Received: 15 February 2024 | Revised: 28 June 2024 | Accepted: 10 July 2024

DOI: 10.1111/epi.18068

Epilepsia

CRITICAL REVIEW

N-of-1 trials in epilepsy: A systematic review and lessons paving the way forward

Victoria M. Defelippe[1,4] | **Eva H. Brilstra**[2,4] | **Willem M. Otte**[1,4] | **Helen J. Cross**[3,4] | **Finbar O'Callaghan**[3,4] | **Valentina De Giorgis**[4,5] | **Annapurna Poduri**[6] | **Holger Lerche**[4,7] | **Sanjay Sisodiya**[4,8] | **Kees P. J. Braun**[1,4] | **Floor E. Jansen**[1,4] | **Emilio Perucca**[4,9,10]

[1]Department of Child Neurology, UMCU Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Department of Genetics, UMCU Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

[3]Developmental Neurosciences, University College London (UCL) Great Ormond Street NIHR BRC, Institute of Child Health, London, UK

[4](Affiliated) member or collaborating partner of the European Reference Network (ERN) for rare and complex epilepsies (EpiCARE), Barcelona, Spain

[5]Fondazione Mondino National Institute of Neurology/University of Pavia, Pavia, Italy

[6]Epilepsy Genetics Program, Boston Children's Hospital and Department of Neurology, Harvard Medical School, Boston, Massachusetts, USA

[7]Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University and University Hospital of Tübingen, Tubingen, Germany

[8]Department of Clinical and Experimental Epilepsy, UCL Queen's Square Institute of Neurology, London, UK

[9]Department of Medicine, University of Melbourne (Austin Health), Heidelberg, Victoria, Australia

Abstract

Objective: Defined as prospective single-patient crossover studies with repeated paired cycles of active and control intervention, N-of-1 trials have gained attention as an option to obtain high-quality evidence of efficacy, particularly for patients with rare epilepsies in whom conduction of well-powered randomized controlled trials can be challenging. The objective of this systematic review is to provide an appraisal of the literature on N-of-1 trials in individuals with epilepsy.

Methods: We searched PubMed and Embase on January 12, 2024, for studies meeting the following criteria: prospectively planned, within-patient, multiple-crossover design in individuals with epilepsy and outcomes related to comorbidities. Information on design, outcome measurements, intervention, and analyses was retrieved. Risk of bias assessment was performed using the Risk of Bias in N-of-1 Trials (RoBiNT) scale. We highlighted methodological aspects of the N-of-1 trials identified and discuss future recommendations.

Results: Five studies met our inclusion criteria. An additional multiple-crossover trial that evaluated treatment effects exclusively at group level was also included because of its relevance to N-of-1 study methodology. The studies enrolled individuals with focal seizures, absences or cognitive impairement and electrographic discharges. Treatments included established or investigational antiseizure medications, off-label medications, neurostimulation or lifestyle intervention. Three of the five N-of-1 trials reported on individual cases. The studies' strengths were the use of individualized treatment dosages and symptom-specific patient-reported outcomes. Limitations were related to minimal reporting of baseline characteristics and seizure burden.

Significance: The trials identified by our search exemplify how the N-of-1 design can be applied to assess interventions in individuals with epilepsy-related

Floor E. Jansen and Emilio Perucca shared last authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2024 The Author(s). *Epilepsia* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

[10]Australia and Department of Neuroscience, Monash University, Melbourne, Victoria, Australia

Correspondence
Victoria M. Defelippe, Department of Child Neurology, UMCU Brain Center, University Medical Center Utrecht, P.O. Box 85090, 3508 AB Utrecht, The Netherlands.
Email: v.m.defelippe-2@umcutrecht.nl

disorders. Future N-of-1 trials of antiseizure interventions should take into account baseline seizure frequency, should apply statistical models suited to capture seizure frequency changes reliably and make predefined interim assessments. Non-seizure outcome measures evaluable over short periods should be considered. Tailored N-of-1 methodology could pave the way to evidence-based, treatment selection for patients with rare epilepsies.

KEYWORDS
antiseizure/therapeutic use, clinical trials methodology, medical care, outcome assessment (healthcare), precision medicine, single-case studies

1 | INTRODUCTION

Epilepsy is a serious and disabling neurological condition that affects 65 million individuals worldwide.[1,2] In the last decade, genomic research, accelerated by next-generation sequencing technologies, has identified pathogenic single gene variants responsible for 20%–40% of epilepsies with onset in the first 3 years of life, leading to improved diagnosis and management.[3–5] Although guidelines for treating epilepsy exist, treatment selection remains challenging, particularly for rare epilepsies, defined as those occurring no more than 1 per 2000 people.[6] Traditionally, physicians rely on available evidence to select a treatment, including guidelines based on results of randomized controlled trials (RCTs). Conventional RCTs are not feasible for many rare epilepsies, for which evidence on the value of existing therapeutic options is restricted mainly to case reports or small retrospective studies. Due to the low prevalence of these disorders and phenotypic heterogeneity, conducting conventional RCTs with sufficient statistical power to assess treatment outcomes reliably can be challenging. Moreover, reported group averages in RCTs may lack relevance for individual patients due to the prominent between-patient heterogeneity. Inadequate or subjective assessment of treatment efficacy might lead to unnecessary continued exposure to medication, or to premature withdrawal of therapies, thereby prolonging the search for an effective treatment.

Key points

- For the majority of rare epilepsies, low disease prevalence and interpatient heterogeneity hamper the feasibility of conventional randomized controlled trials. N-of-1 trials can provide a valuable option to assess the effectiveness of therapeutic interventions in these patients.
- We define N-of-1 trials as prospective single-patient studies with an active and comparator intervention as well as more than one crossover period, with the individual as the unit of observation.
- Five N-of-1 trials that assessed the efficacy of different epilepsy treatments met our inclusion criteria.
- The design of future N-of-1 trials in epilepsy should be adjusted to take into consideration treatment characteristics, baseline seizure frequency and relevant non-seizure outcomes.

1.1 | Single-patient crossover "N-of-1" trials

The challenges summarized in the preceding could be addressed by conducting N-of-1 trials. Although the term "N-of-1 trial" is sometimes used broadly to indicate trials in an individual patient that assess outcomes after an intervention compared with baseline or natural history,[7,8] N-of-1 trials are defined here as prospective single-patient crossover studies with repeated paired cycles with an active intervention ("A") and a control intervention ("B"), which could be placebo or another active treatment, with monitoring of treatment outcomes at the individual level.[9–13] This design may include key components of RCTs to counteract sources of bias, such as the use of blinding and randomization of treatment sequences. An additional advantage is the option of aggregating results from multiple N-of-1 trials to determine effects at the population level.[14–17] The N-of-1 trial design is suitable for chronic diseases, which are not rapidly progressive, provided the targeted outcome can be reliably measured.[18] Treatments with rapid-onset and rapidly reversible therapeutic effects can be compared.[18] On the other hand, the N-of-1 design with multiple crossover periods is unsuitable to investigate

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatments whose effects are slowly reversible (e.g., antisense oligonucleotides) or potentially irreversible (e.g., gene therapies). When assessing treatments with rapidly reversible effects, drug-resistant epilepsies with frequent seizures are uniquely well situated for implementation of the N-of-1 design,[19] because seizures can be quantitated objectively and a high frequency of events provides the basis for robust statistical analysis.

1.2 | N-of-1 trials in medicine

In 1986, *The New England Journal of Medicine* was the first medical journal to publish the results of an N-of-1 trial to determine optimal therapy in an individual with poorly controlled asthma.[20] Since then, variations of the N-of-1 design have been applied for various medical purposes (Box 1). A well-known example is the N-of-1 study of stimulants in children with attention deficit/hyperactivity disorder (ADHD), which was prompted by variability in treatment responses despite existing therapeutic guidelines.[21] Using N-of-1 trials in the context of ADHD induced changes in clinical management for half of the patients, increased persistence with the selected treatment, and improved patient participation and empowerment in therapeutic decisions.[21] In clinical practice, the N-of-1 approach can also help to assess an individual responsiveness to an intervention in order to prevent unnecessary continuation of an ineffective treatment, or too early discontinuation of a potentially effective treatment.[22,23] The range of applications of the N-of-1 design underscores how similar challenges in the management of epilepsy could also be addressed using this design (Box 1).

A recent systematic review of n-of-1 trials in neurology included only two, N-of-1 trials in individuals with epilepsy, highlighting the lack of experience in applying this design in this condition.[24] To our knowledge, no other review has analyzed the methodological issues that apply to N-of-1 designs in epilepsy.

1.3 | Aim

This review systematically appraises the literature on N-of-1 trials in people with epilepsy to analyze design aspects used, and to signal methodological considerations for future N-of-1 trials in epilepsy-related disorders.

2 | METHODS

We conducted a systematic review of N-of-1 trials in epilepsy by using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[25,26] The search was conducted by V.M.D. in PubMed and Embase from inception until January 12, 2024 and included terminology potentially related to N-of-1 trials, considering variations used throughout the years and in different fields of research. Specifically, the search included the term "epilepsy" and one of the following terms: "n-of-1 trial," "n-of-1 study," "single-patient trial," "multiple crossover trial," "single-case experimental design," and "crossover studies" (Table S1). In addition, titles, abstracts, and indexing terms of articles of interest were reviewed to further refine our search. One article was published recently and not fully indexed with Medical Subject Headings (MeSH) terms in PubMed; as a result, this article was excluded when the filter for humans was applied and had to be added to the list of articles of interest afterwards.[27] The results of our search reported according to the PRISMA scheme are depicted in Figure S1.

Based on a review of key publications in N-of-1 trial methodology,[9,18,24,28,29] we defined N-of-1 trials as prospective, crossover studies with multiple alternating active and control intervention periods, with the

BOX 1 Applications of the N-of-1 design in medicine

- Assessment of the efficacy of therapeutic interventions in cases of heterogeneity of treatment effects in conditions with or without established therapies
- Assessment of tolerability
- Identification of the optimal dosage for an individual
- Assessment of treatment effects in conditions with phenotypic pleiotropy requiring individualized outcomes
- Assessment of treatment effects in conditions with low prevalence
- Assessment of the effect of de-prescribing (in polypharmacy or long-term monotherapy)
- Exploration of the impact of treatment in contrast to the natural course of disease
- Assessment of treatment effects in patients who do not meet eligibility criteria for conventional randomized trials

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

individual patient as the observation unit. Only peer-reviewed articles in English describing studies in children and adults with epilepsy with a within-patient multiple–crossover design with repeated cycles of treatment (e.g., ABAB or ABA) were included. To be eligible for inclusion, studies had to report at least one of the following predefined outcome measures: seizure burden or electroencephalography (EEG) epileptiform abnormalities, as well as, cognition, memory, mood, behavior, daily life functioning, (emergency) medication use, or adverse effects. N-of-1 trial series including more than one patient were also included, even when results were analyzed statistically at the group-level only, provided that detailed outcome information for each individual participant was made available. We excluded studies reporting temporary treatment withdrawal with no predefined outcome monitoring, parallel-group trials, or studies reporting pharmacokinetic parameters only. We also excluded studies with more than one crossover between treatments using only one cycle of comparison (e.g., ABC).

All titles and abstracts were screened independently by two authors (W.M.O and V.M.D), using Rayyan[30] for relevance, according to the inclusion and exclusion criteria. The screening was done inclusively to avoid missing crossover studies not labeled as N-of-1 studies. Subsequent screening was based on review of full text. Conflicts after full-text review were resolved between E.H.B., F.E.J., W.M.O., and V.M.D. Data on patient (baseline) characteristics, study design, seizure and (non)-seizure outcomes, treatment schedule, other methodological aspects and information on institutional review board (IRB) approval were extracted independently by V.M.D and E.H.B. Discrepancies in data extraction were discussed and resolved between E.H.B., V.M.D., and F.E.J. Heterogeneity in reporting seizure frequency outcomes was considered informative for the purpose of this review and extracted and reported as in the original publication. The lack of reporting on baseline or treatment characteristics was also considered informative for this review and included as a discussion point. Authors were contacted by V.M.D. if additional information on IRB approval status of the studies was necessary.

The selected studies were appraised by V.M.D. and E.H.B. for risk of bias using the Risk of Bias in N-of-1 Trials (RoBiNT) Scale[31] We considered the RoBiNT Scale more suitable for our objectives than the Consolidated Standard of Reporting Trials (CONSORT) extension for N-of-1 trials (CENT) 2015.[31,32] CENT 2015 focuses on the quality of reporting of published N-of-1 trials and does not assess the impact that aspects of the design can have on the reported results (bias). The RoBiNT Scale was developed from the single-case experimental design scale and adapted to be also used for medical N-of-1 trials.[31] The RoBiNT Scale consists of subscales rating internal validity, external validity, and interpretation. No overall judgment across domains was made because several items of the score were not fully applicable to the N-of-1 studies identified. Discrepancies in RoBiNT Scale scores were discussed and resolved by E.H.B and V.M.D. Interpretations of design components in relation to trial implementation and outcome assessment are discussed in depth.

The PRISMA checklist is provided in the Supplementary material. This systematic review was not registered in PROSPERO due to the initial search and data extraction being conducted for other research purposes. The protocol and any other materials regarding this review can be obtained by contacting the corresponding author.

3 | RESULTS

Of a total of 1133 studies identified, 574 articles were reviewed for title and abstract after removal of duplicates detected with Rayyan.[30] Two publications described an N-of-1 trial protocol for people with epilepsy (or epilepsy-related syndromes) and were excluded.[33,34] Of the 84 articles that described crossover studies potentially fulfilling our inclusion criteria, 80 could be retrieved and underwent full-text screening. Of these 80 articles, 74 were excluded because they described single crossover studies ($n=48$); multiple crossover studies comparing three or more interventions without repeated cycles[35–51] ($n=17$); studies labeled as N-of-1[7,8,52,53] but not involving multiple within-patient crossovers ($n=4$); and other design aspects ($n=5$), such as temporary treatment withdrawal,[54] trial of treatment without crossovers,[55,56] and two studies in patients with brain injury, which used a multiple baseline design and temporary treatment withdrawal approach[57,58] ($n=2$). Only five articles met all the required inclusion criteria. An additional study that used multiple crossover cycles of active intervention and placebo only analyzed results at the group level and, therefore, did not meet our eligibility criteria, but it was included in our analysis because some aspects of this study are relevant to the N-of-1 design. We labeled the six studies as Studies 1–6 in chronological order of publication (Table 1), and we outline the aims, methods, results, and conclusions of each.

3.1 | Individual study characteristics and summary of results

Study 1, reported by Theodore et al.,[59] was a series of within-subject crossover studies to establish the efficacy and tolerability of felbamate in 30 randomized patients

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Characteristics of N-of-1 trials in epilepsy.

	Study 1: Theodore et al. 1991[59]	Study 2: Privitera et al. 1994[60]	Study 3: Gordon et al. 1996[61]	Study 4: Willoughby et al. 2003[62,63]	Study 5: Tellez-Zenteno et al. 2006[64]	Study 7: Salman et al. 2023[27]
Patient characteristics	Focal, focal to bilateral tonic–clonic seizures	Intractable focal seizures	Learning disorder with history of clinical seizure, epileptiform EEG discharges	Refractory sleep-related hypermotor epilepsy (*CHRNA4* genetic variant)	Mesial temporal lobe epilepsy, contraindication for surgery	Intractable generalized tonic–clonic seizures, absences with eyelid myoclonia
Number of participants	30	15	1	1	4	1
Intervention	Felbamate	Dezinamide Individualized dose	Valproic acid	Transdermal nicotine patch	Unilateral hippocampal stimulation. Intensity determined for each patient	Swimming googles
Comparator	Placebo	Placebo	Placebo	Placebo patch None, during open-label phase	Stimulation turned off	None
Concomitant medication	Carbamazepine	Phenytoin	NA	Carbamazepine	More than 2 ASMs	Vagal nerve stimulator, 4 ASMs
Primary outcomes measurement	Seizure frequency[a]	Seizure frequency[a]	Wechsler Intelligence Scale for Children–Revised Coding subtest[d]	Number of seizures per day[a]	Average percent difference in monthly seizure frequency[a]	Absence with eyelid myoclonia[c]
Secondary outcome measurement(s)	Patient judgment on seizure control and toxicity [a]	Adverse effects; behavior; information processing speed and depression with validated questionnaires; Pharmacokinetic parameters	Behavioral tests, including Conners Teacher and Parent Rating scales[b,d]; EEG discharges[e]	None	Memory function using neuropsychological test battery; Liverpool impact of epilepsy and seizure severity-ictal scales[a]; mood[a]; quality of life[a] with validated questionnaires. Likert scale for most important symptoms[a]; Adverse effects[a]	Duration of seizure
Baseline period	3 weeks	5 weeks	No	3 months	3 months	N/A
Period duration	4 weeks, including 2 week run-in period	5 weeks	1 week	2 weeks	4 weeks	Daily showering
Number of periods	3 periods	6 periods	8 periods	4 open-label periods 6 double-blind periods	6 periods	14 periods

(Continues)

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 (Continued)

	Study 1: Theodore et al. 1991[59]	Study 2: Privitera et al. 1994[60]	Study 3: Gordon et al. 1996[61]	Study 4: Willoughby et al. 2003[62,63]	Study 5: Tellez-Zenteno et al. 2006[64]	Study 7: Salman et al. 2023[27]
Washout period	Run-in periods after each crossover excluded from efficacy outcome assessment	First week after each crossover excluded from efficacy outcome assessment	No	No	First week after each crossover excluded from efficacy outcome assessment	N/A
Randomization	Yes	Yes	Yes	Yes	Yes	No
Blinding	Yes, double-blind. Self-reported primary outcome	Yes, double-blind stated. Self-reported primary outcome	Yes, double-blind stated	Open-label, followed by double-blind. Self-reported primary outcome	Yes, double-blind. Self-reported primary outcome	No
Analysis	Statistical (parametric)	Tabular; statistical (non-parametric)	Tabular: statistical (non-parametric)	Visual; statistical (non-parametric)	Visual; tabular; statistical (parametric)	Tabular

Note: The table also includes a multiple crossover trial (study 1) for which data were analyzed at aggregate level only, without detailed information on outcomes for individual participants. Although this study did not strictly meet eligibility criteria, it was included in this review because other aspects of the design are relevant to N-of-1 trial methodology. Reporting of outcome by: [a]Patient, [b]Parent or caregiver, [c]Physician, [d]Teacher, [e]Epileptologist/Electroencephalographer.

Abbreviations: ASM, antiseizure medication; CHRNA4, Cholinergic Receptor Nicotinic Alpha 4 Subunit; EEG, electroencephalography; N/A, not applicable.

with focal seizures concomitantly treated with carbamazepine.[59] Because results were analyzed at the group level only, this study did not meet strictly our eligibility criteria but the use of a multiple-crossover design raised methodological issues similar to those applicable to N-of-1 trial series. The design included a 3-week in-hospital baseline period, followed by three, randomized 2-week periods with felbamate or placebo, with alternating 2-week titration periods. No difference in seizure frequency between felbamate and placebo periods was detected at the group level. Patients were asked to rate seizure burden and side-effects at each period. Fourteen of 28 patients rated felbamate periods superior to placebo periods and entered an extension phase with open-label felbamate treatment.[59]

Study 2, by Privitera et al.,[60] was an N-of-1 series aimed at establishing the safety and efficacy profile of dezinamide in the treatment of focal seizures at an individual and group-level.[60] The study included 15 patients with focal aware or impaired awareness seizures, with or without progression to bilateral tonic–clonic seizures.[60] The design included a 5-week baseline period, followed by three blocks of randomized, paired periods of 5 weeks with dezinamide at different doses or placebo treatment. Seizure frequency was lower during the dezinamide periods compared to placebo periods, with 6 of 15 patients having 50% fewer seizures while on dezinamide. Statistical analysis showed a significant reduction in seizure frequency at the group level but statistical tests were not performed at an individual level. The authors did not report on the continuation of treatment after completion of the trial.

Study 3, conducted by Gordon et al.,[61] was an N-of-1 trial in a 7-year old child with a learning disorder with bifrontal spike–wave discharges on EEG and a history of a tonic–clonic seizure 3 years earlier.[61] The study aimed to assess the potential efficacy of valproic acid in treating cognitive dysfunction related to EEG epileptiform discharges. The design included 8- 1-week crossover periods (four on valproic acid 125 mg twice daily and four on placebo). The study assessed improvements in short-term memory, attention, and psychomotor speed. Valproic acid treatment was associated with a significant improvement in the Wechsler Intelligence Scale for Children-Revised (WISC-R) Coding subset scored weekly.

Study 4, reported by Willoughby et al.,[62,63] assessed the efficacy of transdermal nicotine in a 33-year-old woman with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE, currently known as sleep-related hypermotor epilepsy [or SHE]), caused by a pathogenic variant in the gene encoding the alpha-4 subunit of the neuronal nicotinic acetylcholine receptor (nAchR).[62,63] The design included a 12-month open-label phase followed by a double-blind phase consisting of three blocked, randomized periods of 21 days. The primary outcome was the

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

number of seizures per day. The authors reported significant seizure frequency reduction during treatment with a nicotine patch (intervention) compared to periods receiving a placebo. Treatment was retained.[62]

Study 5 was an N-of-1 series of 4 patients, reported by Tellez-Zenteno et al.,[64] which assessed the safety and efficacy of hippocampal electrical stimulation (HES) for seizures associated with mesial temporal lobe epilepsy (MTLE) related to hippocampal sclerosis.[64] The design included a 3-month baseline period and three randomized blocks with an active HES and inactive HES (stimulation off) period for 1 month each. The patient and physician were blinded to the period allocation. The study allowed concomitant medication changes by an epileptologist blinded to the HES status.[64] HES treatment was associated with a median percent reduction in seizure frequency of 15% (inter-quartile range [IQR] 29%–2%), suggesting a modest overall benefit at group level with no statistical significance. Statistical analysis was performed but only descriptive statistics were reported at the individual and group levels. This n-of-1 series did not report which patients remained on treatment.

Study 6, reported by Salman et al.,[27] was a N-of-1 trial in the case of a 27-year-old woman with drug-resistant epilepsy as well as weekly generalized tonic–clonic seizures and daily absences. The study assessed the efficacy of wearing swimming goggles while showering on preventing absences hypothesized to be triggered by fixation off-sensitivity. The study included seven consecutive cycles of showering with and without goggles for 14 days. Prior to the intervention, a baseline visit to review seizure semiology was conducted and long-term video EEG was performed. The study was not randomized nor blinded. The authors report significant reduction in the occurrence of absences during showering while wearing goggles. As such, the intervention was considered succesful.

3.2 | Common study characteristics

In Studies 3, 4, and 6, the N-of-1 approach was designed to aid clinical decision-making after open-label treatment because there was uncertainty about the treatment effect for the individual.[27,61,62] In Studies 1, 2, and 5, the aim was to study the efficacy and safety of the intervention both at individual and group levels. All individuals followed an identical N-of-1 design, with adjustments in dose (or HES stimulation settings) being permitted in each individual.[59,60,64] In the N-of-1 series assessed (Studies 1, 2, and 5), inclusion criteria were based on seizure type and seizure frequency.[59,60,64] Seizure frequency was the primary outcome measurement in five of the six studies (Studies 1, 2, 4–6).[27,59,60,62–64] Studies 2, 3, and 5 also monitored non-seizure outcomes.[60,61,64] Frequentist, (non)-parametric analysis for primary outcomes was performed in four studies.[59–62,64] For five of the six studies (Studies 1, 2, 4–6), IRB approval was obtained.[27,60,62,64] Upon contact, the authors of Study 3[61] clarified that their IRB did not require approval for a clinical care N-of-1 trial.

3.3 | Assessment of risk-of-bias

3.3.1 | Internal validity scores

On the RoBiNT Scale, the internal validity scores of the identified studies ranged between 5 and 11 points, of 14. Studies 2–6 had at least three paired crossover periods and fulfilled the most stringent design criteria with control periods. Study 1 included only two crossovers, but there were three periods assessed in each patient.[59] Studies 1–5 employed randomization.[62–64] The frequency of observation of the target outcome could be considered a limitation because, despite use of daily seizure diaries, only aggregated data per period were provided[59,60,64] and Study 6 reported only on occurrence of an event per period as a binary outcome.[27] Studies 1–5 were reportedly double-blind, but only Studies 1, 4, and 5 specified procedures for blinding of the investigator.[59,62,64] Study 6 used goggles as an intervention and could not implement patient or assessor blinding due to the nature of the intervention.[27] The four studies monitoring self-reported (daily) seizures as primary outcome (Studies 1, 2, 4, and 5) received full scores if the individual was also blinded to the treatment phase.[59,60,62,64] Study 6 reported obtaining a video of the participant's seizures for the authors to evaluate occurrence of events and duration jointly but did not report on inter-rate agreement.[27] Only one study used a validated outcome measurement as primary outcome and inter-rater agreement was not reported.[61] The studies that described the types of seizures recorded in seizure diaries were considered as using a "reasonably objective" outcome and given a moderate score for inter-rater agreement. Studies 1, 2, 3, and 4 did not evaluate treatment adherence optimally according to the RoBiNT Scale score.[59–62]

3.3.2 | External validity scores

The studies' external validity scores ranged between 8 and 11, of 15 points. The primary outcome was rated as the dependent variable and received the highest score for study 2, which described seizure types to be recorded by patients.[60] Study 3 used a validated scoring system to monitor the cognitive functioning of the participant.[61]

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

All studies but Study 4 provided limited information on baseline characteristics (e.g., biological characteristics), disease severity, or an analysis of the impact of baseline characteristics on the outcome.[60,62,64] Study 6 included a thorough description of patient characteristics at baseline visit but did not provide objective measures of seizure frequency prior to the start of the study.[27] Studies 1 and 3 provided limited information on the titration doses of felbamate and description of the placebo.[59,61] Raw data records of the primary outcome were provided for Studies 3, 4, and 6.[27,61,62] Studies 1 and 2 provided only aggregated data of all periods together, whereas Study 5, also an N-of-1 trial series, provided aggregated data per patient across intervention and control periods.[59,60,64] All studies, except for Study 6, reported results of statistical (or descriptive) analysis, but only Studies 1 and 4 provided a rationale for statistical test selection and related implications.[59,62] Studies 1, 2, and 6 described the setting in which intervention was provided.[27,59,60] Generalization measures are described in the RoBiNT Scale score as measures to determine whether the effects of the intervention could be applicable to other behaviors.[31] Studies 2, 3, and 5 included secondary outcome measurements such as validated quality of life scores and neuropsychological testing, which we considered generalization measures.[60,61,64] Studies 1, 2, and 5 reporting on an N-of-1 trial series on more than three patients scored the highest points for replication.[59,60,64]

The included studies scored low in reporting of baseline characteristics (5/12 points), treatment adherence (6/12 points), sampling of the outcome (2/12 points), provision of raw data records (7/12 points), and providing a rationale for data analysis (7/12 points). Greater attention could have been paid to the description of the dependent variable to improve interpretation of the results and the reliability of the inter-rater agreement scores (4/12 points).

4 | DISCUSSION

The results of this systematic literature review show that the N-of-1 design has been used rarely in epilepsy trials, but also highlight the potential value of this design in epilepsy care and research. Only five studies meeting our criteria were identified. All identified studies aimed to explore or ascertain the efficacy and tolerability of interventions in cases of clinical equipoise. The studies included mostly individuals with stable chronic disease and measurable focal seizure frequency. The treatments included established or investigational antiseizure medications (ASMs) with reversible effects, one off-label repurposed medication targeting the epilepsy etiology, a neurostimulation modality, and a lifestyle intervention.

Analysis of the identified articles suggests that future N-of-1 studies in epilepsy could be improved by more detailed and objective reporting of baseline characteristics, explicit reporting on blinding and randomization procedures following the CENT 2015 guidelines,[32] and reporting on rationale for selected statistical analysis method. In addition, reporting of the outcome measurement could be improved by defining seizure types reported and providing raw data records on seizure events or several measurements per period. Evaluation of the methodological aspects of these studies can help frame the discussion on how the N-of-1 design could be suitable in assessing epilepsy treatments, and which aspects should be considered in future N-of-1 studies in individuals with epilepsy (Table 3).

4.1 | Design aspects of the included studies

Aspects of concern for neurologists interested in the N-of-1 design to evaluate therapeutic interventions for people with epilepsy include (a) drug dosage, (b) crossover periods with alternating treatments, and (c) use of a placebo. Aspects of study design that could lead to risk of withdrawal seizures, seizure exacerbation, and suboptimal treatment need to be considered. Failure to demonstrate a treatment effect or overestimating a treatment effect could be related to bias introduced or unaccounted for in the design, such as the confounding effect of a nonstable course of disease, carryover effects, as well as suboptimal assessment and analysis of the outcome.

4.1.1 | Concerns with applying the n-of-1 design for individuals with epilepsy

Dosage selection

N-of-1 studies offer the advantage of individualized dose selection or the use of multiple dosages, but concerns related to complex titration schemes and trial length should be addressed. The three N-of-1 series included here exemplify the use of individualized doses. The study with dezinamide and felbamate used multiple doses adjusted according to tolerability.[59,60] The study with unilateral HES allowed for determination of optimal intensity of HES per individual.[64] The use of individualized dosages may pose logistical challenges, potentially prolonging trial duration and limiting generalizability of the results[65] (Table 3).

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

The duration of uptitration and downtitration schedules is another important consideration, particularly for treatments for which excessively fast titration has been associated with poor tolerability and potentially non-adherence.[66,67] For medications requiring prolonged titration (more than 4–6 weeks), such as cenobamate and lamotrigine, the N-of-1 design is unfeasible. Finally, during downtitration periods, care should be taken to minimize the risk of withdrawal seizures and related carryover effects at completion of each treatment period.[66,67]

Crossover periods with alternating treatments

The use of the crossover design to evaluate therapeutic interventions in epilepsy generates ethical concerns due to the potential impact of alternating active and inactive (or less-active) treatments on seizure control; particularly in vulnerable individuals such as those with developmental and epileptic encephalopathies (DEEs) and highly disabling or potentially life-threatening seizures. Vulnerable individuals typically include children and people with intellectual disability. Ethical boards need stronger justification to approve studies for these groups and may require consent from their legally designated representative(s), at least for high-risk studies. Historically, epilepsy trials have addressed these challenges by including exit criteria within the framework of adjunctive-therapy or non-inferiority designs.[68,69] Interventions to be investigated in N-of-1 trials should be applied adjunctively to the best standard of care and only after carefully balancing risks and potential benefits. For DEEs, there are often strong ethical arguments to support N-of-1 studies because these disorders are generally very rare and there are few, if any, known treatments - a consideration that may be used to justify adjunctive use of placebo. In fact, individuals with DEEs could benefit from a more scientific and systematic approach to treatment selection and evaluation. These individuals often have very frequent seizures, which may permit assessment of response over relatively short periods, thereby reducing duration of exposure to less-effective treatments as well as the overall duration of the trial. To minimize risks, the design of these trials should incorporate predefined exit criteria or other measures, such as close monitoring of the patient's response by an Independent Drug Safety Monitoring Board. The flexibility of the N-of-1 trial design allows use of interim assessments linked to safety and permits earlier termination of the trial without sacrificing the scientific validity of the results. The adaptability of the N-of-1 design to reduce exposure to inferior treatments using interim assessments is exemplified by N-of-1 trials on first-line antihypertensive drugs in children.[70] Safety criteria can ensure early termination of the trial should there be clear evidence of poor tolerability or lack of efficacy. Likewise, trial termination after only one treatment block may be warranted if definite evidence of benefit emerges, particularly in terms of a clearly reduced sudden unexpected death in epilepsy (SUDEP) risk. Four of the studies identified by our review monitored focal seizures,[59,60,62,64] five studies provided treatments as add-on therapy,[27,59,60,62–64] and none of the studies used exit rules or interim analysis.

Use of placebo

Studies 1–5 used placebo[59–62] or sham-stimulation as a comparator.[64] Studies 3 and 4 used placebo in the context of clinical decision-making. Blinding in clinical N-of-1 trials has been well accepted to minimize the influence of confounders such as patient or observer bias, which can lead to erroneous estimates of treatment effects. This is exemplified by double-blind N-of-1 trials to assess statin intolerance and effectiveness of pain management strategies in adults with osteoarthritis.[71–74] In routine practice, the use of placebo may be challenging and costly, and may also raise serious ethical concerns in individuals with life-threatening seizures when other potentially effective treatments exist. Notably, a comparator does not necessarily need to be placebo. Even when active comparators are used, such as multiple first-line treatments, blinding should be preferred to minimize the risk of bias, particularly in research N-of-1 trials.

4.1.2 | Design aspects affecting the reliability of the results measured

Randomization

Studies 1–5 reported using randomization.[59–62,64] In other words, period sequence order is determined randomly, and the participant is exposed both to the intervention and comparator.[31] In single-case study designs, employing counterbalanced order randomization enhances internal validity by minimizing confounding effects resulting from time trends, natural course of disease, and setting.[31,75] By using order randomization in N-of-1 trials, disease symptoms would be measured frequently in several periods with the treatment and comparator, thereby providing insights into symptom fluctuations over time, with and without the treatment of interest. Recent studies aim to comprehend the patterns of transient increases in seizures and discuss potential implications on clinical management and trial design.[76–79] In the context of RCTs assessing therapy efficacy by evaluating mean seizure rates at group-level and over short periods of time, it may be particularly challenging to distinguish individual responders from non-responders without accounting for patient-specific seizure rates and regression to the mean.[79] In N-of-1 studies, employing multiple, crossover

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

block-randomized periods can counteract or account for this source of variability and, therefore, prevent a biased interpretation of treatment effect. Assessing the potential for time-related bias requires detailed knowledge of the time course of symptoms prior to trial initiation and other individual characteristics, including disease etiology and expected course of the disease.

Carryover effects

The use of washout periods is intended to remove, or at least minimize, the carryover of treatment effects into the control period, which could impact the estimate of treatment outcomes. This is particularly important when testing medications with long half-lives or interventions with effects that may persist, such as brain-stimulation devices. Another confounding factor is the potential occurrence of withdrawal seizures. Use of downtitration and incorporation of an appropriate washout period can only minimize the effect of these potential confounders. In the two, N-of-1 series (Studies 2 and 5), carryover effects were minimized by excluding seizure counts in the first week of each period from the analysis. Still, the authors did not justify the duration of this censored period.[60,64] In Study 1, 2-week titration periods were excluded from analysis and carryover effects were statistically analyzed.[59,80] Study 3 omitted a washout period, despite reports on delayed effects of sodium valproate for up to 5 days.[81] Based on the half-life of the medications tested or, in the case of HES, available data on carryover effects, we estimated the washout periods that would have been appropriate for these studies (Table S2). The results of the HES study were affected by carryover effects due to their short, censored period.[64] Subsequent studies by the same team suggested that the prolonged carryover effect after stopping stimulation requires washout periods longer than 3 months.[82]

Measurements

Aspects that can impact the reliability and generalizability of the measured treatment effect in N-of-1 trials include the choice and assessment modalities of the selected outcome measures, including the frequency at which these measures are assessed. Relevant outcome measurements in epilepsy N-of-1 trials would be seizure frequency and severity as well as non-seizure outcomes such as cognition, language, motor function, quality of life, and encephalographic biomarkers.

Choice of the outcome measures. The outcome measure used in four of the identified studies was the change in seizure frequency.[59,60,62,64] Monitoring seizure frequency presents several challenges. Patients may be unaware of at least some of their seizures, and subtle seizures such as non-motor seizures or motor seizures with minimal behavioral manifestations may not be detected by caregivers. Seizures that occur very frequently and/or are very brief (e.g., epileptic spasms, absences) cannot be counted reliably by observers. Nocturnal seizures can also easily escape observation. Some patients may present with different types of seizures, not all of which can be assessed reliably. Some individuals are susceptible to seizure clusters, and it is important to predefine how seizures occurring in clusters are counted. In patients with very frequent seizures, video-EEG monitoring can be useful to assess response to treatment. Use of EEG biomarkers may be considered, but there are limitations with using EEG endpoints in epilepsy trials.[83] One advantage of N-of-1 trials is that the trial design, including duration of treatment periods and the methodology for assessing seizure response, can be tailored to the characteristics of the individual.

Irrespective of the challenges discussed, optimal assessment of seizure outcomes requires defining which seizure types are primarily assessed, explaining how those are recognized and classified, and obtaining an estimate of their severity whenever feasible. For example, for the studies included in the present review, it would have been important to report how ictal episodes were monitored in patients with sleep-related seizures, or which was the most burdensome seizure type in those with MTLE.

Non-seizure outcomes can also impact the quality of life of individuals with epilepsy.[84–87] Outcome measurements related to cognition, behavior, communication, and motor development should be considered.[83] This is a timely topic in view of ongoing efforts to develop precision treatments that target the etiology of rare epilepsies, especially DEEs. Some of these treatments aim at improving not only seizure control, but also any relevant comorbidities. N-of-1-trials may have a role in assessing non-seizure outcomes, provided that studies can be designed to address challenges related to practice effects, potentially persistent effects despite wash-out, and ethical issues associated with long study duration. Recent N-of-1 trials in neurodevelopmental disorders highlight the importance of using personalized, disease-specific, and generic outcome measurements in patients with complex phenotypes.[88] Generic outcome and disease-specific outcome measurements should be validated tools with known psychometric qualities and indication for applicability to repeated measurements during multiple crossovers.

When selecting non-seizure outcomes as endpoints in N-of-1 trials, it is important to consider whether clinically relevant effects can be expected to occur over a time window compatible with a crossover trial design, and to be reversible during washout. In this respect, behavior, daily life functioning and alertness may be more suitable than

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

outcomes such as cognition or intelligence. The study by Gordon and colleagues[61] assessed cognitive outcomes weekly by using the WISC-R Coding subtest. The results reported by the authors display an increase in WISC-R scores throughout the study. Although the scores during valproic acid treatment periods were significantly higher than those of the placebo, the authors did not account for potential practice effects that had previously been described.[89,90] These studies illustrate the importance of appropriate implementation of outcome measures. Future studies, particularly for rare monogenic epilepsies with complex phenotypes, for which available validated epilepsy-related scoring tools may not be available, could use personalized outcome measurements.[91] Similar to N-of-1 trials in neurodevelopmental disorders and rehabilitation medicine, a self-defined scale reflecting the changes in symptom severity (as defined by the patient) could help quantify change in the patient's experience.[92,93]

Repeated measurements: Duration of the assessment period. For frequency-based outcomes, such as seizures, the recommended minimum duration of each period should be based on pre-existing seizure frequency and the "relevant seizure frequency change" desired by the patient/caregiver or defined as the primary trial endpoint. N-of-1 trial manuals recommend using an "inverse rule of three" as a general guidance for N-of-1 trials with endpoints based on frequency of events.[9,19] For example, if seizures occur at intervals of up to 1 week, a 3-week evaluation period should be sufficient to have 95% certainty that at least one seizure will occur during that period, unless the intervention has been effective in reducing seizure frequency. If seizures are infrequent, differences between periods would be difficult to capture reliably unless period duration is prolonged and an unequivocal effect is maintained over time. Table 2 exemplifies how the inverse rule of three applies to the N-of-1 studies included in this review that had seizures as outcomes. In three of the four trials, the actual period duration for at least some of the included participants was below the minimum duration calculated by the "inverse rule of three."

In interpreting these findings, it is important to recognize that (a) duration according to this rule of thumb will have limited power in measuring change, and (b) for outcomes that may occur in clusters, the rule of thumb alone may be difficult to apply unless clusters are quantifiable and occur at frequent intervals. Study 1 explicitly excluded patients with focal seizures occurring in clusters to avoid inaccurate reporting but did not consider intervals between clusters.[59] Ideally, period duration should be justified based on the event frequency during the baseline period and the maximum intervals between events (Table 2). A more robust method would involve the use of statistical modeling to determine the minimum period duration and treatment cycles required, based on seizure frequency and the minimally clinically relevant effect expected depending on treatment and patient characteristics.[94] Finally, investigators should consider whether an N-of-1 trial is suitable if the required period duration is too long, resulting in increased patient burden and poor

TABLE 2 *Period duration according to (seizure) frequency outcomes in N-of-1 trials in epilepsy.*

Authors	Outcome measure of interest at baseline (duration of baseline)	Minimum duration according to rule of thumb "inverse rule of 3"[a]	Actual period duration in trial design
Theodore et al.[59]	At least 6 seizures per a 3-week period, at least one seizure every week and no more than 1 week with a single seizure (3-week prospective baseline)	21 days	14 days
Privitera et al.[60]	Four focal seizures per month, with no more than 20 consecutive seizure-free days (5 weeks)	21 days 60 days	28 days excluding washout days
Tellez-Zenteno et al.[64]	2.3 to 25 seizures per month	52 days for the patient with lowest seizure frequency	21 days excluding washout days
Willoughby et al.[62,63]	Based on open-label phase, average 1–2 seizures per day 1–5 consecutive seizure-free days[b]	3–6 days 15 days	14 days

[a]We compare the actual period duration from the included N-of-1 trials to what would be recommended by the "inverse rule of 3." No information was available on the inter-seizure interval of the included patients at baseline and an estimated average inter-seizure interval was calculated based on the baseline seizure frequency of the included patients[62–64] or minimum seizure frequency required for inclusion criteria.[59,60] This may not reflect true seizure intervals of the patients included.

[b]Published seizure diary from open-label phase used to estimate average inter-seizure intervals to estimate minimum period duration according to "inverse rule of 3."

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

adherence to treatment and reporting requirements. In line with this, a statistical model to accelerate N-of-1 trial decision-making, by estimating treatment effects continuously during trial periods, could allow shortening of the trial duration without compromising the reliability of the results.

Statistical analysis

Graphical representation of N-of-1 trial results provides an initial basis for visual interpretation.[18] A combined approach with statistical analysis, however, is desirable to aid in decision-making, and this is feasible for single-patient studies and a series of N-of-1 trials. The studies included used frequentist statistical tests, including the Wilcoxon rank-sum test,[62] randomization test,[60] one-tailed Mann–Whitney test,[61] and paired *t* tests.[64] These statistical tests can assess the difference between interventions but do not account for the time-series aspect of the data and are unsuitable for aggregate results. N-of-1 trial analysis can be performed using frequentist mixed-effects models or Bayesian models, which can address complex aspects of time-series data such as time trends, auto-correlation, outliers, and heterogeneity of treatment effects between individuals and aggregate results to generate group-level estimates.[14,15,95–103]

The use of Bayesian inference for N-of-1 trials has gained special attention for trials due to several advantages.[104,105] It computes the probability of minimally clinically relevant treatment effect given the data obtained and previously available data. In contrast to frequentist analysis in which the results reflect the probability of results compared to the null hypothesis and estimates do not necessarily reflect a meaningful clinical effect. Knowledge of estimated effect size over successive N-of-1 trials can be incorporated into "informed Bayesian models," which can update the estimates continuously for each patient and be used as interim analysis to establish with sufficient certainty whether a predefined outcome has been obtained and terminate an individual trial accordingly.[104] Similarly, updating group-level estimates with each individual case, or "borrowing strength" from previous cases, can lead to terminating a trial in cases when a meaningful treatment effect has been achieved.[14,106,107] As an example, the study by Stunnenberg et al.[14] assessed the efficacy of mexiletine in patients with non-dystrophic myotonia in aggregated N-of-1 trials, highlighting the benefits of a Bayesian compared to a frequentist approach. Although the effect size for the primary outcome was comparable to that estimated by frequentist analysis, Bayesian analysis showed that a meaningful difference at group level could be identified with sufficient certainty after 11 individual N-of-1 treatment sets had been completed.[14] Of the 27 patients included, 23 completed a single treatment cycle and 4 completed a second treatment cycle, highlighting how an interim assessment demonstrating a difference between treatments can lead to early termination of a trial.[14] This approach allows robust analysis of N-of-1 studies for rare diseases at the individual and group levels, and aligns well with the clinical decision-making process.

4.2 | Strengths and limitations of this study

The RoBiNT Scale score for risk of bias assessment of the n-of-1 trials identified in this review has some limitations.[31] The RoBiNT Scale was adjusted from behavioral trials to application in N-of-1 trials in medicine, but it has not been validated formally for pharmacological N-of-1 trials (personal communication with Prof. Robyn Tate, April 2022). Items of the RoBiNT Scale score that seem less applicable to N-of-1 trials in patients self-reporting the occurrence of seizures in ambulatory care are inter-rater agreement and setting. Currently, there is no risk of bias assessment tool validated for N-of-1 trials in medicine.

This review applied strict criteria in defining N-of-1 studies and included only predefined, crossover studies with more than one repeated cycle, which differs from the criteria used by another recent systematic review on N-of-1 trials in neurological diseases[24] and could be considered a limitation. This decision was made to learn from N-of-1 trial methodology specifically, rather than variants of single crossover studies. Despite the stringent inclusion criteria, we identified two studies, which, to our knowledge, had not been reviewed previously.[59,64] The strengths of this review are the signaling of design aspects relevant to N-of-1 trials in epilepsy, along with recommendations for future studies.

4.3 | Paving the way forward

Our review sets the stage for a broader discussion of the role of the N-of-1 trial design in future epilepsy research and care. We provided an analysis of relevant methodological aspects (Table 3) and outlined implications for using this design in addressing challenges in demonstrating treatment effects and optimizing treatment selection in epilepsy. The trials identified by our systematic review were conducted mainly in individuals with stable disease and recurrent focal seizures. By reviewing methodological issues related to these studies, we illustrate key points to be addressed in N-of-1 epilepsy trials, including the temporal distribution of seizures, non-seizure outcomes, subtle seizure types, and

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Design aspects to be improved in N-of-1 trial designs in epilepsy.

Methodological aspects	Challenge	Recommendations
Rationale	Well-defined rationale for treatment selection, based on etiology or patient characteristics and comorbidities, as well as rationale for use of the N-of-1 design, will aid in interpretation and generalization of results	Define inclusion and exclusion criteria considering objective baseline characteristics (using known diagnostic criteria or classification) to interpret and generalize results. Clinical or research question should be defined
Dose-selection	Although N-of-1 trials allow for selection of individualized dosages, optimizing choice of doses and controlling for drug interactions could be problematic. Generalizing results from N-of-1 trials with individualized doses might also be challenging	Patients could be randomized to receive different dosages consecutively
	If an initial open-label treatment phase is used to identify optimal dose or responders, exposure prior to double-blinding could lead to bias due to learning effects and limit external validity of results	If an enrichment phase is included (i.e., open label treatment to identify potential responders to be included in the double-blind trial), results will be generalizable only to initial responders
	Interactions with concomitant ASMs leading to changes in drug concentration may confound assessment of efficacy and tolerability data	Monitor serum concentration of concomitant ASMs and intervention of interest
Number of periods	Defining number of periods and measurements required to demonstrate effect of intervention	The standard recommendation for N-of-1 trials is the use of at least three pairs of active and comparator intervention (ABABAB, in randomized order) to provide sufficient data to demonstrate an effect
	Maintaining compliance during the trial	It is desirable to keep the trial duration as short as feasible considering the tendency of patients to reduce compliance with trial procedures (and increased chance of dropout) when trial duration is prolonged. However, this is dependent on burden imposed by trial procedures
	Interim analysis and premature termination of the study for safety, demonstrated benefit or futility reasons provides a more-patient friendly alternative, but can hinder statistical analysis in aggregated trials	Define unequivocally safety, efficacy and exit criteria for interim analysis. Use Bayesian analysis to circumvent threshold for statistical significance required in frequentist analysis. Provide outcomes as probabilities for the hypotheses. Consider having an Independent Data Safety Monitoring Committee in place
Period duration	Duration of period should be defined based on treatment characteristics, time required to measure outcome repeatedly, and compromise to minimize burden for patient and maintain compliance. Baseline seizure frequency (when seizure frequency is the efficacy endpoint) and need for dose titration are key factors in deciding optimal trial duration	Properties of the outcomes measured used and treatment characteristics should be substantiated when explaining design For frequency-based outcomes such as seizures, period duration should be long enough to capture enough events and changes. Statistically substantiated period duration could be established
Carryover effects	Carryover effects can confound results if treatment effects are not rapidly reversible. This will affect trial validity	Include appropriate washout period or censoring of outcome measures during the initial part of each subsequent treatment period, based on careful consideration of expected duration of carryover effects Some treatments with a "long" run-in period (until full effectiveness) introduce a natural washout at the beginning of a period. Given these treatments have no interaction with the treatment in subsequent period the "long" run-in period can overlap with the subsequent or preceding period

(Continues)

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 (Continued)

Methodological aspects	Challenge	Recommendations
Randomization	Non-stable course of disease, progression, or natural fluctuations	Use counterbalanced order randomization to minimize time-related bias, and distinguish between treatment effects and course of disease
	Reporting on randomization strategy used	Report according to CENT 2015[32]
Use of placebo and blinding	Obtaining placebo as sole comparator or as double-dummy in blinded active-control trials may be expensive both in research as well as clinical care	For clinical care, advocate for ad hoc funding within specific institutions. For research, advocate for funding applications within appropriate sources. Consider asking for support from industry as applicable
	Blinding patient, providers of the intervention and/or outcome assessor stated but not demonstrated	Report according to CENT 2015[32]
Outcome measurement	Time required to assess outcome relates to type of outcome seizure, characteristics of the patient and time course of drug effect. For some measures. several data points per period may be desirable to improve accuracy of estimates	See discussion on period duration and outcomes in the included studies. Frequency of measurements should also be defined
	Choice of primary and secondary outcome measures should be justified. Outcome measures (disease-specific or generic) should be individualized and as objective as possible	Select appropriate outcome measures to reflect disease manifestations, clinical meaningfulness and burden for patient. Increase objectivity of outcome with adaptable validated questionnaires such as: Goal Attainment Scale to predefine and standardize response options
	Generalizable, disease-specific outcomes may not have been used or validated for N-of-1 trials	If disease-specific outcomes are not validated for complex phenotypes or use in N-of-1 studies, preliminary pilot studies could aid in assessing their performance in this context. Psychometric qualities of some score may allow repeated measurements at intervals suitable for application in N-of-1 trials
Analysis	Choice of statistical design appropriate for data analysis can be challenging for N-of-1 trials. Aspects such as order of periods, time-series data, autocorrelation are not accounted for in simple (non-parametric) frequentist tests	Statistical testing should support visual inspection of data
	Low prevalence and interpatient heterogeneity hamper efforts to conduct many N-of-1 trials to generate population level conclusions	Mixed linear models or hierarchical Bayesian analysis would be most suitable. User-friendly, open-access, statistical software can provide step by step guidance and support adequate analysis and interpretation of N-of-1 trial results
		Bayesian inference can 'borrow strength' from prior knowledge to optimize estimates for individual patients and group-level[14,105–108]
Ethical aspects and regulatory procedures	There can be uncertainty regarding which aspects render an N-of-1 trial a research endeavor or part of clinical care Informed consent procedures for N-of-1 trials in care and n-of-1 trials in research may differ and should be defined	Ethical framework on N-of-1 strategies in research and care could define level of required oversight, and which informed consent procedures apply[112]

complex phenotypes. The N-of-1 design can be especially valuable for rare DEEs, including the increasingly diagnosed array of monogenic epilepsies. Many of these disorders could benefit from personalized precision treatments supported by robust statistical analysis as an advance over therapeutic trials taking place in the setting of routine clinical care. Results of N-of-1 trials in rare epilepsies should be interpreted in the context

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

of natural history studies. N-of-1 trials can also be conducted in other areas, for example, to assess the feasibility of treatment discontinuation, especially in cases of polypharmacy,[23] using adaptive designs.

The range of existing epilepsy-related phenotypes and emerging therapies calls for tailored N-of-1 trial methodologies that can be applied readily with varying degrees of methodological rigor. Motivated by the need to improve evidence-based treatment selection for rare epilepsies, several authors of this review are part of a consortium formed by members of the European Reference Network for Rare and Complex Epilepsies (EpiCARE) that has set out to develop tailored N-of-1 trial methodology for rare and drug-resistant epilepsies. Tailored N-of-1 methodology addresses aspects such as dose selection, optimal baseline monitoring, randomization strategies, frequency of outcome measurement, adequate duration of treatment periods, and statistical analysis. All the aforementioned aspects (also in Table 3) are within the remit of our consortium. Due to the hybrid nature of N-of-1 trials, which can incorporate components of research as well as individualized care, it has been debated whether some of these trials should be conducted under the rules of research or clinical care.[28,108–111] Members of our consortium have recently proposed an ethical framework defining the standards for N-of-1 trials in research or care, and the respective oversight procedures.[112] Carefully designed N-of-1 trials in clinical care can be considered an advance over the common utilization of trials of off-label treatments in routine clinical care. The incremental value provided by these studies in terms of improved clinical care and scientific knowledge is an important issue that will require formal assessment in parallel with increasing utilization of this trial design.

Both the European Medicines Agency and the U.S. Food and Drug Administration have issued guidance documents on the use of N-of-1 trials to investigate novel treatments targeting rare diseases.[113,114] In addition, a formal network of individuals with an interest in N-of-1 trials has been established at the international level, aimed at providing opportunities for collaboration, a global communication channel, resource sharing, and knowledge exchange.[115] Ultimately these efforts (tailored N-of-1 methodology within an ethical framework) could provide the grounds to obtain group-level evidence to support the licensing and reimbursement policies for repurposed or novel treatments.[116,117]

AUTHOR CONTRIBUTIONS

Victoria M. Defelippe: Conceptualization; literature review; data curation; writing and reviewing original draft. **Eva H. Brilstra**: Conceptualization; literature review; data curation; writing and reviewing original draft; supervision. **Willem M. Otte:** Conceptualization, literature review; data curation; writing and reviewing. **Valentina De Giorgis**, **Finbar O'Callaghan**, and **Helen J. Cross**: Conceptualization; reviewing and editing. **Holger Lerche**, **Sanjay Sisodiya**, and **Annapurna Poduri:** Supporting conceptualization, reviewing and editing. **Kees P.J. Braun**: Conceptualization; reviewing and editing; supervision. **Floor E. Jansen** and **Emilio Perucca:** Conceptualization; writing and reviewing original draft; reviewing and editing; supervision.

FUNDING INFORMATION

The study was funded by the MING II Fund and the Health-Holland PPP allowance (LSHM21053-SGF).

CONFLICT OF INTEREST STATEMENT

F.E.J. has served as consultant/advisor for UCB, GW Pharma (now Jazz Pharmaceuticals), and Novartis for which remuneration was made to the department, outside of the submitted work. J.H.C. has received research grants from Zogenix (now a part of UCB), Marinus, GW Pharma (now Jazz Pharmaceuticals), Vitaflo, Stoke Therapeutics, Ultragenyx, National Institute of Health Research (NIHR), EPSRC, GOSH Charity, ERUK, the Waterloo Foundation, and the Great Ormond Street Hospital NIHR Biomedical Research Centre; and has served as consultant/advisor for Zogenix (now a part of UCB), GW Pharma (now Jazz Pharmaceuticals), and Biocodex for which remuneration was made to the department, outside of the submitted work; serves as Chair of the Medical Board for DravetUK, Hope for Hypothalamic Hamartoma, and Matthew's Friends and endowed chair at UCL Great Ormond Street Institute of Child Health. E.P. received speaker's or consultancy fees from Eisai, GRIN Therapeutics, Janssen, PMI Life Sciences, Sanofi group of companies, Shackelford Pharma, Sintetica, SKL Life Science, Sun Pharma, Takeda, UCB Pharma, Xenon Pharmaceuticals, and royalties from Wiley, Elsevier, and Wolters Kluwers. F.O.C. has received speaker or consultancy fees from Eisai, UCB Biopharma, GW Pharma (now Jazz Pharmaceuticals), and Novartis. V.D. received a consultancy fee from Nutricia Gmbh. H.L.'s contribution was supported by grants from the German Research Foundation (DFG FOR-2715, Le1030/16-2, Le1030/23-1), the German Federal Ministry of Education and Research (Treat-ION, 01GM2210A), and the Else-Kröner-Fresenius Stiftung (EKFS, http://precise.net). H.L. received speaking or consultancy fees from Arvelle, Bial, Eisai, Lario Therapeutics, Praxis, UCB/Zogenix, and research support from Bial, Boehringer Ingelheim and Lario Therapeutics.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

report is consistent with those guidelines. None of the authors have conflicts of interests to disclose related to this review.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Victoria M. Defelippe https://orcid.org/0000-0002-3080-5008
Eva H. Brilstra https://orcid.org/0000-0001-5793-9623
Willem M. Otte https://orcid.org/0000-0003-1511-6834
Helen J. Cross https://orcid.org/0000-0001-7345-4829
Finbar O'Callaghan https://orcid.org/0000-0002-7499-6029
Valentina De Giorgis https://orcid.org/0000-0002-5828-7070
Annapurna Poduri https://orcid.org/0000-0002-7350-5136
Holger Lerche https://orcid.org/0000-0002-1783-8710
Sanjay Sisodiya https://orcid.org/0000-0002-1511-5893
Kees P. J. Braun https://orcid.org/0000-0003-3631-0003
Floor E. Jansen https://orcid.org/0000-0003-0745-5668
Emilio Perucca https://orcid.org/0000-0001-8703-223X

REFERENCES

1. Fiest KM, Sauro KM, Wiebe S, Patten SB, Dykeman J, Pringsheim T, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017;88:296–303.
2. Singh A, Trevick S. The epidemiology of global epilepsy. Neurol Clin. 2016;34(4):837–47.
3. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142(8):2303–18.
4. Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18(9):898–905.
5. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol. 2016;15(3):304–16.
6. Unknown. European Commission – research and innovation. Rare diseases. [cited 2024 Apr 30]. Available from: https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en
7. Krey I, von Spiczak S, Johannesen KM, Hikel C, Kurlemann G, Muhle H, et al. L-serine treatment is associated with improvements in behavior, EEG, and seizure frequency in individuals with GRIN-related disorders due to null variants. Neurotherapeutics. 2022;19(1):334–41.
8. Hedrich UBS, Lauxmann S, Wolff M, Synofzik M, Bast T, Binelli A, et al. 4-aminopyridine is a promising treatment option for patients with gain-of-function KCNA2-encephalopathy. Sci Transl Med. 2021;13(609):eaaz4957.
9. Guyatt G, Sackett D, Adachi J, Chong J, Rosenbloom D, Pharm D. A clinician's guide for conducting randomized trials in individual patients. CMAJ. 1988;139:497–503.
10. Mirza RD, Punja S, Vohra S, Guyatt G. The history and development of N-of-1 trials. J R Soc Med. 2017;110(8):330–40.
11. Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. Our three-year experience. Ann Intern Med. 1990;112(4):293–9.
12. Lobo MA, Moeyaert M, Cunha AB, Babik I. Single-case design, analysis, and quality assessment for intervention research. J Neurol Phys Ther. 2017;41(3):187–97.
13. Nikles J, Mitchel G., editors. The essential guide to N-of-1 trials in health. Dordrecht: Springer Netherlands; 2015.
14. Stunnenberg BC, Raaphorst J, Groenewoud HM, Statland JM, Griggs RC, Woertman W, et al. Effect of mexiletine on muscle stiffness in patients with nondystrophic myotonia evaluated using aggregated N-of-1 trials. JAMA. 2018;320(22):2344–53.
15. Samuel JP, Bell CS, Samuels JA, Rajan C, Walton AK, Green C, et al. N-of-1 trials vs. usual care in children with Hypertension: a pilot randomized clinical trial. Am J Hypertens. 2023;36(2):126–32.
16. Herrett E, Williamson E, Brack K, Beaumont D, Perkins A, Thayne A, et al. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. BMJ. 2021;372:n135.
17. Zucker DR, Schmid CH, McIntosh MW, D'Agostino RB, Selker HP, Lau J. Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. J Clin Epidemiol. 1997;50(4):401–10.
18. DEcIDE Methods Center N-of-1 Guidance Panel, Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, et al. Design and implementation of N-of-1 trials: a user's guide. No. 13(14). Rockville, MD: Agency for Healthcare Research and Quality; 2014.
19. Margolis A, Giuliano C. Making the switch: from case studies to N-of-1 trials. Epilepsy Behav Rep. 2019;12:100336. https://doi.org/10.1016/j.ebr.2019.100336
20. Guyatt G, Sackett D, Taylor D, Ghong J, Roberts R, Pugsley S. Determining optimal therapy — randomized trials in individual patients. N Engl J Med. 1986;315(12):767–8.
21. Nikles CJ, Mitchell GK, Del Mar CB, Clavarino A, McNairn N. An n-of-1 trial service in clinical practice: testing the effectiveness of stimulants for attention-deficit/hyperactivity disorder. Pediatrics. 2006;117(6):2040–6.
22. Clough AJ, Hilmer SN, Naismith SL, Kardell LD, Gnjidic D. N-of-1 trials for assessing the effects of deprescribing medications on short-term clinical outcomes in older adults: a systematic review. J Clin Epidemiol. 2018;93:112–9.
23. Goyal P, Safford M, Hilmer SN, Steinman MA, Matlock D, Maurer MS, et al. N-of-1 trials to facilitate evidence-based deprescribing: rationale and case study. Br J Clin Pharmacol. 2022;88:4460–73. https://doi.org/10.1111/bcp.15442
24. Stunnenberg BC, Berends J, Griggs RC, Statland J, Drost G, Nikles J, et al. N-of-1 trials in neurology a systematic review. Neurology. 2022;98(2):E174–E185.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, Antes G, Atkins D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
26. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration:

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
27. Salman S, Freund B, Tatum WO. N-of-1 trial in epilepsy with fixation-off sensitivity. Neurol Clin Pract. 2023;13(5):11–4.
28. Stunnenberg BC, Deinum J, Nijenhuis T, Huysmans F, van der Wilt GJ, van Engelen BGM, et al. N-of-1 trials: evidence-based clinical care or medical research that requires IRB approval? A practical flowchart based on an ethical framework. Healthcare. 2020;8(1):49.
29. Gabler NB, Duan N, Vohra S, Kravitz RL. N-of-1 trials in the medical literature: a systematic review. Med Care. 2011;49(8):761–8.
30. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):1–10.
31. Tate RL, Perdices M, Rosenkoetter U, Wakim D, 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(5):619–38.
32. Vohra S, Shamseer L, Sampson M, Bukutu C, Schmid CH, Tate R, et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015 statement. BMJ. 2015;350:h1738.
33. Ong KS, Carlin JB, Fahey M, Freeman JL, Scheffer IE, Gillam L, et al. Protocol for a single patient therapy plan: a randomised, double-blind, placebo-controlled N-of-1 trial to assess the efficacy of cannabidiol in patients with intractable epilepsy. J Paediatr Child Health. 2020;56(12):1918–23.
34. Müller AR, den Hollander B, van de Ven PM, Roes KCB, Geertjens L, Bruining H, et al. Cannabidiol (Epidyolex®) for severe behavioral manifestations in patients with tuberous sclerosis complex, mucopolysaccharidosis type III and fragile X syndrome: protocol for a series of randomized, placebo-controlled N-of-1 trials. BMC Psychiatry. 2024;24(1):23.
35. Stolarek I, Blacklaw J, Forrest G, Brodie MJ. Vigabatrin and lamotrigine in refractory epilepsy. J Neurol Neurosurg Psychiatry. 1994;57(8):921–4.
36. Leach JP, Girvan J, Paul A, Brodie MJ, Leach JP, Girvan J, et al. Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy. J Neurol Neurosurg Psychiatry. 1997;62:372–6.
37. Hart YM, Meinardi H, Sander J, Nutt DJ, Shorvon SD. The effect of intravenous flumazenil on interictal electroencephalographic epileptic activity: results of a placebo-controlled study. J Neurol Neurosurg Psychiatry. 1991;54:305–9.
38. Gurrell R, Gorman D, Whitlock M, Ogden A, DSR, DiVentura B, et al. Photosensitive epilepsy: robust clinical efficacy of a selective GABA potentiator. Neurology. 2019;92:e1786–e1795.
39. Binnie CD, De Beukelaar E, Meijer JWA, Meinardi H, Overweg J, Wauquier A, et al. Open dose-ranging trial of flunarizine as add-on therapy in epilepsy. Epilepsia. 1985;6(5):424–8.
40. Crawford P, Chadwick D. A comparative study of progabide, valproate, and placebo as add-on therapy in patients with refractory epilepsy. J Neurol Neurosurg Psychiatry. 1986;49:1251–7.
41. McKee PJW, Blacklaw J, Friel E, Thompson GG, Gillham RA, Brodie MJ. Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients? Epilepsia. 1993;34:937–43.
42. McKee PJ, Blacklaw J, Carswell A, Gillham RA, Brodie MJ. Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. Br J Clin Pharmacol. 1993;36(3):257–61.
43. Tergau F, Neumann D, Rosenow F, Nitsche MA, Paulus W, Steinhoff B. Can epilepsies be improved by repetitive transcranial magnetic stimulation? – Interim analysis of a controlled study. Suppl Clin Neurophysiol. 2003;56:400–5.
44. Barkley CM, Hu Z, Fieberg AM, Eberly LE, Birnbaum AK, Leppik IE, et al. An association between resting state EEG parameters and the severity of topiramate-related cognitive impairment. Epilepsy Behav. 2021;114(Pt A):107598.
45. Turner RP. The acute effect of music on interictal epileptiform discharges. Epilepsy Behav. 2004;5(5):662–8.
46. Seynaeve L, Devroye A, Dupont P, Van Paesschen W. Randomized crossover sham-controlled clinical trial of targeted low-frequency transcranial magnetic stimulation comparing a figure-8 and a round coil to treat refractory neocortical epilepsy. Epilepsia. 2016;57(1):141–50.
47. Koskiniemi M, Van Vleymen B, Hakamies L, Lamusuo S, Taalas J. Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. J Neurol Neurosurg Psychiatry. 1998;64:344–8.
48. De Giorgio CM, Miller PR, Harper R, Gornbein J, Schrader L, Soss J, et al. Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study. J Neurol Neurosurg Psychiatry. 2015;86(1):65–70.
49. Adams J, Alipio-Jocson V, Katherine Inoyama M, Bartlett V, Saira Sandhu B, Jemima Oso B, et al. Methylphenidate, cognition, and epilepsy a double-blind, placebo-controlled, single-dose study. Neurology. 2016;88:470–6.
50. Loiseau P, Hardenberg JP, Pestre M, Guyot M, Schechter PJ, Tell GP. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia. 1986;27(2):115–20.
51. French JA, Wechsler R, Gelfand MA, Pollard JR, Vazquez B, Friedman D, et al. Inhaled alprazolam rapidly suppresses epileptic activity in photosensitive participants. Epilepsia. 2019;60(8):1602–9.
52. Hughes E, Oates S, Pal DK. Intolerance to quinidine in a n-of-1 trial for KCNT1 associated epilepsy of infancy with migrating focal seizures. Seizure. 2022;103:46–50.
53. Lewis SA, Shetty S, Gamble S, Heim J, Zhao N, Stitt G, et al. Intrathecal magnesium delivery for Mg++−insensitive NMDA receptor activity due to GRIN1 mutation. Orphanet J Rare Dis. 2023;18(1):1–5.
54. Major P, Greenberg E, Khan A, Thiele EA. Pyridoxine supplementation for the treatment of levetiracetam-induced behavior side effects in children: preliminary results. Epilepsy Behav. 2008;13(3):557–9.
55. Feely M, Calvert R, Gibson J. Clobazam in catamenial epilepsy. Lancet. 1982;320(8289):71–3.
56. Hussain SA, Dlugos DJ, Cilio MR, Parikh N, Oh A, Sankar R. Synthetic pharmaceutical grade cannabidiol for treatment of refractory infantile spasms: a multicenter phase-2 study. Epilepsy Behav. 2020;102:106826.
57. Sathananthan N, Dimech-Betancourt B, Morris E, Vicendese D, Knox L, Gillanders D, et al. A single-case experimental evaluation of a new group-based intervention to enhance adjustment to life with acquired brain injury: VaLiANT

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(valued living after neurological trauma). Neuropsychol Rehabil. 2022;32(8):2170–202.
58. FitzGerald A, Main L, Duff U, Foggo J, Rowney F, Haire N, et al. Does amantadine maintain function in long-established brain injury? A single case experimental design. Brain Inj. 2021;35(11):1443–50.
59. Theodore WH, Raubertas RF, Porter RJ, Nice F, Devinsky O, Reeves P, et al. Felbamate: A clinical trial for complex partial seizures. Epilepsia. 1991;32(3):392–7. https://doi.org/10.1111/j.1528-1157.1991.tb04668.x
60. Privitera M, Treiman D, Pledger G, Sahlroot J, Handforth A, Linde M, et al. Dezinamide for partial seizures: results of an n-of-1 design trial. Neurology. 1994;44(8):1453–8.
61. Gordon K, Bawden H, Camfield P, Mann S, Orlik P. Valproic acid treatment of learning disorder and severely epileptiform EEG without clinical seizures. J Child Neurol. 1996;11(1):41–3.
62. Willoughby JO, Pope KJ, Eaton V. Nicotine as an antiepileptic agent in ADNFLE: an N-of-one study. Epilepsia. 2003;44(9):1238–40.
63. Willoughby JO, Pope KJ, Eaton V. Erratum: nicotine as an antiepileptic agent in ADNFLE: an N-of-one study. Epilepsia. 2003;44:1238–40.
64. Tellez-Zenteno JF, McLachlan RS, Parrent A, Kubu CS, Wiebe S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. Neurology. 2006;66(10):1490–4.
65. Perucca E. From clinical trials of antiepileptic drugs to treatment. Epilepsia Open. 2018;3(S2):220–30.
66. Seiden LG, Connor GS. The importance of drug titration in the management of patients with epilepsy. Epilepsy Behav. 2022;128:e108517.
67. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol. 2011;10(5):446–56.
68. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10:961–8.
69. Perucca E. Designing clinical trials to assess antiepileptic drugs as monotherapy difficulties and solutions. CNS Drugs. 2008;22:917–38.
70. Samuel JP, Tyson JE, Green C, Bell CS, Pedroza C, Molony D, et al. Treating hypertension in children with n-of-1 trials. Pediatrics. 2019;143(4):e20181818.
71. Nikles CJ, Clavarino AM, Del Mar CB. Using n-of-1 trials as a clinical tool to improve prescribing. Br J Gen Pract. 2005;55(512):175–80.
72. Wood FA, Howard JP, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, et al. N-of-1 trial of a statin, placebo, or No treatment to assess side effects. N Engl J Med. 2020;383(22):2182–4.
73. He W, Cui Z, Chen Y, Wang F, Li F. Status of N-of-1 trials in chronic pain management: a narrative review. Pain Ther. 2021;10:1013–28.
74. Keppel Hesselink JM, Kopsky DJ, Bhaskar AK. Ethical justification of single-blind and double-blind placebo-controlled response tests in neuropathic pain and N-of-1 treatment paradigm in clinical settings. J Pain Res. 2019;12:345–52.
75. Tanious R, Onghena P. Randomized single-case experimental designs in healthcare research: what, why, and how? Healthcare (Switzerland). 2019;7(4):143.
76. Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, Cook MJ, et al. Cycles in epilepsy. Nat Rev Neurol Nat Res. 2021;17:267–84.
77. Leguia MG, Andrzejak RG, Rummel C, Fan JM, Mirro EA, Tcheng TK, et al. Seizure cycles in focal epilepsy. JAMA Neurol. 2021;78(4):454–63.
78. Baud MO, Ramantani G. Seizure remissions and cycles in pediatric focal epilepsy. Dev Med Child Neurol. 2023;65(3):308–9.
79. Karoly PJ, Romero J, Cook MJ, Freestone DR, Goldenholz DM. When can we trust responders? Serious concerns when using 50% response rate to assess clinical trials. Epilepsia. 2019;60(9):e99–e103.
80. Ebbutt AAF. Three-period crossover designs for two treatments. Biometrics. 1984;40(1):219–24.
81. Rowan AJ, Binnie C, Warfield CA, Meinardi H, Meijer JWA. The delayed effect of sodium valproate on the Photoconvulsive response in man. Epilepsia. 1979;20(1):61–8.
82. McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia. 2010;51(2):304–7.
83. Buchhalter J, Neuray C, Cheng JY, D'Cruz ON, Datta AN, Dlugos D, et al. EEG parameters as endpoints in epilepsy clinical trials - an expert panel opinion paper. Epilepsy Res. 2022;187:107028.
84. Sinoo C, de Lange IML, Westers P, Gunning WB, Jongmans MJ, Brilstra EH. Behavior problems and health-related quality of life in Dravet syndrome. Epilepsy Behav. 2019;90:217–27.
85. Birbeck GL, Hays RD, Cui X, Vickrey BG. Seizure reduction and quality of life improvements in people with epilepsy. Epilepsia. 2002;43(5):535–8.
86. Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. Epilepsia. 2011;52(12):2181–91.
87. Ronen GM, Streiner DL, Rosenbaum P. Health-related quality of life in childhood epilepsy: moving beyond "seizure control with minimal adverse effects". Health Qual Life Outcomes. 2003;1(36):1–10.
88. Müller AR, Brands MMMG, van de Ven PM, Roes KCB, Cornel MC, van Karnebeek CDM, et al. Systematic review of N-of-1 studies in rare genetic neurodevelopmental disorders: the power of 1. Neurology. 2021;96(11):529–40.
89. Zimmerman IL, Woo-Sam JM. Review of the criterion-related validity of the WISC-III: the first five years. Percept Mot Skills. 1997;85:531–46.
90. Wechsler D. Manual for the Wechsler intelligence scale for children-revised. San Antonio, TX: Psychological Corp; 1997.
91. Slade A, Isa F, Kyte D, Pankhurst T, Kerecuk L, Ferguson J, et al. Patient reported outcome measures in rare diseases: a narrative review. Orphanet J Rare Dis. 2018;13(1):1–9.
92. Donnelly C, Carswell A. Individualized outcome measures: a review of the literature. Can J Occup Ther. 2002;69(2):84–94.
93. Harpster K, Sheehan A, Foster EA, Leffler E, Schwab SM, Angeli JM. The methodological application of goal attainment scaling in pediatric rehabilitation research: a systematic review. Disabil Rehabil. 2019;41(24):2855–64.
94. Brandon Westover M, Cormier J, Bianchi MT, Shafi M, Kilbride R, Cole AJ, et al. Revising the "rule of three" for inferring seizure freedom. Epilepsia. 2012;53(2):368–76.

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

95. Punja S, Schmid CH, Hartling L, Urichuk L, Nikles CJ, Vohra S. 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. 2016;76:76–81.
96. Nikles J, Mitchell G, McKinlay L, Waugh MC, Epps A, Carmont SA, et al. A series of n-of-1 trials of stimulants in brain injured children. NeuroRehabilitation. 2017;40(1):11–21.
97. Germini F, Coerezza A, Andreinetti L, Nobili A, Rossi PD, Mari D, et al. N-of-1 randomized trials of ultra-micronized Palmitoylethanolamide in older patients with chronic pain. Drugs Aging. 2017;34(12):941–52. https://doi.org/10.1007/s40266-017-0506-2
98. Nathan PC, Tomlinson G, Dupuis LL, Greenberg ML, Ota S, Bartels U, et al. A pilot study of ondansetron plus metopimazine vs. ondansetron monotherapy in children receiving highly emetogenic chemotherapy: a Bayesian randomized serial N-of-1 trials design. Support Care Cancer. 2006;14(3):268–76.
99. Kaplan HC, Opipari-Arrigan L, Yang J, Schmid CH, Schuler CL, Saeed SA, et al. Personalized research on diet in ulcerative colitis and Crohn's disease: a series of N-of-1 diet trials. Am J Gastroenterol. 2022;117(6):902–17.
100. Mitchell GK, Hardy JR, Nikles CJ, Carmont SAS, Senior HE, Schluter PJ, et al. The effect of methylphenidate on fatigue in advanced cancer: an aggregated N-of-1 trial. J Pain Symptom Manag. 2015;50(3):289–96. https://doi.org/10.1016/j.jpainsymman.2015.03.009
101. Sung L, Tomlinson GA, Greenberg ML, Koren G, Judd P, Ota S, et al. Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. Eur J Cancer. 2007;43(8):1269–75.
102. Roustit M, Giai J, Gaget O, Khouri C, Mouhib M, Lotito A, et al. On-demand sildenafil as a treatment for raynaud phenomenon: a series of n-of-1 trials. Ann Intern Med. 2018;169(10):694–703.
103. Ma Y, Fu Y, Tian Y, Gou W, Miao Z, Yang M, et al. Individual postprandial glycemic responses to diet in n-of-1 trials: Westlake N-of-1 trials for macronutrient intake (WE-MACNUTR). J Nutr. 2021;151(10):3158–67.
104. Ursino M, Stallard N. Bayesian approaches for confirmatory trials in rare diseases: opportunities and challenges. Int J Environ Res Public Health. 2021;18(3):1–9.
105. Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. J Clin Epidemiol. 2009;62(1):13–21.e5. https://doi.org/10.1016/j.jclinepi.2008.07.006
106. Zucker DR, Ruthazer R, Schmid CH, Feuer JM, Fischer PA, Kieval RI, et al. Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. J Rheumatol. 2006;33(10):2069–77.
107. Zucker DR, Ruthazer R, Schmid CH. Individual (N-of-1) trials can be combined to give population comparative treatment effect estimates: methodologic considerations. J Clin Epidemiol. 2010;63(12):1312–23.
108. Irwig L, Glasziou P, March L. Ethics n-of-1 trials. Lancet. 1995;345:469.
109. Synofzik M, van Roon-Mom WMC, Marckmann G, van Duyvenvoorde HA, Graessner H, Schüle R, et al. Preparing n-of-1 antisense oligonucleotide treatments for rare neurological diseases in Europe: genetic, regulatory, and ethical perspectives. Nucleic Acid Ther. 2021;32:83–94.
110. Samuel JP, Burgart A, Wootton SH, Magnus D, Lantos JD, Tyson JE. Randomized n-of-1 trials: quality improvement, research, or both? Pediatrics. 2016;138(2):1–7.
111. Kane PB, Bittlinger M, Kimmelman J. Individualized therapy trials: navigating patient care, research goals and ethics. Nat Med. 2021;27(10):1679–86.
112. Defelippe VM, J M W van Thiel G, Otte WM, Schutgens REG, Stunnenberg B, Cross HJ, et al. Toward responsible clinical n-of-1 strategies for rare diseases. Drug Discov Today. 2023;28(10):103688.
113. European Medicines Agency. Committee for medicinal products for human use (CHMP) guideline on clinical trials in small populations. London; 2006 Jul [cited 2024 May 22]. Available from: http://www.emea.eu.int
114. Food and Drug Administration. IND submissions for individualized antisense oligonucleotide drug Products for severely debilitating or life-threatening diseases: clinical recommendations guidance for sponsor-investigators. 2021 Dec [cited 2024 May 22]. Available from: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
115. Nikles J, Onghena P, Vlaeyen JWS, Wicksell RK, Simons LE, McGree JM, et al. Establishment of an international collaborative network for N-of-1 trials and single-case designs. Contemp Clin Trials Commun. 2021;23:103688.
116. Weinreich SS, Vrinten C, Kuijpers MR, Lipka AF, Schimmel KJM, Van Zwet EW, et al. Aggregated N-of-1 trials for unlicensed medicines for small populations: an assessment of a trial with ephedrine for myasthenia gravis. Orphanet J Rare Dis. 2017;12(1):1–18.
117. Selker HP, Cohen T, D'Agostino RB, Dere WH, Ghaemi SN, Honig PK, et al. A useful and sustainable role for N-of-1 trials in the healthcare ecosystem. Clin Pharmacol Ther. 2022;112(2):224–32.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Defelippe VM, Brilstra EH, Otte WM, Cross HJ, O'Callaghan F, De Giorgis V, et al. N-of-1 trials in epilepsy: A systematic review and lessons paving the way forward. Epilepsia. 2024;65:3119–3137. https://doi.org/10.1111/epi.18068

15281167, 2024, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/epi.18068, Wiley Online Library on [25/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License