI 10.1007/978-94-017-7200-6_1

> modern wireless medical monitoring devices in their execution. We ultimately argue that N-of-1 trials demand serious attention among the health research and clinical care communities given the contemporary focus on individualized medicine. (Lillie et al. 2011)

This book presents a comprehensive compendium of issues around the design, conduct, implementation and interpretation of N-of-1 trials in a health system. The contributors are all experts in their own fields as they relate to N-of-1 trials or in N-of-1 trials themselves.

How This Book Came About

Our centre has conducted over 600 N-of-1 trials in areas ranging from osteoarthritis in adults to Attention Deficit Hyperactivity Disorder in children to palliative care. We have experience in conducting the trials face to face and by post and telephone; and both individually and aggregated together.

Our colleagues felt that the expertise we had developed in over 15 years of conducting N-of-1 trials was worth sharing more broadly and more in-depth than is possible in journal articles. The idea for a book was born.

At the time we commenced writing, there were no in depth books on N-of-1 trials in the health setting such as this one. However, Kravitz et al. (2014) have recently published a comprehensive text entitled "Design and Implementation of N-of-1 Trials: A User's Guide." Our book intentionally avoids significant overlap with their book.

How to Use This Book

The readers we hope to reach with this book are clinicians, academic researchers, health professionals or practitioners, scientists, and pharmaceutical company staff in the broad area of health; and funders and regulators in various countries who wish to investigate or conduct N-of-1 trials.

The book may also be useful for graduate students in methodologically based courses or doing research higher degrees in areas such as public health, and also for undergraduate students or interested consumers not trained in the health sphere.

We have written this book with two discrete audiences in mind. The first is interested clinicians who will gain benefit from an overview of the N-of-1 technique. We have included chapters that look at the clinical applicability of the technique, how to run an N-of-1 trial in individuals and how to combine results to gain a population estimate. We would suggest reading Chaps. 2, 3, 4, 5, 9, and 15 for this broader overview.

For those readers who desire in-depth examination of N-of-1 trial design, conduct and analysis, we have included chapters that are more technical in nature. This will be of considerable use to people designing high quality trials, and analyzing the data that arises from them, both in terms of determining individual treatment effects

and when aggregating the data to generate a population estimate. We would suggest reading Chaps. 6, 7, 8, 10, 11, 12, 13, 14, 16, and 17 for this more in-depth discussion.

A brief description of the chapters follows.

What are N-of-1 trials? In Chap. 2, Jane Nikles defines N-of-1 trials and provides a brief historical perspective. She discusses the background and rationale for N-of-1 trials, and describes their benefits.

Robyn Tate and Michael Perdices' chapter on N-of-1 trials in the behavioral sciences (Chap. 3) describes the application of N-of-1 trials in the behavioural sciences, where they are commonly referred to as single-case experimental designs (SCEDs). Four essential features demarcate single-case methodology from between-group designs: (i) the individual serves as his or her own control, (ii) use of a specific and operationally-defined behaviour that is targeted by the intervention, (iii) frequent and repeated measurement of the target behaviour throughout all phases of the experiment, and (iv) issues surrounding external validity. Features that strengthen internal and external validity of SCEDs are discussed in the context of a standardised scale to evaluate the scientific quality of SCEDs and N-of-1 trials, the Risk of Bias in N-of-1 Trials (RoBiNT) Scale. New work in developing a reporting guide in the CONSORT tradition (the Single-Case Reporting guideline In BEhavioural interventions, SCRIBE) is referenced. Subsequent sections in the chapter highlight differences among the prototypical single-case designs reported in the literature, both experimental (withdrawal/reversal, multiple-baseline, alternating-treatments, and changing-criterion designs) and non-experimental (biphasic A-B design, B-phase training study, preintervention/ post-intervention design, and case description/report), along with illustrative examples reported in the literature. The final section of the chapter describes available methods to analyse data produced by SCEDs, including structured visual analysis, randomization tests and other statistical procedures.

Following on from this, Geoff Mitchell in N-of-1 trials in medical contexts (Chap. 4) argues the case for N-of-1 studies assuming a place in the clinical armamentarium. Clinicians make treatment decisions on a regular basis, and some decisions may result in patients taking treatments for years. This decision-making is a core skill of clinicians, and if possible it should be evidence based. The problem is that the most common tool to aid this decision making, the RCT, has many problems which can lead to a patient being prescribed a treatment that may not work for them. N-of-1 studies may be useful tools to assist in making the best decision possible. This chapter argues the case for N-of-1 studies assuming a place in the clinical armamentarium. It describes the rationale for and uses of N-of-1 trials, the advantages and limitations of N-of-1 trials, and discusses aggregation of N-of-1 trials to generate population estimates of effect.

In the next chapter (Chap. 5) he outlines the rationale, methods, benefits and limitations of combining N-of-1 trials. The original purpose of N-of-1 trials is to determine whether a treatment works in a person. However, these trials can be considered as mini-randomized controlled trials (RCTs), with the person providing multiple datasets to the intervention and control groups. Therefore, several people undergoing the same N-of-1 trial can contribute many data sets and this rapidly

scales up to the point where the power of the trial can equate to a normal RCT, but with far fewer participants. This characteristic means that RCT-level evidence can be derived from populations that are almost impossible to gather data from, because of low prevalence conditions, or difficulty in recruiting or retaining subjects. This chapter describes the method in detail, along with methodological challenges and limitations of the method.

Chapter 6 on major design elements of N-of-1 trials by Kimmie Carriere, Yin Li, Geoff Mitchell and Hugh Senior discuss some important considerations when choosing a particular individual N-of-1 trial design. N-of-1 trials are extremely useful in subject-focused investigations, for example, medical experiments. As far as we are aware, no guidelines are available in the literature on how to plan such a trial optimally. In this chapter, they discuss the considerations when choosing a particular N-of-1 trial design, assuming that the outcome of interest is measured on a continuous scale. The discussion is limited to comparisons of two treatments, without implying that the designs constructed can apply to non-continuous or binary outcomes. Optimal N-of-1 trials under various models are constructed depending upon how we accommodate the carryover effects and the error structures for the repeated measurements. Overall, they conclude that alternating between AB and BA pairs in subsequent cycles will result in practically optimal N-of-1 trials for a single patient, under all the models considered, without the need to guess at the correlation structure or conduct a pilot study. Alternating between AB and BA pairs in a single trial is nearly robust to misspecification of the error structure of the repeated measurements.

In Chap. 7 Hugh Senior discusses a major concern in N-of-1 trials, common to any epidemiological approach – the introduction of bias and confounding. These factors may modify the size of the treatment estimate or shift the treatment estimate away from its true value. The methodological approaches of randomization, allocation concealment, and blinding are employed to prevent or minimize confounding and bias in trials. This chapter provides definitions and describes the various methods of randomization, allocation concealment, and blinding that can be adopted in N-of-1 trials. In addition, the chapter details the roles of specific research staff and the information required for the reporting of N-of-1 trial blinding methods in medical journals.

In Chap. 8 on data collection and quality control, Hugh Senior explains how to achieve a reliable data set for analysis that complies with the protocol. A system of clinical data management (the planning and process of data collection, integration and validation) is critical. This chapter provides a synopsis of the key components of clinical data management which need to be considered during the design phase of any trial. Topics addressed include the roles and responsibilities of research staff, the design of case report forms for collecting data; the design and development of a clinical database management system, subject enrolment and data entry, data validation, medical coding, database close-out, data lock and archiving. An additional section discusses the rationale for the requirement of trial registration.

Chapter 9, by Michael Yelland, offers a very practical account of the reporting of N-of-1 trials to patients and clinicians, using trials for chronic pain conditions as models which may be applied to many other forms of N-of-1 trials. It draws from

the author's experience in managing N-of-1 trials comparing celecoxib with extended release paracetamol for chronic pain and osteoarthritis and comparing gabapentin with placebo for chronic neuropathic pain. Reporting the results of N-of-1 trials to patients and health care professionals requires considerable planning to make reports user-friendly and an efficient tool for clinical decision making. Decisions need to be made about key elements of the report, how to order them with the most important summary elements first followed by detailed results, and how to set thresholds for clinically important changes. The inclusion of tables and graphs in reports should improve readability. An example of an individual report is provided.

Adverse events are covered by Hugh Senior in Chap. 10. The safety of subjects who volunteer to participate in clinical trials is paramount. ICH-Good Clinical Practice (ICH-GCP) guidelines assert that 'the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society'. This chapter describes the internationally accepted standard of the (ICH-GCP) guidelines. It introduces important clinical research terminology, and provides definitions of various types of adverse events, describes the roles and responsibilities of investigators and sponsors, and the processes needed to promote safety through the assessment, recording, evaluating and reporting of adverse events during the design and conduct of clinical trials.

Chapter 11, Research ethics and N-of-1 trials, by Andrew Crowden, Gordon Guyatt, Nikola Stepanov and Sunita Vohra, is an exploration of the ethics of N-of-1 trials and the nature of the relationship between clinical care and clinical research. Some N-of-1 trials are conducted as part of clinical care, others are developed as research. For those that are research, unless they are deemed exempt from formal review, a relevant Human Research Ethics Committee or Institutional Review Board should review specific projects before they are approved. N-of-1 trials should also be authorized by institutions before commencing. The level of risk to the patient/participant should guide and determine whether a particular project is exempt from review, subject to a low/negligible risk review, or should be reviewed by a full committee. Research ethics reviewers must develop a heightened ethical sensitivity toward ensuring that a misguided approach to N-of-1 review does not occur. Clinical researchers, institutions and research review committees, should recognize the continuum of clinical care and clinical research, in order to set and act from explicit standards which are consistent with the clinical practice – clinical research continuum.

Chapter 12 (Kerrie Mengerson, James McGree and Chris Schmid) discusses some techniques for exploratory data analysis and statistical modeling of data from N-of-1 trials, and provides illustrations of how statistical models and corresponding analyses can be developed for the more common designs encountered in N-of-1 trials. Models and corresponding analyses for other designs, perhaps involving different nesting of treatments, order and blocks, can be developed in a similar manner. The focus of this chapter is on continuous response outcomes, that is, numerical response data. The chapter is presented in tutorial style, with concomitant R code and output provided to complement the description of the models. Mixed effects models are also discussed. Such models can be extended to account for a variety of factors whose effects can be considered as random draws from a popula-

tion of effects. A taxonomy of relevant statistical methods is also presented. This chapter is aimed at readers with some background in statistics who are considering an analysis of data from an N-of-1 trial in the R package.

The economics of N-of-1 trials, Chap. 13, is written by Jennifer Whitty, Joshua Byrnes, and Paul Scuffham, who provide the rationale, challenges and methodological considerations for evaluating the economics of N-of-1 trials. First, they outline the rationale for undertaking an economic evaluation alongside an N-of-1 trial, by describing two key economic questions that are likely to be of interest to researchers, policy makers and clinicians. Then they outline the methods for undertaking an economic evaluation, highlighting some methodological aspects that are of particular relevance for the economics of N-of-1 trials as opposed to more traditional clinical trials. Finally, they acknowledge that the economic evaluation of N-of-1 trials is still in its infancy. We reflect on the research agenda to further develop the potential for N-of-1 trials to inform optimal decision-making around treatment and the appropriate allocation of health care resources.

Next, in Chap. 14, Margaret Sampson, Larissa Shamseer, and Sunita Vohra consider how to describe the individual and aggregated symptom data of N-of-1 trials for professional audiences. Whether an N-of-1 trial is undertaken to inform a particular clinical decision or to test a hypothesis, publishing it in the professional literature may inform other clinical decisions and contribute to the research evidence base. A well-reported N-of-1 trial will provide the transparency needed for readers to critically appraise the work and determine if it is applicable to their situation. A well reported trial can be replicated and, once replicated, results can be aggregated to provide stronger and more compelling evidence. The chapter describes in detail a reporting guideline for N-of-1 trials, CENT (**C**onsort **E**xtension for reporting **N-of-1 T**rials). CENT provides a structured format to ensure that the main journal report is sufficiently detailed that it can be critically appraised and replicated. As well, prospective registration of the trial and data deposit is discussed as means to further increase the transparency and completeness of reporting.

Single Patient Open Trials (SPOTs) are described by Jane Smith, Michael Yelland and Chris Del Mar (Chap. 15). Single patient open trials (SPOTs) are nearly identical to standard trials of treatment. The added essential ingredient is a (commonly arrived at) set of symptoms to monitor (the *outcome measure*). This means they lie somewhere in between formal N-of-1 trials and totally informal trials of treatment in terms of rigour. SPOTs are accordingly less demanding to arrange (for both the patient and clinician) than N-of-1 trials, but they require considerably more effort and commitment than casual trials of treatment. This chapter defines and describes the rationale for SPOTs, discusses when and why they could be used, as well as their limitations, and describes outcome measures and analysis. As well as describing the use of SPOTs in clinical contexts, it covers the extra considerations required when using SPOTs in research. Several examples of the practical application of SPOTs are given, some with the resulting data. It is anticipated that the examples may be adapted to enable other clinicians and their patients to perform their own SPOTs to validate other medical interventions in the context of the individual.

Next, Kerrie Mengersen, James McGree and Christopher Schmid discuss issues and approaches related to systematic review and meta-analysis of N-of-1 trials. Chapter 16 describes some basic guidelines and methods, and some important steps in a systematic review of these types of trials are discussed in detail. This is followed by a detailed description of meta-analytic methods, spanning both frequentist and Bayesian techniques. A previously undertaken meta-analysis of a comparison of treatments for fibromyalgia syndrome is discussed with some sample size considerations. This is further elaborated on through a discussion on the statistical power of studies through a comparison of treatments for chronic pain. The chapter concludes with some final thoughts about the aggregation of evidence from individual N-of-1 trials.

Finally, in Chap. 17, Jane Nikles looks at the current status of N-of-1 trials and where N-of-1 trials are headed. N-of-1 trials and review articles have recently been published in the areas of chronic pain, pediatrics, palliative care, complementary and alternative medicine, rare diseases, patient-centered care, the behavioral sciences and genomics. These are briefly reviewed and the current place of N-of-1 trials discussed. The chapter concludes with a vision for the future of N-of-1 trials.

We trust you find the book useful. Feedback that might inform later editions is welcomed.

References

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). Design and implementation of N-of-1 trials: a user's guide. AHRQ Publication No. 13(14)-EHC122-EF. Agency for Healthcare Research and Quality, Rockville, February 2014. www.effectivehealthcare.ahrq.gov/N-1-Trials.cfm

Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ (2011) The N-of-1 clinical trial: the ultimate strategy for individualizing medicine? Pers Med 8(2):161–173