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Toward responsible clinical *n*-of-1 strategies for rare diseases

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N-of-1 strategies can provide high-quality evidence of treatment efficacy at the individual level and optimize evidence-based selection of off-label treatments for patients with rare diseases. Given their design characteristics, *n*-of-1 strategies are considered to lay at the intersection between medical research and clinical care. Therefore, whether *n*-of-1 strategies should be governed by research or care regulations remains a debated issue. Here, we delineate differences between medical research and optimized clinical care, and distinguish the regulations which apply to either. We also set standards for responsible optimized clinical *n*-of-1 strategies with (off-label) treatments for rare diseases. Implementing clinical *n*-of-1 strategies as defined here could aid in optimized treatment selection for such diseases.

Keywords: single patient trial; methodology; clinical care; rare diseases; personalized medicine; learning healthcare systems

Introduction

Rare diseases affect fewer than 1 in 2000 people,[1] collectively affecting ~6% of the global population.[2,3] Effective treatment options have been licensed for <5% of rare diseases. As a result, patients are often treated with repurposed, off-label treatments, or treatments authorized for a different condition, age group,

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or form of administration, which, based on clinical experience or mechanism of action, are prescribed to reduce burden of symptoms or target the underlying etiology of disease.[4] Despite advances in the scientific discovery of treatments, prospects of conducting randomized controlled trials (RCTs) to inform treatment recommendations in rare populations are hampered by the inherent low prevalence of these conditions and interpatient heterogeneity.

Traditionally, evidence-based medicine relies on results from RCTs providing group-level evidence of treatment efficacy and safety, which can be translated into clinical guidelines. These trials require recruitment of sufficient patients for statistical analysis to provide adequate population-level estimates. In addition, RCTs have limited predictive value with regard to treatment efficacy for an individual patient and, particularly in a heterogeneous patient population, results can be a poor reflection of actual clinical response for individuals. For example, patients with a disease associated with the same rare, pathological genetic variant can present with varying ages of onset (neonates and adults), severity of disease, and comorbid symptoms, and assessment of treatment efficacy using the same outcome measures in all individuals might lack clinical relevance. Therefore, although physicians are eager to improve the quality of care offered to patients with rare diseases, following conventional clinical trial practices remains challenging.

An *n*-of-1 approach provides a strategy to optimize treatment selection in clinical care, as well as an avenue for scientifically sound research in small patient populations.[5–7] In an *n*-of-1 strategy, the individual serves as their own control following multiple, crossover, randomized periods with an active and comparator intervention, according to a predefined plan (Figure 1). An additional advantage is the option to analyze *n*-of-1 results both at the individual level and by aggregating results to obtain group-level conclusions. Given their design qualities resembling research and the potential to obtain generalizable conclusions, *n*-of-1 strategies have been considered a hybrid between research and care. As the use of *n*-of-1 strategies gained attention during the 1990s, *The Lancet* published the first commentary on the value of *n*-of-1 strategies as quality improvement of care and the ethical implications of this approach.[8] Irwig and colleagues argued that using within-patient order randomization, placebo, and registering of outcomes provides ethical advantages compared with usual care, and does not require the ethical oversight required for medical research.[8] After more than two decades, it remains a topic of debate whether *n*-of-1 strategies should abide by the same legislation and ethical guidelines established for medical research or clinical care.[9–12]

The contention regarding the applicability of clinical research regulations to *n*-of-1 strategies is illustrated by the number of published *n*-of-1 interventions that received Institutional Review Board (IRB) approval and the available frameworks to assess which regulations apply to these interventions. Interestingly, almost 80% of IRBs in the USA had no fixed policy regarding assessing whether *n*-of-1 interventions would be considered medical research.[10] A systematic review showed that ~70% of all n-of-1 strategies published from 1985 to 2010 were subject to IRB approval because of their systematic approach following

a protocol with randomized, crossover periods, and the aim of providing generalizable knowledge.[10,13] When confronted with aspects such as randomization or placebo, the subtleties of *n*-of-1 strategies aiming to improve individual patient care might be underappreciated by IRBs. As a result, *n*-of-1 approaches might 'by default' be seen as research on humans. Although the incentive of ethical oversight for medical research is to protect patient well-being, the associated demanding administrative procedures can lead physicians and patients to shy away from *n*-of-1 strategies for single patients in clinical care, and opt for more pragmatic, less methodologically sound, approaches. The paucity of policies mapping how to navigate the ethical and legal aspects of *n*-of-1 strategies has stalled efforts to conduct *n*-of-1 interventions for patients with rare conditions.

Here, we contribute to responsible high-quality n-of-1 strategies by setting the standards for these practices and providing a practical framework to distinguish between clinical care and medical research, and the regulations these abide to. To do so, we first delineate the distinction between medical research and quality improvement of care. Thereafter, we define research and clinical *n*-of-1 strategies and the ethical considerations regarding these approaches. By building on previously published proposals,[8,9,11,14,15] we outline those *n*-of-1 strategies that fulfil the criteria for optimized care and should not be subject to the regulations of medical research.

The distinction between research and care

The roadmap to clarify the regulations governing *n*-of-1 strategies deviates from the current notion of clinical and research ethics. The Belmont Report, published in 1979, distinguishes clinical practice as 'interventions designed solely to enhance the well-being of an individual' with 'reasonable expectation of success',[16] and medical research as 'activities designed to…contribute to generalizable knowledge', usually 'in a formal protocol that sets forth an objective and set of procedures designed to reach that objective'.[16] Although the Belmont Report acknowledged the overlap between research and clinical care, ethical and regulatory procedures developed thereafter maintained a sharp distinction based on: (i) the aim to create new knowledge with implications that extend beyond the study population (i.e., generalizable); and (ii) the procedures or rules of behavior required to reach that objective and the degree to which these infringe on patient comfort and well-being. In line with this, human subject research with a medicinal product, including RCTs, is tightly regulated. In Europe, for example, European Clinical Trial Regulation no. 536/2014 (EU CTR) recently came into effect, aiming to maintain the highest standards for patient safety in clinical trials.[17]

Emerging initiatives to optimize clinical practice, such as *n*-of-1 strategies, challenge the distinction between research and care and expose the limitations of this dichotomy. These strategies emerge from the inherent and empirical learning in clinical practice, and the implied need to document or monitor patient outcomes more methodically to verify clinical benefit and minimize risks related to a 'trial-and-error' approach.[18,19] Optimized clinical practice or quality improvement can use aspects of research methodology, such as data collection or improved outcome

monitoring, although the primary aim is to improve care for the individual patient. Particularly in the fields of pediatric and rare disease, efforts are being made to shape quality improvement of care practices into learning health systems (LHS), in which data from clinical practice is systematically collected and analyzed to improve outcomes and efficiency of healthcare.[18,20,21] LHS and n-of-1 strategies stem from a similar clinical need to respond to the scarcity of knowledge to guide clinical practice in conditions for which conducting RCTs is unfeasible. By using aspects that resemble research in clinical practice, these activities are considered a hybrid between research and care. In attempting to implement these optimized care activities, it is difficult to define the level of ethical oversight required and, as a result, these efforts might be stalled. It has been argued that a transition toward risk-proportionate ethical oversight of quality improvement of care initiatives is warranted.[23]

Despite calls to abandon this dichotomy,[18,24,25] the sharp distinction between care and research regulations prevails in the current regulatory ecosystem. To help clinicians and researchers responsibly navigate the system, we illustrate the spectrum of design aspects used, the objectives that n-of-1 strategies might have, and the corresponding implications for ethical oversight as research or care.

N-of-1 strategies in clinical care

N-of-1 strategies emerged formally to optimize treatment selection for an individual when the case history of a patient with poorly controlled asthma that had resisted several attempted interventions was first published in the New England Journal of Medicine in 1986.[7,26] Since then, n-of-1 strategies have been used to aid in individualized treatment selection in patients with conditions such as attention deficit and hyperactivity disorder (ADHD), osteoarthritis, and neuropathic pain, whenever, despite existing clinical guidelines, experience showed heterogeneity of treatment response between individuals.[7,27,28] In addition, this methodology has been used for rare diseases and in cases where there is lack of, or conflicting, evidence to guide clinical management.[27–31] N-of-1 trials are considered suitable for conditions that are chronic and stable (or slowly progressive), provided the outcome of interest can be measured and quantified and with the impact of treatment on such outcome is rapid in onset and readily reversible (Box 1).[7,26,32] Recommendations for how to apply a methodologically sound n-of-1 strategy are addressed elsewhere.[32]

Box 1 Questions to determine suitability of an n-of-1 approach for assessing treatment response, based on criteria established by previous publications[7,26,32].

Is an n-of-1 approach suitable?

- Is the condition chronic, with stable or fluctuating symptoms, or slowly progressive?
- Can the outcome of interest be measured in short periods of time and over time?
- Does the recommended treatment have a quick on and off-set, reversible effect on the outcome of interest?

The N-of-1 trial as a research methodology

We propose that n-of-1 trials be considered a research activity when the primary aim is to generate novel medical knowledge based on the results of n-of-1 in a (typically small) group of individuals, which can be subsequently aggregated to obtain group-level results. In these n-of-1 trials, all patients receive the same predefined treatment(s) according to a common protocol designed to address a specific question on the safety or efficacy of a treatment. In this context, additional measurements or interventions that might infringe on patient comfort or well-being might be required to address the scientific question. The outcome measures used in research n-of-1 trials would be generic or disease specific, prioritizing generalization and external validity over individualized outcomes or design. A recent example is the double-blind randomized n-of-1 trial with mexiletine for patients with a rare neurological condition, non-dystrophic myotonia, for which authors provided individual and group-level results.[33,34]

In the EU, all research n-of-1 strategies should adhere to the EU CTR and local regulations for human subject research. The investigational medicinal product (IMP) characteristics might further define the level of oversight required. According to the new definition in the EU CTR, some n-of-1 trials can be considered low-intervention clinical trials if they meet certain conditions. These include minimal risk when compared with clinical care and use of an IMP according to market authorization or off-label, but supported by sufficient scientific evidence. Low-intervention research n-of-1 trials should follow risk-based evaluation according to local norms to determine regulatory requirements governing monitoring, traceability and administration.[17,35–37]

Optimizing n-of-1 strategies in clinical care

Based on the above considerations, a clinical care n-of-1 strategy can be defined as an intervention planned and performed to improve clinical outcomes for an individual patient. Such intervention would not meet the definition of medical research. The clinical care n-of-1 strategy can include randomization of the sequence of treatments and use of placebo, to minimize sources of bias in optimizing clinical care.[38–40] In optimized clinical care n-of-1 strategies, outcome measures can be individualized and the design can be adjusted to the patient's characteristics and care priorities. In contrast to common clinical practice, the clinician and patient engage in predefining objective outcome measurements, and ensuring a more consistent monitoring plan. Improved outcome monitoring, use of a control (comparator) treatment, and statistical analysis of results are aimed at promoting rational treatment selection for that individual. In the routine clinical management of conditions for which treatment guidelines are lacking, suboptimal assessment of treatment effects can lead to incorrect withdrawal or unnecessary exposure to medication, thereby prolonging the search for an adequate therapy. Optimized clinical care n-of-1 strategies could provide a safer way to evaluate treatment efficacy in cases of clinical equipoise in patients with rare diseases.

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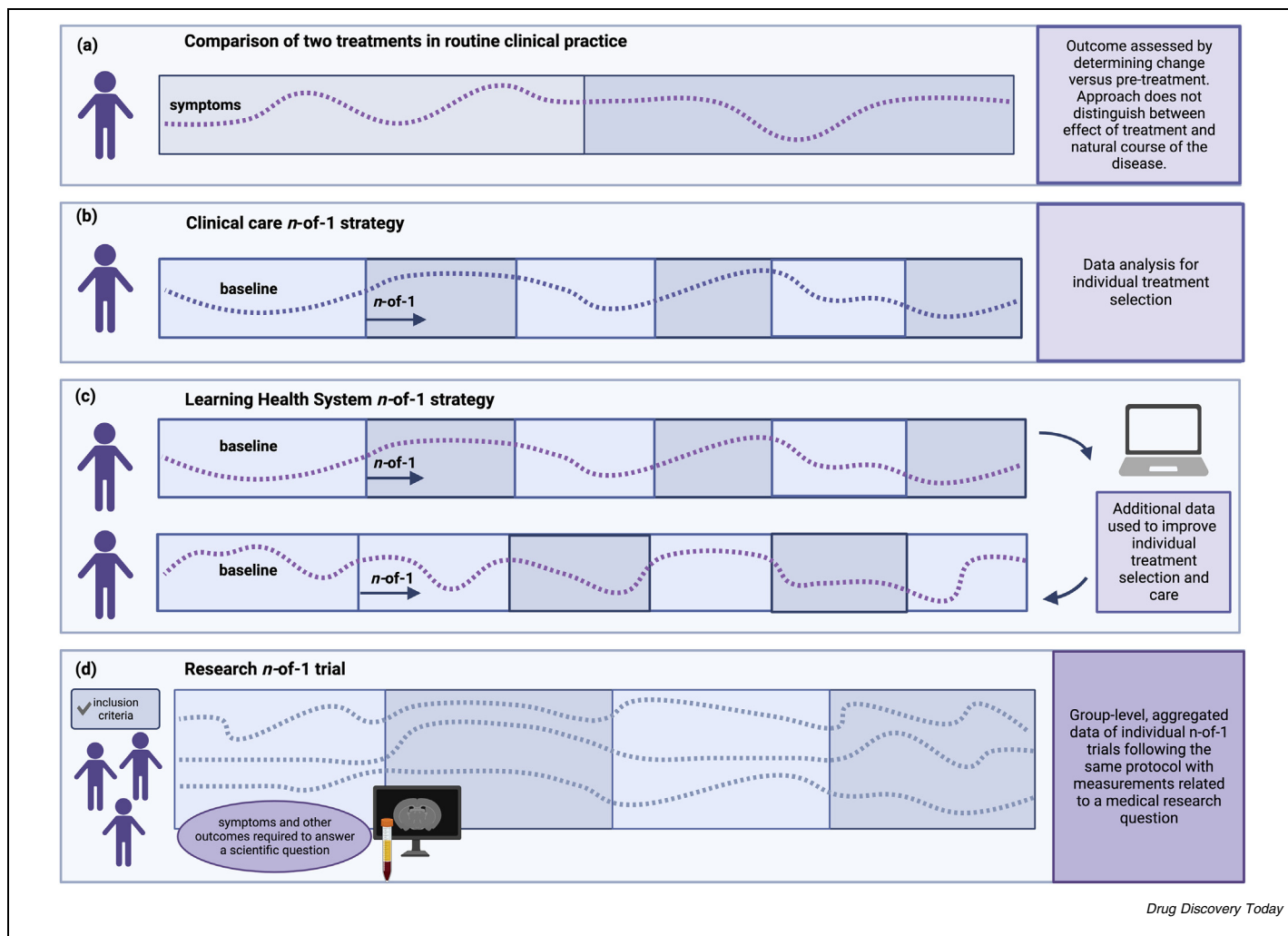
FIGURE 1

Schematic of *n*-of-1 strategies. **(a)** Comparison of two treatments in clinical practice. Magnitude of the outcome of interest, in this case clinical symptoms, is represented by the dotted line throughout over time. **(b)** Clinical *n*-of-1 strategies can be used to assess treatment efficacy following a predefined treatment monitoring plan and data analysis, thereby providing a method for personalized, evidence-based, treatment selection. **(c)** Learning health systems (LHS) *n*-of-1 strategies allow collection of data from several clinical care *n*-of-1 strategies to optimize care by combining with other clinical data (from the same or other patients) to improve estimates on treatment efficacy for the individual patient. All the aforementioned initiatives use solely interventions tailored to the individual's characteristics. **(d)** Research *n*-of-1 strategies involve a fixed *n*-of-1 protocol, including eligibility criteria, which must be followed by all individuals. This can include additional measurements (e.g., imaging or blood samples) compared with clinical care, required to answer a scientific question.

We also need to consider clinical care *n*-of-1 strategies embedded in LHS, or LHS *n*-of-1 strategies. The primary aim of LHS *n*-of-1 strategies remains to improve quality of care, with the additional component of optimized data collection for individual patients to learn about the care offered and patient characteristics in the specific clinical setting.[32] Similar to optimized clinical care *n*-of-1 strategies, assessment procedures are limited to those required for optimal care according to patients and treatment characteristics. Given that data are systematically collected and analyzed, LHS *n*-of-1 strategies fall under the regulations of data protection EU General Data Protection Regulation (EU GDPR).

Given that *n*-of-1 strategies lay at the interface between research and care, and we propose to place the clinical care *n*-of-1 strategies under the domain of care, clear standards must be formulated on how such strategies should be implemented. For clinical care *n*-of-1 strategies for rare diseases, the standards should address the risks associated with selected (off-label) treatment and the specific design aspects, such as randomization, use of placebo, frequency of hospital visits, and outcome measurements. Here, we propose standards for clinical care *n*-of-1 practice. Interventions conducted according to these standards should fall under regulation for clinical care rather than research. We recommend that a multidisciplinary expert panel should ensure that the proposed n-of-1 intervention is methodologically sound and that the expected benefits to the individual outweigh the risks. The expert panel should not be a duplicate IRB but, a lean body tasked with judging whether the proposed intervention fulfills the criteria for clinical care or research, and applies a sound methodological approach. The multidisciplinary panel should include experts with adequate competences in the relevant disciplines (e.g., general medicine, neurology, oncology, pharmacology, etc.), *n*-of-1 trial design, and ethics.

Treatment selection, including off-label use

In clinical care *n*-of-1 strategies, medications can be compared according to their market authorization, but off-label use can also be involved. Off-label prescribing is part of clinical care and is common for rare diseases and many pediatric conditions.[42–44] It is regulated as care by national guidelines and competent authorities; therefore, regulations vary across regions. Recent guiding frameworks published by the European Academy of Pediatrics, the European Society for Developmental, Perinatal, and Pediatric Pharmacology, and others[41,45] are valuable for assessing the risks and benefits of off-label prescribing. These frameworks take into consideration pharmacological data (including pharmacokinetics), level of available evidence, clinical experience, as well as factors that mitigate risks. For *n*-of-1 approaches, previous ethical frameworks proposed that a marketed drug can be prescribed off-label as clinical care if its side-effects are mild, or when the risk of potentially serious side-effects is offset by the expected benefit and the seriousness of the condition.[9] Given the nature of rare diseases in which the number of proposed repurposed treatments increases rapidly, we favor additional oversight to improve monitoring, risk mitigation, and follow-up. Specifically, we propose to add, as criteria to conduct a clinical care *n*-of-1 intervention, an explicit benefit–risk assessment according to the recently published guidelines for adequate off-label prescribing and a positive judgement from an external multidisciplinary *ad hoc* expert panel.[41,45] The intervention can be applied if the potential benefits to the individual of the proposed (off-label) treatment and *n*-of-1 design are deemed by the expert panel to outweigh potential risks. This approach would improve monitoring, risk mitigation and follow-up of off-label prescribing for rare diseases.

Designing a methodologically sound n-of-1 intervention in clinical care

The design of a methodologically sound *n*-of-1 intervention in clinical care typically involves adopting concepts and procedures commonly used in medical research. Considering these methodological aspects can explain concerns that IRB members might have in applying clinical care strategies.[23] We discuss some critical design aspects and recommendations to apply these design aspects in quality improvement of care initiatives (Table 1).

Randomization

Clinical care *n*-of-1 strategies could use a randomized crossover design to determine whether the treatment outcomes observed are the effect of treatment rather than a reflection of fluctuations in the manifestations of the disease.[38] In clinical care, worsening of the symptoms, as a result of fluctuations in the expression of the disease, often leads to changes in medication dosages or additional interventions. However, whether increasing the burden of medications at that point is justified is not always clear. Order randomization can minimize the impact of spontaneous fluctuations of the symptoms of the disease in the treatment efficacy assessment. Recently, the use of microrandomization in mood and behavioral studies, in which an app-based intervention is delivered to one individual according to a randomization scheme alternating between hundreds of exposure (or control) moments, has emerged. Similarly to order randomization in *n*-of-1 strategies, microrandomization provides temporal-distribution data sets and can be used to assess whether the intervention effects vary with the moment or the context in which it is being delivered.[46,47] Many ethical concerns regarding the use of randomization refer to randomized allocation to groups leading to a patient being deprived of a potentially superior treatment.[23] However, in clinical care *n*-of-1 strategies, patients always receive the treatments of interest. In addition, predetermined analyses of the accrued evidence can be used to ensure that switching across treatments (including, if applicable, placebo treatment) can be terminated when the data collected indicate superiority (or ineffectiveness) of a given treatment for the individual.

Blinding procedures and use of placebo as comparator

Outcome assessment is subject to patient- and observer-related bias, which can be minimized using a double-blind design. The use of blinding minimizes the influence of confounders and facilitates decision making by strengthening the quality of the results. Concealment of order of treatment allocation from those involved in the management of patients and collecting and analyzing the data is important to minimize possible bias in assessing disease status, dosage adjustments, or termination of the *n*-of-1 treatment plan. Facilitating processes to enable blinding of physicians, assessors, or others involved in patient management throughout the intervention might be logistically challenging in clinical care *n*-of-1 strategies. Sometimes, a physician blinded to treatment allocation is responsible for adjustments in (concomitant) medication dosages.[48] Moreover, in LHS *n*-of-1 strategies, data collected in electronic patient files could be analyzed by an external data analyst blinded to treatment order allocation and inform the treating physician of results at specific time points. Where there is uncertainty about whether applying a treatment carries a better risk-benefit ratio for the individual compared with withholding such treatment or using an alternative intervention, the comparator period can include the use of placebo.[39,40] Use of placebo allows to correct for confounders, such as regression to the mean, the influence of emotional factors on the course of the disease, or the presence of potential patient or observer-related bias. Placebo has been used for care improvement purposes, for example in *n*-of-1 clinical strategies in individuals with ADHD and in pain clinics.[27,28,39,50,51]

Outcome measurements

An advantage of *n*-of-1 strategies is the use of individualized outcome measurements. An ethical concern with outcome monitoring is that using additional questionnaires or tests compared with standard clinical care could burden patients. This concern stems from research protocols in which many outcome measures are applied to improve the generalization of study results, or to fulfill regulatory requirements. In clinical care *n*-of-1 strategies, extensive outcome monitoring is typically not required because assessment can focus on the clinical manifestations (or outcomes) most relevant to the individual's well-being. This approach can benefit from use of patient-reported outcome measurements (PROMs), the application of which in clinical practice has been shown to improve patient satisfaction, self-management, and quality of life.[49,53–55] When disease-specific PROMs or other sensitive tools are unavailable, physicians are

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TABLE 1

Methodological aspects in clinical care *n*-of-1 strategies: ethical concerns, reasons justifying their application, and recommendation for implementation.

N-of-1 strategy design aspect	Ethical concern	Justification for use in quality improvement of care	Recommendation for application in clinical care *n*-of-1 intervention
Formal and predefined outcome selection	Could include measurements in addition to those required to assess outcome in routine clinical care; e.g., including extensive scores or evaluations that can result in additional burden for patients	In many situations, it might be difficult to differentiate response to treatment from the natural course of the disease. Uncertainty about the real impact of the treatment could lead to a prolonged search for optimal treatment Formalizing (subjective) outcomes into individualized scales based on patient goals or disease-specific manifestations can facilitate clinical decision making and improve self-management and compliance[28,52–55]	Include only those measures required to assess outcome as needed to optimize individual's clinical care to minimize patient burden Select individualized, clinical, or laboratory outcomes and treatment goals, as defined in advance
Order randomization	Treatment and/or comparator are temporarily withheld, which might infringe on patient well-being. However, patient receives the two treatments that need to be compared and, therefore, these would have to be administered irrespective of randomization	Order randomization is key to minimize time-related bias in assessment of treatment effects.[32,38] When the individual receives both treatments, use of randomized treatment periods does not involve additional risk or burden compared with a standard-of-care approach in which the same treatments are tested sequentially in non-randomized order[23]	Determine whether there is added value of use of order randomization Transparent communication over randomization strategy with patient[23] Predefine efficacy rules and ensure early termination if unequivocal effect or harm identified
Blinding and use of placebo	Use of blinding and placebo in care can hamper trust in physician–patient relations	Blinding is necessary to minimize patient- and observer-related bias in assessing outcomes. Placebo might be needed when no treatments with demonstrated efficacy exist and when there is a balance over whether the risk-benefit ratio associated with intervention differs from that of withholding that intervention Blinding of person delivering intervention, outcome assessor, and data analyst to treatment allocation phase will minimize bias	Provide patient with detailed and balanced information about rationale for blinding and, if applicable, use of placebo.[39] Ensure that informed consent is obtained Assign independent physicians for outcome assessment, data analysis, and changes in concomitant medication, and/or delivering intervention
Analysis	Use of statistical analysis can lead to incentive to follow fixed-protocols to achieve statistical power. This could undermine patient well-being.	Statistical analysis provides objective way to support decision making and permits meaningful interpretation of outcome data[32] Bayesian analysis can provide estimates as probability of clinically relevant effect, which aligns with clinical decision-making practices[58]	If aim is improvement of individual care, rationale of ensuring sound interpretation of outcome data shall not be compromised Statistical analysis facilitates assessment of outcome data and shared-decision making process

TABLE 2

Characteristics of clinical *n*-of-1 strategies and research *n*-of-1 trials, and proposed oversight responsibilities.

Context and design	Characteristics
Clinical *n*-of-1 strategy	• Approach being applied to improve clinical management of the individual. • The treatment is approved for this indication and/or population, or used off-label. • A multidisciplinary expert panel assesses: potential risks, benefits and uncertainties of treatment and the *n*-of-1 strategy. • The *n*-of-1 intervention does not require burdensome procedures in addition to those involved in optimal clinical management of the individual. • Informed consent procedures as in clinical care are followed • Consider embedding clinical *n*-of-1 strategies in Learning Health Systems to optimize clinical care. If so, follow EU GDPR procedures.
Low-intervention research *n*-of-1 trial	• The *n*-of-1 approach is applied to answer a scientific question beyond the participant. • The intervention is a medicinal product used according to the terms of market authorization or used off label supported by sound scientific evidence. • The assignment of the subject to a particular therapeutic strategy is decided in advance by a protocol. • The intervention does not pose more than minimal additional risk or burden to the patient. • The protocol is submitted for IRB review as a low-intervention n-of-1 research trial.
Research *n*-of-1 trial	• The *n*-of-1 approach is applied to answer a scientific question beyond the participant. • The intervention is 'non-licensed' medicinal product. • The assignment of the subject to a particular therapeutic strategy is decided in advance by a protocol. • The intervention may involve additional burden required to answer a scientific question. • The protocol is submitted for IRB review as a n-of-1 research trial.

encouraged to develop scales adapted to individual care aims, such as Goal Attainment Scaling.[55]

Statistical analysis

In clinical care *n*-of-1 strategies, statistical methods are applied to uncover treatment effects for the individual patient. The patient and physician can predefine a minimal threshold effect to support clinical, shared-decision making. Although *n*-of-1 strategies can be analyzed using frequentist approaches, Bayesian analysis offers several advantages in the context of rare diseases.[56] In fact, studies based on frequentist approaches rely on sample size and power analysis to provide robust results. Achieving sufficient statistical power is challenging for conditions with low prevalence and clinical heterogeneity, such as rare diseases. Bayesian modeling offers the possibility of optimizing use of the limited available data by increasing the statistical power by better estimation of fixed and random treatment effects, especially when each patient is measured multiple times. Knowledge of estimated effect size or subsequent *n*-of-1 trials can be incorporated into 'informed Bayesian models', which can update the provided estimates continuously for each patient.[56] This approach also allows robust analysis of *n*-of-1 studies for rare diseases at the individual and (sub)group level(s) simultaneously, despite the challenge of low disease prevalence. Finally, Bayesian analysis yields probabilistic estimates of clinical relevant effects (e.g., 80% probability of 50% symptom reduction), rather than rejecting a null hypothesis. This can be applied more intuitively in clinical decision making because it closely resembles how doctors think during the diagnostic and therapeutic process. In line with this, the probabilistic outcomes emerging from Bayesian analysis might be easier to interpret by all end users involved (patients, physicians, and regulatory authorities).

Statistical analysis can also be used for interim analysis to facilitate early termination of the crossover process if efficacy (or no benefit), as defined in the individual's *n*-of-1 intervention plan, is observed. Embedding clinical care *n*-of-1 strategies in LHS allows rapid analysis of the data collected from patients' electronic health records to support the clinical decision-making process with probabilistic estimates of treatment effects.

Data collection

The low prevalence of rare diseases and the associated scarcity of relevant knowledge of their optimal management strategies requires physicians to learn from each case and to adopt infrastructure for enhanced learning, such as LHS. Embedding clinical care *n*-of-1 strategies in LHS creates opportunities to understand the variations in the disease and treatment outcomes. Whereas in clinical care *n*-of-1 strategies treatment outcomes are recorded only in the patient's file, in LHS the data from *n*-of-1 strategies can be further analyzed and used to improve overall quality of care.

Regulatory implications of *n*-of-1 strategies

We have outlined the aims of clinical care *n*-of-1 strategies and research *n*-of-1 trials. We argue that oversight procedures should be proportionate to these objectives and potential risks of these practices (as summarized in Table 2). Research *n*-of-1 trials aim to create generalizable medical knowledge. They are subject to research regulations, including mandatory IRB review for interventional research and compliance with EU CTR and EU GDPR 2016/679 norms.

We propose that clinical care *n*-of-1 strategies that meet the standards that we have outlined should obtain approval from an external multidisciplinary expert panel. IRB approval should not be considered mandatory and informed consent procedures should apply as in clinical care.[57,58] Although IRBs have been involved in oversight of activities at the interface of research and care (such as LHS, pragmatic clinical trials, and *n*-of-1 interventions), we encourage shared, proportionate oversight respon-

sibilities. The ad hoc expert panel holds a high ethical standard to support optimized clinical *n*-of-1 strategies to be pursued in the care domain following procedures in proportion to risks and aims of the intervention. Finally, in LHS *n*-of-1 strategies, the process should be streamlined to obtain broad informed consent for data collection, analysis of pseudonymized data for learning activities according to EU GDPR 2016/679.

Concluding remarks

This paper distinguishes between research *n*-of-1 trials and clinical care *n*-of-1 interventions. Our proposal aligns with recent publications suggesting that *n*-of-1 interventions that aim solely at improving the management of an individual's condition constitute a form of care.[14,15] Distinguishing the aims, design, and ethical aspects of clinical care *n*-of-1 strategies is crucial to address the existing evidence gap in the field of rare disease therapies. Adopting this distinction enables optimized treatment selection for individual patients in situations where adequate evidence is lacking and conducting RCTs is unfeasible.

We also propose standards for implementing clinical care *n*-of-1 strategies. Interventions that comply with these standards can be conducted under the oversight and norms of clinical care and, in the case of LHS *n*-of-1 strategies, also the norms of good data governance. This distinction allows risk-proportionate oversight of quality improvement of care activities, and encourages discussions on shared oversight responsibilities between IRBs and other entities, such as multidisciplinary expert panels or hospital ethics committees.[11,20,57,58]

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Declaration of interests

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Acknowledgments

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