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A Useful and Sustainable Role for N-of-1 Trials in the Healthcare Ecosystem

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Clinicians and patients often try a treatment for an initial period to inform longer-term therapeutic decisions. A more rigorous approach involves N-of-1 trials. In these single-patient crossover trials, typically conducted in patients with chronic conditions, individual patients are given candidate treatments in a double-blinded, random sequence of alternating periods to determine the most effective treatment for that patient. However, to date, these trials are rarely done outside of research settings and have not been integrated into general care where they could offer substantial benefit. Designating this classical, N-of-1 trial design as type 1, there also are new and evolving uses of N-of-1 trials that we designate as type 2. In these, rather than focusing on optimizing treatment for chronic diseases when multiple approved choices are available, as is typical of type 1, a type 2 N-of-1 trial tests treatments designed specifically for a patient with a rare disease, to facilitate personalized medicine. While the aims differ, both types face the challenge of collecting individual-patient evidence using standard, trusted, widely accepted methods. To fulfill their potential for producing both clinical and research benefits, and to be available for wide use, N-of-1 trials will have to fit into the current healthcare ecosystem. This will require generalizable and accepted processes, platforms, methods, and standards. This also will require sustainable value-based arrangements among key stakeholders. In this article, we review opportunities, stakeholders, issues, and possible approaches that could support general use of N-of-1 trials and deliver benefit to patients and the healthcare enterprise. To assess and expand the benefits of N-of-1 trials, we propose multistakeholder meetings, workshops, and the generation of methods, standards, and platforms that would support wider availability and the value of N-of-1 trials.

For individuals with chronic conditions, such as asthma, heart failure, inflammatory diseases, and many more, it is common for clinicians to try a medication for an initial period to learn how well it works for that patient, to inform a decision about longer-term treatment. Even when there are good data from randomized controlled trials (RCTs), clinical guidelines, and/or systematic reviews to guide treatment, it may be difficult to apply the results to an individual patient. This could be because a patient does not meet the eligibility requirements of the original trials, the trials show evidence of harm or nonresponse in some patients, or an RCT had negative results, but some patients responded. In addition, for rare diseases, RCT data may not be available and clinical guidelines may be based solely on expert opinion. These challenges lead to trial-and-error prescribing. A more rigorous approach to trial-and-error prescribing can be N-of-1 trials. This process is patient centric and reinforces patient-physician shared decision making about treatments.[1] N-of-1 trial has been explored by clinical researchers for over 30 years.[2] Using rigorous clinical trial processes, patients are given candidate treatments (which may include placebo) over a series of time periods, with structured data collection. Ideally treatments are given in a randomized order in a double-blinded manner, so that neither the patient nor the

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clinician knows which treatment is being given in a certain period. Thereby, N-of-1 trials combine foundational elements of clinical practice with clinical research procedures to determine the most effective treatment for a particular patient.

By supporting personalized, evidence-based decision making as part of patients' usual clinical care, N-of-1 trials are examples of *effectiveness* trials, studies that test treatments *in usual care conditions*, as distinguished from *efficacy* trials, which test treatments in ideal subjects, under optimized conditions. Because they typically compare alternative treatments, N-of-1 trials often can be considered *comparative effectiveness* trials that are customized to the care of a single patient, thus also very much aligned with *patient-centered research*. These features make N-of-1 studies attractive for application to usual care in real-world settings. However, despite over three decades of research literature to date, N-of-1 trials have not been widely used in usual clinical practice and have not been appreciated for their potential benefits by other parts of the healthcare ecosystem. In this article, we consider reasons and remedies for this lack of use of N-of-1 trials in order to widen their benefit. We review opportunities, challenges, and potential approaches that could encourage stakeholders to support widespread use and lead to benefits for patients and the healthcare enterprise. Ultimately, we believe that multistakeholder work, and the generation of methods, standards, platforms, and policies, could provide the pathway to more widely available and valued N-of-1 trials.

Type 1 N-of-1 trials

N-of-1 trials most commonly have been used for chronic conditions with relatively slow progression; here, we refer to these as type 1 N-of-1 trials (**Table 1**). The stability of the condition over the period of the trial allows for legitimate comparisons of the candidate treatments. The N-of-1 sequential treatment approach is generally not appropriate for rapidly progressive conditions, as the changeable underlying trajectory could undermine treatment comparisons. Additionally, for a patient with a rapidly deteriorating condition, if an effective treatment were already known, such experimentation might not be ethical or justified given the risks and time requirements of testing multiple treatments.

For those with suitable conditions, data on symptoms, signs, and/or markers of disease activity for each treatment period are collected by the patient, clinicians, and others involved in the patient's care, taking into account the timing of carryover of some drug effects. For example, for patients with fibromyalgia, relevant outcomes include pain, sleep patterns, and other symptoms.[3] For patients with heart failure, symptoms, signs, functional assessments, and biomarkers can be followed.[2] For asthma, symptoms and pulmonary functions can be tracked.[4] For diabetes, adverse effects and blood glucose levels can be assessed.[5] This approach also can be useful in sorting out perceived adverse effects from drugs, such as from statins used for hyperlipidemia.[6] For pediatric patients, with inflammatory bowel disease, autism spectrum disorders, and attention-deficit/hyperactivity disorders, N-of-1 trials have followed clinical features, patients' experiences, and when available, biomarkers. In these conditions, in addition to the patient and his or her clinician, data frequently are collected by parents, teachers, and various types of therapists.[7] In all these instances, N-of-1 trials

Table 1 Descriptions of type 1 and type 2 N-of-1 trials

N-of-1 type	Typical target conditions	Study design	Patient objective	Generalized evidence
Type 1	Chronic conditions with relatively stable disease course, typically using already-approved treatments	Candidate treatments are given in a series of time periods, ideally randomized and double-blinded, potentially including placebo	Leads to decisions about the best treatments for individual patients by comparing interventions	By combining N-of-1 trials that use the same protocols one can generate evidence of overall effectiveness of therapies as a larger crossover trial
Type 2	Conditions, not necessarily chronic or stable, for which there are no accepted treatments and/or for which a new targeted treatment is being tested, e.g., in a patient with a specific mutation or ultrarare disease	Administration of a single treatment given to individual patients without alternative treatments. For bespoke treatments, discovery, development, and administration of a therapy are done in a single patient	Tests the effectiveness and safety of a targeted personalized treatment for an individual patient	May be able to aggregate results of multiple trials of specific treatment for a biological target in a rare disease as evidence for regulatory approval

Descriptions of type 1 and type 2 N-of-1 trials, including typical target conditions, study design, and objectives.

not only yield results specific to individual patients, but enhance the comparisons of treatments by patients serving as their own controls.[8]

In addition to identifying the best treatment for individual patients, N-of-1 trials also can provide generalizable evidence for wider use. Data from multiple N-of-1 trials that use the same treatment and evaluation protocol can be combined together as a multicrossover design trial evaluating one or more treatments. This combination allows N-of-1 trials to inform individual treatment decisions and also to provide group data.[9,10] Individual patients can thereby get optimal care, and the medical community can get evidence about the comparative effectiveness of treatments. This approach has been successfully tried in a number of conditions (e.g.,[9–11] although to our knowledge, as of yet, it has not been used to obtain regulatory approval for a treatment.

Type 2 N-of-1 trials

Recently, a new application of N-of-1 trials has emerged, focused on assessing treatments for rare conditions and/or for highly personalized treatments in a single patient, potentially testing only one rather than multiple treatments; here, we refer to these at type 2 N-of-1 trials (**Table 1**). These trials are motivated by circumstances of a devastating disease, typically a rare or ultrarare condition, for example, a genetic variant or molecular disease about which there may be some pathophysiologic understanding, but no effective treatment. With no known alternative, only one cycle of the candidate treatment may be required, rather than multiple, sequential treatment periods. Because comparisons between sequential treatments are not required, the focus on slowly progressive conditions, the hallmark of type 1 N-of-1 trials, may be lifted. This single-cycle design is intrinsically more susceptible to changes in the underlying condition and secular trends than the repeated crossovers typical of type 1 N-of-1 trials. However, it may be justified if the type 2 N-of-1 trial success indicators are achieved and compelling.

The growing understanding of genetic or epigenetic underpinnings of disease prompts a move towards a more personalized definition of conditions, and thus the need for these approaches. Moreover, many of the conventional trials for these conditions are below sample sizes that would meet statistical significance in standard RCTs. Additionally, the generalizable inclusion/exclusion criteria traditionally used in clinical trials may limit the ability to see individual disease. Further, effect sizes have proven very difficult not just because of limited sample size, but also because of heterogeneous presentations of rare diseases (even if monogenic), thus making end-point definition a major challenge. In this context, a type 2 N-of-1 trial in an individual patient can address and assess treatment effects on that individual's presentation.

As in type 1 trials, data on clinical measures and patient experience, biomarkers, and/or physiologic evidence of efficacy specific to that condition may be collected. For example, in patients given a targeted treatment for a physiologic defect related to a specific genetic variant of cystic fibrosis, data collection included measurement of change in mucosal ion transport, physiologic function, and propensity for infections.[12] Such trials also can be used for evaluating the impact of individualized genetic drug products, such as antisense oligonucleotide products[13] and cell-based treatments.[14]

With the growth of personalized treatments and their potential importance, it can be expected that type 2 N-of-1 trials will find increasing use. This is reflected in the recently released US Food and Drug Administration (FDA) draft guidance on the use of such trials in individualized drug development.[15] Although the kinds of conditions and treatments studied in type 2 trials differ from those in the classic type 1 N-of-1 trials, they have many of the same features of focus on personalization of an individual patient's treatment.[16,17] Because they could therefore potentially benefit from many of the same operational procedures, systems, and infrastructures, we include both N-of-1 trial types in this paper.

Aggregation of data from multiple N-of-1 trials

For both types of N-of-1 trials, there has been more focus on discerning individuals' optimal treatment, and less focus on aggregating data from multiple N-of-1 trials to obtain generalizable evidence. At its core, aggregation of N-of-1 trials is similar to the classic randomized, multiple crossover design. Like a classic randomized crossover design, there are advantages and disadvantages to the approach. These are beyond the scope of this article; however, the utility of aggregating data from multiple N-of-1 trials has been demonstrated across multiple chronic conditions[3,17] and in rare diseases,[18] but to date, this design has not been widely used. We believe this is, in part, because there has been no sustained, accepted, and widely available infrastructure to facilitate the use of standard N-of-1 practices, procedures, and processes. Moreover, pharmaceutical manufacturers have not promoted this approach in preference to traditional parallel arm clinical trials, nor have regulators encouraged this approach.

A path forward for N-of-1 trials

To date, most N-of-1 trial infrastructures have depended on research grant support, and have withered and disappeared after the funding ends. The question arises as to why these efforts have not been sustainable and have not spread more widely. The creation of N-of-1 trial software platforms and services, which would seem to be an important foundation for wider use, has not proven to be sustainable.[19] This may result from the lack of a successful economic model for the support of N-of-1 trials, leading to the absence of a market for such an infrastructure. This lack of an economic model may reflect the absence of adequate exploration of the benefits to the overall healthcare ecosystem and to each of its stakeholder components.

Believing that N-of-1 trials have much to contribute to patient-centered care and evidence building for common and rare conditions and for personalized medicine, we address the absence of a standard infrastructure and processes for general use, considering business models and stakeholders that could generate economic benefit from, and consequently support for, N-of-1 trials in the US healthcare ecosystem. We believe this will be required to sustain the capacity for high-quality, standardized N-of-1 trials. Without the availability of standard N-of-1 platforms and services trusted by stakeholders, and without business models that generate value for key stakeholders, the approach will not be widely used and leveraged.

Stakeholders, Issues, and Approaches

Stakeholders

In order to design an effective business model, we must consider the stakeholders in the healthcare ecosystem who would benefit from N-of-1 trials. Those who could gain value that could support an N-of-1 trial enterprise include:

1. *Patients:* The individualized assessment of treatments by an N-of-1 trial informing care should yield the best and preferred outcomes for a given individual and is naturally attractive to patients.[20,21] Additionally, aggregating an individual patient's data with data from those with a similar condition may further improve care by discerning treatment effects across subgroups.

   The N-of-1 process has the benefit of engaging patients and clinicians together in shaping care, and potentially, also engaging family members, caregivers, therapists, teachers, and others involved in a patient's life. Indeed, building patient and patient-group understanding, support, and engagement will be key to patient acceptance of the requirements of the overall approach and any rigorous study. Participation will not be attractive if it induces additional financial burdens on patients; therefore, arrangements will be needed among the other stakeholders to address costs.
2. *Clinicians:* As allies of their patients, and seeking evidence for the treatments they prescribe, clinicians generally are attracted to the idea of N-of-1 trials, if they can be practically and efficiently executed without disrupting the process and economics of patient care.[21] Clinicians also may welcome the opportunity for structured shared decision making and the engagement of the broader care team.[22,23] However, the logistics and economics of the approach must be attractive for adoption in routine clinical practice. This will require easy-to-use processes and platforms to implement N-of-1 studies, and coverage of expenses by healthcare payers and/or sponsors.
3. *Clinical researchers:* Clinical epidemiologists and researchers long have been attracted to type 1 N-of-1 trials in chronic conditions. Besides supporting rigorous trial processes to reveal what treatments work best, when combined, sample size requirements are reduced because participants serve as their own controls. More recently, researchers have used type 2 N-of-1 trials to assess cutting-edge, highly personalized treatments.[13,18] As a potential addition to the drug development and evaluation toolkit, the use of N-of-1 trials highlights the need for standard processes and platforms, such as those used for phases I, II, and III trials, including to meet regulatory requirements to bring a new treatment to the public. This would greatly facilitate the use of these studies by academic and industry researchers. For this structuring of clinical research practices to happen, there will need to be support by the stakeholders who derive economic value from these trials, such as pharmaceutical and biotech companies and contract research organizations.
4. *Medical product developers:* For prevalent and rapidly progressing conditions, and for sponsors seeking regulatory approval for a new drug, conventional phase III randomized parallel group controlled trials are likely to remain more attractive than type 1 N-of-1 trials. Although aggregated N-of-1 trials need fewer participants than traditional parallel group trials, the perception is that N-of-1 trials are more difficult to stage and require more time to execute. In drug development, this could mean more expensive studies and greater opportunity costs from lost time of limited market protection. In addition, for the manufacturer, there may be more incentive for broad sales of a drug based on the average effect seen in a parallel arm trial rather than in a trial that emphasizes the heterogeneity of benefit among different patients. Thus, at this point, N-of-1 trials do not appear likely to supplant extant clinical trial practices. However, there are some specific circumstances where they could potentially be part of drug development. In early drug development for a new molecule being studied for the first time in patients, such as in phase Ib trials, including dose-escalation studies in planning for phase II trials, N-of-1 trials potentially could be useful. N-of-1 trials may also be attractive as part of an overall development program for treatments of chronic conditions when a key objective is to investigate heterogeneity of treatment and/or adverse effects (especially short-term). Also, N-of-1 trials could be considered for a run-in period preceding a traditional parallel group randomized controlled trial in order to identify treatment responders.

For rare and ultrarare diseases, and for precision treatments based on individual patient characteristics and responses, which represent significant market opportunities, type 2 N-of-1 trials could enable collection of the needed data. In these cases, standardized N-of-1 protocols and platforms could be used in geographically diverse sites. When appropriate patients are found, using an N-of-1 protocol, uniform data could be collected and then aggregated to provide cohort evidence for regulatory approval. This could provide a practical way to collect clinical trial data in circumstances in which the usual enrollment of a finite number of study sites would likely be insufficient. A recent example was the testing of a specifically targeted treatment for a rare genetic variant of cystic fibrosis[12] that could not have been studied using a classical prespecified site in a parallel arm clinical trial design.

Widespread adoption of N-of-1 trials of drugs approved for marketing could help inform individual patient-treatment decisions and reduce clinical uncertainty, but also would impact the market for medical product developers. Potentially, the patient population continuing on chronic therapy following an N-of-1 trial, i.e., N-of-1 trial responders, would be smaller. This situation could provide rationale for a higher price because the improved clinical effectiveness at the population level would impact the incremental cost-effectiveness ratio and result in a higher value-based price range. Additionally, cost savings could occur due to avoided adverse events in N-of-1 trial nonresponders who do not progress to chronic therapy. The details of changes to the business model would need to be discussed further among relevant stakeholders.

5. *Healthcare payers:* Although the mission of the overall healthcare system is to provide optimal care and outcomes for patients, once a treatment is available on the market, it falls to payers to cover expenses of N-of-1 trials. Patients, clinicians, and healthcare systems will be unable to sustain such evaluations if they induce additional costs. However, although the conduct of N-of-1 studies will have immediate costs even when standardized study infrastructure exists, potential direct and indirect benefits to payers will need exploration.

Currently, healthcare payers are at the center of disputes among stakeholders over coverage for new treatments. Of many facets of these determinations, one is the strength of evidence (or lack thereof) for benefit of a treatment. Uncontrolled studies may not adequately clarify the decision and could contribute to overtreatment.[19] In this context, even when there is evidence for average group effectiveness, N-of-1 trials could assist insurers if used as a condition for payment for tailored and expensive treatments.[8] For example, three N-of-1 trials carried out in Australia identified optimal treatment for those whose disease management was unclear, while providing cost offsets from reduced usage of nonoptimal drugs as well as reduced medical consultations.[24] Expenses for the N-of-1 assessment could be shared between payers and medical product developers and the assessment itself could be considered by payers as a condition for coverage, similar to coverage with evidence development policies. These stakeholders must agree on an acceptable level of rigor that will not impede N-of-1 uptake or negate its advantages. Despite these challenges to N-of-1 adoption, this approach may be preferable to just paying for the newest and potentially most expensive treatment, or engaging in unproductive disputes about their use and coverage. Additionally, some patients and their providers currently engage in random, unstructured trial-and-error approaches for which payers cover the medical and pharmacy expenses with no clear assessment of overall costs or patient benefits. An N-of-1 strategy could provide a framework for coverage decisions based on individualized evidence rather than on blanket rules. This would be attractive to patients, clinicians, and the public, and could lead to better acceptance of insurers' administrative practices.

6. *Healthcare delivery systems:* Being paid by insurers to undertake type 1 N-of-1 trials, and being paid for the treatments shown to be effective, should encourage healthcare delivery systems to incorporate N-of-1 trials into care. Accountable care organizations should particularly benefit because they could accrue benefits as both the payer and the care provider. Additionally, care delivery systems that are learning health systems should be able to integrate N-of-1 patient-centered generation of evidence into care. Thereby, as individual patients benefit, evidence will be generated to improve care in the healthcare system and to contribute generalizable knowledge.
7. *Regulatory Agencies:* In their role of ensuring efficacy and safety of treatments brought to the public, using the best available science and evidence and established regulatory processes, regulatory agencies' incentives are especially aligned with those of patients. To date, type 1 N-of-1 trials have not been part of the regulatory process. However, as agencies are being pressed to respond to new types of specialized treatments and to calls for the use of real-world evidence, patient-centered effectiveness evidence from N-of-1 trials that address the heterogeneity of treatment and adverse effects should be attractive—especially if there are widely agreed-upon standards. Such standards have been proposed in the CONSORT (Consolidated Standards of Reporting Trials) extension for N-of-1 trials (CENT), but they have not yet been widely accepted and applied.[25,26]

Standards will differ for the testing of treatments for chronic conditions (by type 1 N-of-1 trials) as opposed to a rapidly progressive serious or rare condition for which an experimental treatment is being tested (by type 2 N-of-1 trials), as they will require different guidance for balancing potential benefits and possible risks.[15] As regulatory agencies play a pivotal role in the business model of pharmaceutical manufacturers and set standards for the public, their acceptance of the utility of N-of-1 platforms and services will be critical.

Beyond trials for regulatory approval, type 1 N-of-1 trials may be helpful in phase IV postmarketing studies, which currently are not uniform in execution. Requiring follow-on N-of-1 trials could be part of a registration decision, generating postmarketing data on safety and more specific effectiveness of new agents in real-world subpopulations.

Requirements for adoption of N-of-1 trials

Taken together, given the stakeholders and their roles, what needs to happen to bring the benefits of N-of-1 trials to general use? We believe that it will be crucial to have business arrangements that are realistic and workable for accruing health benefits and financial value in the current healthcare ecosystem. The following actions could promote these goals.

- *Patients, patient advocates, and clinicians* need to clearly articulate the motivating reasons for a patient to participate in an N-of-1 trial. This will require that these and other stakeholders be partners in the development and execution of N-of-1 trials in the determination and delivery of care. They will need to identify the treatments for which uncertainty exists, the outcomes that matter, and the treatments likely to have heterogeneity in effects that would be difficult to predict. They also will need to formulate the standards for evaluating new treatment options, and how equipoise and treatment preferences will be determined and implemented. These will differ for type 1 N-of-1 testing of treatments for chronic conditions vs. for type 2 trials of experimental treatments for rapidly progressive serious or rare conditions, as they will have different benefit–risk considerations. Guidance also will be needed to address, after N-of-1 assessments, what should be the expectations and obligations for treatment of patients. It will be especially important that trial participants' intentions and expectations be understood prior to undertaking the trial. Also, there should be appropriate expectations for trial participants when aggregation of data from multiple patients will be done to generate more generalizable evidence.

- *Clinicians and care providers* must define the needs, standards, and costs for the clinical care required for N-of-1 trials. They also should transparently articulate and agree upon the expectations and obligations when a treatment is supported by N-of-1 results, ideally in broadly accepted guidelines.
- *Researchers, clinicians, payers, regulators, and others* should come to a common understanding of the degree of heterogeneity among patients, clinical conditions, and care processes that would be acceptable in aggregating data from multiple N-of-1 trials as generalized evidence of a treatment's effectiveness. This might include considering when it would be appropriate to aggregate across conditions to assess treatment effects on certain disease mechanisms.
- *Medical product developers* will need to determine the potential benefits to their product development programs, including what kind of treatments, target patients, and care processes are most likely to benefit from N-of-1 trials. It will be important to specify the processes, operational platforms, and software needs for conducting standardized high-quality N-of-1 trials. Additionally, the potential benefits of N-of-1 studies may differ when conducted for regulatory purposes prior to market approval vs. those conducted after market approval. Presumably, as regulators and healthcare payers show openness to using such data and as demand for N-of-1 studies increases, the issues outlined above will be satisfied.
- *Healthcare payers* need to specify the parameters and criteria for paying for the execution of N-of-1 trials and for paying for treatments found to be effective by such assessments. The parameters and criteria will need to be built on a business model that allows patient-specific costs to be absorbed into the larger healthcare system, not putting individual patients at financial risk for treatment determinations of their N-of-1 evaluations. For example, patients currently pay out-of-pocket co-pay/insurance costs for office visits and for each drug tried as part of care, often with escalating co-pays as differing drug tiers are tried, but that is not in an N-of-1 trial. Requirements and standards for evidence (e.g., what constitutes proof) and for heterogeneity of treatment effects for candidate medications will need to be established and agreed upon by all stakeholders.
- *Healthcare delivery systems*, including accountable care organizations and/or learning health systems, will need to understand their particular benefits based on their care delivery roles and payment mechanisms to define how N-of-1 trials can serve their patients and their healthcare objectives. These trials will allow identification of appropriate and personalized care and understanding of treatment effectiveness in the system's care environment.
- *Regulatory agencies* will have to specify the types of evidence and standards as well as the pathways by which N-of-1 trials can suffice for marketing approval.[15] For many drugs, this will be a mapping onto extant development and approval pathways, but for personalized precision treatments, new processes will be needed. These standards for evidence might define when comparators, placebos, or other treatments are, or are not, needed. In all cases, assuming that there will be platforms for executing N-of-1 trials, specification will be required for evidentiary standards, including collection of data from various digital, device-based, and other sources. It also will be important to define when data from the equivalent of phases I, II, and/or III N-of-1 trials could be combined as evidence to support drug efficiency and safety, and when N-of-1 trials might be appropriate for phase IV studies.

Potential benefits of wider use of N-of-1 trials

The incorporation of these (and other) stakeholders' needs, and the creation of guidelines, policies, and requirements for the use of N-of-1 trials, will depend on extensive and coordinated work. Without this, we believe N-of-1 trials will not come into general use. Committed multistakeholder efforts will be necessary to create the ecosystem that would benefit, in measurable ways, from N-of-1 trials. This will require the engagement of all stakeholders and convening multiple meetings, work groups, and writing groups, with extensive iteration. This may well lead to pilot projects, based on local arrangements, national partnerships, and mechanisms such as supported by the Centers for Medicare and Medicaid Innovation Center. We believe that the potential fruits of this work should motivate and reward this effort. Some examples of what might arise include the following:

- For patients with rare and/or life-threatening conditions, and for biotech and pharmaceutical companies, type 2 N-of-1 trials could be used to rigorously demonstrate effectiveness of expensive treatments in a special patient cohort as the basis for full reimbursement. Facilitating this approach could accelerate the development and use of treatments for the many rare and ultrarare conditions that, taken together, constitute a large burden of disease.
- For investigational molecules targeted for disorders for which therapeutic interventions are associated with high placebo response rates (e.g., pain, rheumatoid arthritis, osteoarthritis, depression, and anxiety), patient-specific, type 1 N-of-1 evidence could be very helpful in adjudicating the use of and payment for these treatments. This could simultaneously promote patients getting the best treatment for them and also mitigate the overuse of expensive new therapies that might be presumed to be effective, but in fact do not offer a given patient discernable benefit.
- For certain treatments and cohorts, during conduct of a conventional clinical trial, N-of-1 trials could be run concurrently at some centers in targeted participants with the same disorder, to detect heterogeneity of treatment and/or adverse effects. If the traditional study is negative, but some of the N-of-1 trials are positive, indicating heterogeneous effects among trial participants, this could support further investigation before the company drops the molecule from its portfolio. Thereby, N-of-1 trial results could inform the design of additional randomized clinical trials, which could facilitate the ultimate availability of useful treatments that otherwise would have been dropped.
- Data could be combined across multiple N-of-1 trials. This could facilitate accrual of participants from different sites that use the same N-of-1 protocol, especially for rare conditions, to

generate evidence on larger samples. This also could allow for combined data in diseases in different stages and with different patient types. This could accelerate the drug development pathway and regulatory evaluation of treatments for rare conditions.

- Moreover, using an N-of-1 platform, combined results from a phase Ib trial (first in human patients) and a phase IIa trial (proof of concept) that elucidate the heterogeneity of treatment effects could allow better decision making on further development of potential drugs. This could obviate the need for larger, expensive, ultimately negative phase III studies. Additionally, potentially phase I and II data might be rolled into the phase III participant numbers, which potentially could reduce phase III enrollment recruitments and help speed getting drugs to approval and available to patients. This also could reduce the duration and costs of clinical trials.
- An N-of-1 study could be kept open long-term, enrolling more patients and adding new treatments, still assessing heterogeneity of effects. In the merging of trial phases, such trials could amount to mini-platform trial opportunities. This could more seamlessly develop evidence through scheduled analysis points, without officially stopping and starting. This could be helpful not only to industry, but also to National Institutes of Health (NIH) research under which a single project grant might cover phase I through phase III, perhaps for multiple agents. Again, this should inform, and potentially accelerate, the drug development pathway, to the benefit of the entire healthcare ecosystem.
- In the assessment of treatment comparative effectiveness through N-of-1 trials, estimates of treatment efficacy and effectiveness should be enhanced by using patients as their own controls. Because this reduces heterogeneity for comparisons, it increases statistical power, thus reducing the needed number of study participants.[27] This should advantage the study, be ethically desirable in minimizing the number of needed participants, and be economically attractive.
- For health organizations aspiring to be genuine learning health systems, the incorporation of N-of-1 trials, with the required systems, processes, and platforms, could be an important asset. This capacity would allow collection of patient-centric treatment information, promote shared decision making, facilitate methods to work with payers on coverage for expensive medications, and serve as a signal that the organization is committed to the principles of evidence-based care improvement. This approach could be seen as a "patient-centered learning health system" approach, featuring the commitment to keeping the patient and their optimal treatment in the center of focus of the learning health system.

Areas of potential benefit of N-of-1 trials that deserve exploration

This discussion is directed at advancing the use of N-of-1 trials with the support of, and benefit to, all stakeholders, and in newer and broader applications. The literature describes various N-of-1 trial methods proposed and used over several decades, and outlines the best use cases for N-of-1 trials, methodologic requirements, pitfalls, and advantages and disadvantages over other approaches.[28–30] The insights provided in this literature should be incorporated into plans for N-of-1 platforms. In addition, wider use of N-of-1 trials will require addressing specific methodological issues, some of which are outlined below.

Wide implementation of N-of-1 trials for other than their long-standing use in chronic conditions will require agreed-upon guidance for testing treatments in special circumstances. One circumstance would be for studying highly morbid, chronic conditions with known progression patterns/rates. Another would be for situations with significant drug–drug interactions and/or spillover into subsequent test periods. For example, what should be the testing procedures, and analytic methods, when drug A's disease-modifying benefits may make the subsequent drug B look better than it is, or vice versa, or facilitate adverse events?

Another circumstance that will need guidance will be when there is a rapid progression of a disease with no accepted treatment available and there is an experimental treatment on which data could be collected—a type 2 N-of-1 trial. Extreme examples of this could be for "bespoke therapies" created for a single patient's condition that has no other known sufferers, perhaps of genetic origin. It is conceivable that a platform could be built that develops dozens or hundreds of individualized therapies for monogenic conditions with single-patient prevalence. A recent example was for an approved backbone drug technology, the splice-modulating antisense oligonucleotide milasen, that could be rapidly customized to create a chronic therapy.[13] Adeno-associated virus and/or CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats–associated protein 9) might provide future examples for curative approaches. In such bespoke cases, the issues are very different from traditional type 1 N-of-1 trials, including understanding the safety of "industrial scale" bespoke processes. The first step for this will be defining the best methods for such investigations, including when crossover back to an alternative or no treatment would be appropriate.

Even with the more conventional (type 1) N-of-1 trials, when integrated into learning health systems, methodologic and logistic challenges will arise. Scalable methods, processes, and metrics will be needed to create the conditions in which patients, clinicians, and systems learn to optimize care. Understanding will need to grow about what technical and methodological approaches will be most helpful. For example, a Bayesian approach could facilitate incorporation of external information from other patients and from routine sources, such as electronic health records,[31] or expanding sources, such as devices or apps.

Besides clinical and organizational objectives, understanding what approaches best improve patient and clinician engagement and satisfaction will be important. Additionally, for utility and acceptance, it will be critical to have simple, easy-to-use systems that return interpretable scientifically valid results and that enable patients to track their outcomes. Experience to date has shown that such features are of great value to patients and enable them to become involved in, and act as partners in, their own care.[20]

A strength of N-of-1 trials has been their ability to focus on patient experience, often via patient-reported outcome measures,

which can promote patient-centered care if properly implemented. However, biomarkers meaningfully linked to a patient outcome are also important. In type 2 trials for rare conditions, as described above, and in conventional type 1 N-of-1 trials, biomarkers could be the primary outcome for certain diseases (e.g., evidence of a molecular effect), and could be secondary for others (e.g., pulmonary function testing in lung disease). They could range from the very common to the exotic. They also could allow for N-of-1 trials that could quickly identify patients most likely to have a positive clinical response. For example, if drug A lowers finger-stick glucose measurements averaged over a series of 5-day periods more than does drug B, the entire study could be quite short. Similarly, markers of molecular impact such as with the cystic fibrosis N-of-1 trial, or in bespoke N-of-1 trials, could serve analogous purposes.[12,32] The main criteria would be that: (i) the biomarker responds relatively quickly to therapy whereas the clinical outcome (e.g., a patient-reported outcome measure) responds slowly, which would ordinarily remove the condition from consideration for N-of-1 trials, and (ii) the biomarker is strongly linked to the outcome.

It should be added to the above that the N-of-1 approach only will work if there is authentic patient engagement. Since the Prescription Drug User-Fee Act IV passed in 2007, there has been an enhanced focus on patient input in benefit–risk determinations. The emphasis on patient input in medical product development, and in drug research and development, has only grown with Prescription Drug User-Fee Act V and VI. This means that the FDA and companies now have an expectation patients will be engaged in research and development in various ways, especially in clinical trial design and outcome–end point selection. It is likely the expectation would be the same for N-of-1 trials. Moreover, to be successful, patients will need to become N-of-1 research collaborators and beneficiaries, not just trial participants. Thus, practices and capacity are needed for N-of-1 researchers to incorporate patient input into their studies. This will include how to work with patients as partners to get their input and to use existing patient experience data in research decision making to translate patient input into study designs, including trial end-point selection. Patient partners (and patient organizations) can provide input on how to inform patients about N-of-1 studies and the advantages they might offer patients, to encourage willingness to enroll. Patient-focused drug development is still a nascent field for the most common trial designs; this approach will need to be reflected in N-of-1 trials.

Conclusion and Next Steps

The accumulated evidence over decades suggests that N-of-1 trials are useful for assessing treatment effectiveness in chronic conditions in a patient-centered way, and now there are also new purposes to which they could be applied. Moreover, advances in information technology in care systems (e.g., integrated electronic health records and data warehouses) and in individual patient devices (e.g., wearable devices and smart phones) have created wider opportunities for data collection for N-of-1 trials. However, many steps remain to bring N-of-1 trials into general use and to provide benefit to patients and the healthcare enterprise. We believe that this will not happen until processes, platforms, methods, and standards are developed, and value-based arrangements are made among the stakeholders. The list of potential implementations above provide examples of important benefits, and should motivate advancing this approach.

The authors of this report represent a wide range of stakeholders and N-of-1 methodologists; however, this article aims only to raise these issues so that they can be addressed. We recommend discussion among all stakeholders directed at the issues raised here, and of the many other questions that will arise as this work progresses. This will require multistakeholder meetings, workshops, and consortia, leading to recommendations, practices, and policies that would promote the wider availability and value of N-of-1 trials. It also will require individual and collaborative innovations and experiments, for example, among health systems and payers. Successful approaches will need to provide benefit in patient outcomes and also to each stakeholder group. As outlined in this paper, there are clear opportunities for this. We believe that the creation of the generalizable infrastructure, processes, practices, and policies for N-of-1 trials will provide unique and important benefits to the healthcare ecosystem, and that this work will be rewarded.

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CONFLICT OF INTEREST

W.H.D. is a former employee at, and shareholder of, Eli Lilly and Amgen. He is on the board of directors of Radius Health, Biomarin, Seres Therapeutics, and Mersana. C.R. is an employee of Bayer. M.T. reports other income from Co-Bio Consulting LLC. N.E.M. works for Boehringer-Ingelheim Pharmaceuticals, Inc. and owns stock in Merck and Pfizer. All other authors declared no competing interests for this work. As an Associate Editor for *Clinical Pharmacology and Therapeutics*, Peter K. Honig was not involved in the review or decision process for this paper.

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