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# Marketing therapeutic precision: Potential facilitators and barriers to adoption of n-of-1 trials

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ABSTRACT

*Background:* N-of-1 trials may enhance therapeutic precision by predicting the long-term effectiveness of medical treatment on an individual basis. However, the n-of-1 approach has gained little traction with the clinical community. To learn why, we interviewed physicians and patients, focusing on the perceived benefits and drawbacks of n-of-1 trials and factors influencing these perceptions.
*Methods:* We convened focus groups and individual interviews with 21 physicians and 32 patients, most with chronic conditions. The study employed qualitative interview methods to explore and analyze subjects' views of n-of-1 trials. Analysis involved an iterative process of review and data abstraction after specific topics for coding, definitions of codes, and strategies for abstraction had been established. Previously defined domains and topics were then expanded and enriched, with key themes emerging during the analytic process.
*Results:* Physicians and patients remarked on 4 salient aspects of n-of-1 trials: scientific, relational, clinical, and logistical. Neither physicians nor patients were highly familiar with the n-of-1 concept, but both groups readily grasped the fundamental logic and appreciated the potential scientific benefits. Physicians saw n-of-1 trials as promoting an exciting but possibly threatening paradigm shift in the doctor–patient relationship, while patients viewed the relational consequences as modest. The best n-of-1 candidates were felt to be proactive, cognitively intact, reliable, motivated, and engaged in a trusting physician–patient relationship.
*Conclusions:* Researchers interested in expanding the appeal of n-of-1 trials will need to address these concerns by carefully explaining the approach, emphasizing the benefits, and minimizing the effort required of doctors and patients.



N-of-1 trials are single-subject trials of treatment effectiveness and safety [1–5]. In a prototypical n-of-1 trial, the patient and physician together identify a clinical question (e.g., "which treatment relieves my back pain more effectively and with fewer side effects?"). Most often the trial is suggested by the physician, agreed to by the patient, and conducted by an n-of-1 trial "service," generally run by a pharmacist [4–6]. The patient then receives treatments A and B in a blinded fashion and random sequence. Outcomes are assiduously recorded. At

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the end of the trial, treatment is unblinded and the results examined clinically and statistically. Over the past two decades, several hundred such trials have been completed (Bloser N. Personal communication. April 1, 2009).

Under selected circumstances, such trials reside at the pinnacle of the "evidence hierarchy" [7] and are the optimum design for establishing the best long-term treatment in an individual patient. By comparing outcomes in the same patient over time, n-of-1 trials can identify therapies that contribute little to the patient's welfare and can safely be discontinued. Conversely, they may reveal dramatic individual benefit despite modest average effects. In an era of rapidly rising pharmaceutical costs, n-of-1 trials can be used to deploy expensive chronic therapies in a cost-effective manner by identifying patients most likely to benefit over the long term [8]. More generally, n-of-1 trials promote therapeutic precision, increasing the likelihood that individual patients will receive the treatment that is best for them.

N-of-1 trials are distinct from parallel group and factorial randomized controlled trials (hereafter referred to as RCTs). However, like RCTs, n-of-1 trials are systematically administered, can be blinded, and produce valid and reliable evidence regarding treatment for an individual patient. N-of-1 trials are complementary to RCTs, which provide evidence aggregated across a large group of patients to produce generalizable knowledge about a treatment. Such evidence is valuable, but RCT samples come from patients likely to differ in critical ways from patients seen in practice.

N-of-1 trials have two broad applications. Most directly, they can support evidence-based therapy for the individual patient. In several published series, n-of-1 trials have led to changes in therapy, cessation of therapy, or confirmation of the original treatment [2,4,5,9–14]. A second application is to develop estimates of the effectiveness and safety of treatment in clinically, geographically, and culturally distinct populations [15–17].

N-of-1 trials were enthusiastically adopted at several academic centers during the early 1990s [4,5] but soon were on the wane. Some insiders have speculated that physicians and patients concluded "it wasn't worth the trouble."[16] Others believe that potential participants may not comprehend what n-of-1 trials can offer.

To explore the acceptability and feasibility of n-of-1 trials in the context of modern practice, we interviewed groups of physicians practicing adult primary care (general internal medicine and family medicine), pediatrics, and one selected subspecialty (rheumatology). We also conducted focus groups with patients and members of the public. The main purpose was to identify potential facilitators and barriers to participation in n-of-1 trials that might be addressed through design modification and/or targeted marketing. Specifically, we sought to address 3 research questions. First, what do physicians and patients see as potentially appealing or beneficial about n-of-1 trials? Second, what do they see as the risks, costs, and barriers? Third, what clinical, social, and contextual factors do clinicians and patients consider most salient in assessing the potential appeal of n-of-1 trials?

## 1. Methods

Our study was approved by the UC Davis and UCLA Institutional Review Boards. The study employed qualitative interview methods to explore and analyze subjects' views of the clinical research enterprise and n-of-1 trials. We recruited purposeful, non-random samples of physicians and patients, aiming to maximize diversity in terms of attitudes about and experience with clinical trials. Pre-established domains of inquiry and topics were used to systematically ask parallel (and in many cases identical) questions and probes of each group. Individual and group interviews with physicians, and focus groups with patients, involved carefully guided and structured conversations, in which the context encouraged expression of the beliefs and opinions of the informants, on comparably-elicited domains and topics. Analysis involved an iterative process of review and data abstraction after specific topics for coding, definitions of codes, and strategies for abstraction had been established. Previously defined domains and topics were then expanded and enriched, with key themes and subthemes emerging during the analytic process.

### *1.1. Sampling of physicians*

Primary care physicians (general internists, family physicians, and pediatricians) and rheumatologists in two California metropolitan areas were recruited to participate in a individual or group interview on the topic of n-of-1 clinical trials. We selected these specialties because they care for a large proportion of conditions that are potentially amenable to n-of-1 trials. A convenience sample of physicians was recruited by electronic mail and word-of-mouth through the Sacramento Sierra Medical Society, Kaiser Permanente, Sutter Health System, UC Davis Health System, and UCLA Medical Center. Personalized introductory emails and letters were sent to 82 physicians describing the project and soliciting their participation in a 60–90-minute focus group or individual interview. A $150 gift card was offered as compensation for their time commitment and expertise.

Forty-four physicians responded with an interest in participating. Group or individual interviews were scheduled based on the availability of physicians and were conducted by telephone conference call. Twenty-one physicians consented to and participated in either a group or individual interview by telephone. Physician groups brought together physicians from similar practices (family and internal medicine, pediatrics, or rheumatology). The sample represents physicians with some interest in this topic and, although of course a volunteer/convenience sample, the comments represented a wide range of opinions and experiences on the topic. Following the interview, participants received a brief questionnaire with exit questions pertaining to demographic and work-related characteristics.

### *1.2. Patient sampling*

Adult patients and parents of children diagnosed with a chronic condition were recruited through flyers posted in participating Sacramento area physicians' offices and universities, local Senior Centers, area websites (Craig's List), and print advertisements in the University of California, Davis school paper. Those who expressed an interest were screened into the study if they were 18 years of age or older, able to speak English, and had been diagnosed with and/or in treatment for one or more chronic medical conditions.

Chronic conditions included but were not limited to heart disease, arthritis, neurological or seizure disorders, cancer, allergies, depression or anxiety, high blood pressure, irritable bowel syndrome, asthma, attention-deficit hyperactivity disorder (ADHD), and fibromyalgia. These conditions have been identified in prior studies as potentially amenable to n-of-1 trials [16]. A $75 gift card was offered as compensation for participation in a 60 to 90-minute focus group discussion.

A total of 32 patients consented and participated in these focus group discussions. Eligible participants were assigned to one of three focus group discussions stratified by age: 18–35 years, 36–60 years, and over 60 years. The demographic characteristics of group participants are reported in Table 1.

### 1.3. Guiding questions and conduct of interviews

Physician and patient focus group interviews were moderated by one of the lead investigators and a research associate; individual physician interviews were conducted by the lead author or a trained research associate. Interviewers all followed a script with guiding questions and specific vignettes (Appendix A). Physicians were prompted to discuss their involvement in clinical trials, perceptions of the differences between parallel group clinical trials and the n-of-1 technique, and views concerning the feasibility of n-of-1 trials, including barriers to physician and patient participation. Patients provided their experiences with clinical trial involvement, perceptions of what it might be like to participate in an n-of-1 trial, including reasons for participation, and views concerning the benefits and potential drawbacks of the n-of-1 method. All focus group and individual interviews were audio-recorded and transcribed verbatim for analysis.

### 1.4. Data analysis

Electronic transcripts were reviewed for accuracy and up loaded to an on-line qualitative data analysis software program [18]. After reviewing the interview transcripts, three of the authors established coding categories and definitions consistent with the guiding questions used for interviews [19]. Three of the focus groups were systematically coded using the established categories to ensure the adequacy of the coding framework and code definitions. The team met to review the coded data, and two additional authors assisted with the task of coding the physician interviews. The coding team found convergence of themes around n-of-1 topics across focus group participants, making segmentation of groups less necessary for this exploratory research stage.

A line-by-line review of the transcripts was conducted and data were sorted into one of 4 categories: need to know to participate (including conditions and risks of participation); benefit of involvement (including outcomes for practices and patients); best patients to participate; impact on practice (positive and negative). The data were reviewed by the two lead authors, and the lead author extracted quotations representing key subthemes within each coding category. Subthemes and exemplar quotations were examined and discussed by the entire team before the analysis was completed. There were no disagreements from the team regarding the prevalent subcategories within each of the coding categories, hence no need to resolve substantial coding differences. Key subthemes and categories that emerged from the inductive process are described below. Comparisons across groups of physicians and patients and within patient groups highlighted similarities and differences in understanding of potential facilitators and barriers to participation in n-of-1 trials.

## 2. Results

### 2.1. Participant characteristics

Twenty-one physician participants took part in one of three group interviews ($n=10$) or an individual interview

**Table 1**
Characteristics of physician and patients.

| Characteristic | Physicians ($n=21$) | All patients ($n=32$) | Younger group ($n=11$) | Middle-aged group ($n=11$) | Older group ($n=10$) |
|---|---|---|---|---|---|
| Age, mean years (range) | 43 (32 to 62) | 48 (18 to 88) | 25 (18 to 43) | 47 (38 to 57) | 79 (68 to 88) |
| Female, % ($n$) | 67 (14) | 78 (25) | 82 (9) | 73 (8) | 80 (8) |
| Non-white, % ($n$) | 38 (8) [1] | 28 (9) | 45 (5) | 36 (4) | 0 (0) |
| Prior participation in clinical research, % ($n$) | 43 (9) | 31 (10) | 18 (2) | 45 (5) | 30 (3) |
| Two or more chronic conditions, % ($n$) | – | 81 (26) | 63 (7) | 91 (10) | 90 (9) |
| Medical specialty, % ($n$) | | | | | |
| Internal medicine | 43 (9) | – | – | – | – |
| Family medicine | 24 (5) | | | | |
| Rheumatology | 19 (4) | | | | |
| Pediatrics | 14 (3) | | | | |
| Clinical setting, % ($n$) | | | | | |
| Solo/small group | 9 (2) | – | – | – | – |
| Medium/large group | 24 (5) | | | | |
| HMO or VA | 24 (5) | | | | |
| Academic medical center | 43 (9) | | | | |
| Half days per week spent with patients, % ($n$) | | | | | |
| 0–4 | 38 (8) | – | – | – | – |
| 5–8 | 48 (10) | | | | |
| >8 | 14 (3) | | | | |

[1] 4 physicians declined to state their race ethnicity and were counted as “white/caucasian”.

($n=11$). Group interviews involved 3–4 physicians and were held by teleconferencing. The 21 physician participants included 14 women and 7 men; 8 were non-white. The average age was 43. About half were general internists; 43% practiced within an academic medical center. Most reported spending at least 4 half-days per week in clinic (Table 1). Thirty-two patients participated in one of three focus groups that each included 10–11 patients; approximately 10% ($n=3$) of the participants reported being a parent or decision-maker for a chronically ill patient. The 32 patients (25 women, 7 men) averaged 48 years of age; about a fourth were non-white (Table 1). The most common chronic conditions reported were allergies ($n=14$), hypertension ($n=9$), depression ($n=9$), and arthritis ($n=8$) (data not shown in table).

### 2.2. Perceived benefits of n-of-1 trials

#### 2.2.1. Physicians' perspectives

While few physicians were familiar with the concept of n-of-1 trials, most quickly grasped the approach once it was explained by the interviewer. Doctors identified two categories of putative benefit: *scientific* and *relational*. From the scientific perspective, several participants noted the ability of n-of-1 trials to enhance therapeutic precision. As summarized by a 41-year-old male community-based family physician, *I think it would very quickly and efficiently let you try medications or doses of medications to identify their efficacy. And I think the benefit is you would probably not use a lot of meds that you think are working and really don't work.* [Excerpt 8540] This idea found further resonance with a 32-year-old female internist: *I think it puts a little bit of structure to the idea of…'why don't we try this medicine and see how it goes*.' [Excerpt 8291]

Other physicians emphasized the potential of n-of-1 trials to enhance communication and thereby support shared decision making in the context of a more secure physician–patient relationship. As a middle aged Veterans Affairs-based male internist explained, *I also think that it would increase their communication…where you're actually talking about what you're thinking, what interventions you're going to be doing, why you're doing them. I think it would make you as a practitioner explain things more thoroughly*. [Excerpt 6785] Recognizing that n-of-1 trials require much more explicit disclosure about the benefits, risks and alternatives related to the therapies at hand, this physician suggests that such trials could support shared decision making to a degree not usually encountered in practice. The same physician also expressed enthusiasm for the ability to custom design n-of-1 trials with input from the patient regarding the therapies to be compared, outcomes to measure, and rules for stopping the trial. In this sense, n-of-1 trials offer patients an opportunity for greater autonomy and control than is afforded in ordinary practice, let alone in parallel group randomized trials. As he explained, *This is a way we can give patients more control over their own care….the idea of how you empower your patient to make changes.* [Excerpt 8302]

Another effect of doctor and patient jointly designing and carrying out an n-of-1 trail is to make clinical uncertainty explicit. While inherent in the clinical enterprise [20], uncertainty is infrequently acknowledged by either physicians or patients. The failure of physicians and patients to grapple with and accept uncertainty may contribute to an unhealthy aggrandizement of the physician's capabilities. N-of-1 trials, suggests this family physician, could be a corrective:

> *I think it would impact the doctor-patient relationship. I think in some ways that would be very good….humbling the physicians because this would let your realize that your perception often [departs from] reality. And I think patients wouldn't put physicians on a pedestal with this approach as well. It's an acceptance of your own ignorance and your own lack of understanding, which is the right direction to go.* [Excerpt 8566]

While the quotations above illustrate the tendency of physician participants to reflect separately on the scientific and relational aspects of n-of-1 trials, the two themes sometimes intertwined. For example, several physicians referred to the way patients and physicians can unintentionally be misled by random fluctuations in clinical status. In this context, notes a 53-year-old male family physician, n-of-1 trials represent a potential counterforce to cognitive bias, equipping the physician with concrete, personalized and credible information with which to counsel the patient.

> *I think that would reinforce something that can otherwise be swayed by variations that don't really have much long-term meaning. For example, patients can be coming in to see me during what happens to be a bad week for their arthritis, and that might sway me to change their treatment away from something that actually was better than what they had used before. You know, there'd be a bias introduced by something that would just be a temporary fluctuation.* [Excerpt 8312]

#### 2.2.2. Patients' perspectives

Like physicians, many patients recognized the *scientific* benefits of n-of-1 trials. Most readily grasped the logic of the method and appreciated the rigor and personalization of the approach. In discussing the potential value-added, one middle-aged woman echoed themes heard from physicians: *I like this idea,* she said. *I think it's very logical much more so because…the baseline's the same [being derived from the same patient] as opposed to [a comparison of outcomes between] groups.*[Excerpt 8855] Another middle-aged female underscored the appeal of having an internal control: *I think the difference is you take the two different things yourself and you don't have to compare yourself to somebody else who's taking A and you're taking B. You're taking A and B, so you can tell.* [Excerpt 8998] Others, like this young man, valued the ability of n-of-1 trials to yield information that is uniquely, personally applicable:

> *….the results of the study, between you and your doctor, will show which one's better for you, personally, rather than which one's better for this group.…Tylenol helps 90% of the people, but it doesn't do you any good to go to your doctor and get Tylenol, if it's not going to help. In this case at least, you'll know specifically if it happens for you….* [Excerpt 8998–9]

In contrast, patients' appreciation for the *relational* benefits of n-of-1 trials was more guarded. Whereas physicians saw n-of-1 trials as potential "game changers," knocking physicians off their pedestals and encouraging greater physician–patient partnership, patients tended to emphasize the utilitarian benefits of more frequent visits, more rigorous recording of outcomes, and more careful monitoring. As one older woman put it, *In these n-of-1 trials, you get more attention and pay more attention to your side effects.* [Excerpt 9119] A related benefit, notes this middle-aged man, is that patients might adhere more rigorously to their physician's advice: *I could see n-of-1 for some people that they'd know that [they're] more accountable to somebody.* [Excerpt 8890] In other words, n-of-1 trials create a nexus of reciprocal obligation. Patients take on the burden of record keeping and other forms of self-monitoring, receiving in return more careful clinical scrutiny than would be expected under usual care.

In evaluating the scientific and relational benefits of n-of-1 trials, patients usually took clinical care as the reference point. However, some directly contrasted n-of-1 trials with other forms of clinical research, especially parallel group randomized trials. For these patients, the most salient distinction was that n-of-1 trials are less likely to involve placebo comparisons. As expressed by a middle aged man, *People are getting relief one way or the other.* [Excerpt 8856] A young woman similarly emphasized avoidance of placebo as a major attractant.

> *I'm kind of leery about the whole placebo versus taking the actual medication. This way [with an n-of-1 trial], if you have something that's working already, then you can try something better. You don't have to completely stop the other thing.* [Excerpt 9002]

In summary, while neither physicians nor patients were very familiar with the n-of-1 concept, both groups readily grasped the fundamental logic and appreciated the potential *scientific* benefits. Physicians saw n-of-1 trials as an exciting but potentially threatening paradigm shift in the doctor–patient relationship, while patients viewed the relational consequences as relatively modest. Patients appreciated the increased attention and liked the idea that they could participate in research while maintaining active treatment.

### *2.3. Potential risks, costs and barriers associated with n-of-1 trials*

#### *2.3.1. Physician perspectives*

Just as some physicians appreciated the scientific and relational benefits of n-of-1 trials, others, evaluating the same dimensions, voiced concerns. *Scientific concerns,* which were especially prominent among academics, centered on statistical power, standardization, and generalizability. For example, one seasoned, university-based, female rheumatologist complained:

> *It raises the question in my mind of the old, you know, statistical significance. You're dealing on a one-to-one basis, and so this works good in this one person…just as glucosamine really helps some patients and doesn't help others. So the fact that it helps your patient, where does that get you to?* (Excerpt 8493]

Similarly, an academic general internist asserted: *it would make sense to have a large number of people and to be able to get different ethnicities and subgroups*, [Excerpt 8657] belying a different assumption — that n-of-1 trials serve in the main to shape inferences about treatment in populations and subpopulations rather than guide care in an individual patient. (In fact they may do both.) Another rheumatologist (middle-aged male) characterized the individualization of outcome measures that many regard as a strength of the method as, instead, a potentially fatal flaw.

> *How do you gather the data at the end? We had to have [statistical] significance….Because we currently [use] standardized protocols, you know, [and this] has some [validity] based on a good amount of evidence….So, the things that you are telling, I will not go for that, rather the things which are existing now [are] more rational to me.* [Excerpt 8451]

From the *relational* perspective, two physicians suggested that by making therapeutic uncertainty explicit, n-of-1 trials represent a departure from usual clinical practice. This shift in the cultural paradigm may not be comfortable for physicians or patients.

> *You're asking them to [take] for the pain, you know, four pills a day. Sometimes they're placebo, sometimes they're meds, a patch a day, two weeks on each one. Six weeks later we unravel all that and review it, discuss it, and say that this it the best one. I mean that's something that's very different culturally for patients. That's not their expectation.* [Excerpt 8557; male internist]

> *It seems like it takes away the doctor's doctoring so that the doctor becomes this scientist. You come to see your doctor because you want their opinion, and [instead] the doctor's response is: 'Well, I don't really know. Let's try these two things. I don't know which one you're going to get but let's give it a go.' So I don't know how patients would respond to that.* [Excerpt 8418; female internist]

Both quotes emphasize the impact of "culture shock" on the patient, but the second also highlights how n-of-1 trials could bring about a tectonic shift in the *physician's* role — from wise dispenser of medical opinion to scientific consultant who helps the patient–client design their own experiment. While in a sense this new role is a natural extension of shared decision making, for this physician it is far more radical than that: an abandonment of the "doctor's doctoring" — a fundamental aspect of what it means to be a physician.

Beyond these scientific and relational issues, physicians also expressed a number of *clinical* and *logistical* concerns. From the *clinical* perspective, several physicians raised questions about the safety of the n-of-1 approach. As one female internist noted, *There's a lot of difficulties in taking people on and off medications, and switching. There are often particular side effects that you got to watch out for.* [Excerpt 8660] A community based family physician (male) emphasized the medicolegal implications of following a research protocol rather than relying on clinical judgment.

*I think you need to be careful about doing things that are outside of the standard practice from a legal perspective. You know, if something would happen on week three of an n-of-1 trial, you know, a trial that has four different phases to it, you got to be able to comfortably support a safe approach to patient care.* [Excerpt 8542]

A female pediatrician, practicing in the community, was more concerned with clinical relevance than safety. *If we're talking about medicines where there's one that's clearly beneficial, but it's not covered by their insurance, and now I'm taking them through this trial and they can't have it anyhow because it's not covered by their insurance, that could be a problem.* [Excerpt 9478] This physician identifies a real-world issue: the results of the n-of-1 trial could be moot unless insurers offer some flexibility on coverage (or, as we consider later, are involved in the sponsorship of such trials). It does no good to identify best therapy for the individual and then tell that person, "you can't have it."

While many physicians were vaguely troubled by scientific, relational, and clinical issues, some were frankly alarmed by *logistical* concerns, particularly time demands. A male community internist said, *Well, I personally would be interested in that, but I think one of the biggest limitations…is time and time constraints.* [Excerpt 8528] A female family physician inferred that n-of-1 trials require effort both cross-sectionally (during a single visit) and longitudinally (across an episode of care): *For me one of the big things is, you know, how much sort of administrative time it takes in addition to the actual work with the patient.* [Excerpt 8486]

In addition to recognizing demands on their own time, several physicians wondered whether their patients would have the desire to participate in n-of-1 trials and the tenacity to complete them. One academic internist compared the requirements of n-of-1 trials with the daily battle to get patients involved in self-management of chronic diseases like diabetes: *They've got to keep daily blood sugar logs and do other things. We can't get most of our patients to do that anyway.* [Excerpt 8655] Another internist whose practice includes large numbers of academics and health care workers, expressed skepticism that her patients would be willing to slow down enough to collect the systematic data n-of-1 trials demand: *A lot of my patients are busy professionals; they wouldn't want to [expend] extra time to do stuff like that.* [Excerpt 8500]

*2.3.2. Patient perspectives*

In terms of broad themes, patients' concerns about n-of-1 trials interlocked neatly with those expressed by physicians; however, the specific content differed. Patients' *scientific* concerns were wide-ranging, extending from skepticism about the validity of short-term cross-over studies (*A lot of medications will take longer than two weeks to see if it works because a lot of times doctors have to tweak your medications to see how many milligrams you need and if it's reacting with something else.* [Excerpt 8853; middle aged female]) to cynical resignation about the practice of medicine (*It sounds like [n-of-1 trials are] the way we go to the doctor now….If it doesn't work, come back and we'll give you something else….They never figure it out. Let's practice until they get it right.* [Excerpt 8902; middle aged male]). Like some of her physician counterparts, a middle-aged woman seemed confused about the purpose of n-of-1 trials and found them wanting in comparison to larger, parallel group studies: *And so I don't know how accurate it would be if you did the n-of-1 versus the group…or how many more people you would have involved in this.* [Excerpt 8858] In contrast, an older woman wondered whether physicians might be overly influenced by results of n-of-1 trials within their own practices: *I would not want results to ride from my experience, to be generalized falsely or inappropriately.* [Excerpt 9099] These contrasting concerns collide in paradox, as it seems unlikely that the same method could lead to both under-generalization (from lack of power) and over-generalization (from undue influence). Of course, there is no real contradiction: the quality of the evidence base that concerns the first patient has no bearing on the cognitive bias that concerns the second.

Patients' *relational* concerns centered on trust. Ideally, said a female participant in the middle-aged focus group, the physician administering the n-of-1 trial should have a continuing relationship with the patient: *So in order to do something like this, you'd have to be seeing the same person each time….* [Excerpt 8871] A man in the same focus group countered that the key element is knowledge of the patient's history, potentially obtainable from medical records: *The person that comes in is…going to know my history before they walk in, my particular history if I'm gonna do an n-of-1. That's the main thing to me.* [Excerpt 8897]

As conceived by researchers, n-of-1 trials are designed to improve therapeutic precision for the individual patient and would not necessarily garner pharmaceutical industry sponsorship, since there would not typically be any generalizable results. Nonetheless, several patients focused on clinician's motives and the role of the pharmaceutical industry. One young man took special exception to the notion that pharmaceutical companies could accrue benefits from n-of-1 data yet might not reimburse patients, on the pretense that n-of-1 is part of clinical care. *It seems that the cost is being dumped on the consumer for studies. Oh, we're going to do free studies now [just] because they (the physicians) agreed to do it?* [Excerpt 9022]

Patients from two different focus groups raised concerns about potential conflicts of interest. They seem to assume, without much justification, that pharmaceutical manufacturers would play a major role in promoting, funding and administering n-of-1 trials.

*I would want to make sure that this doctor was concerned about me and not just money he was getting paid from a medical company, you know, to be participating in this.* [Excerpt 8874; female, middle-aged focus group]

*I would be very concerned whether what kind of benefits my doctor's getting from the company….I've had doctors push different drugs on me because they're getting kickbacks and stuff. So I'd have to know that this doctor didn't benefit financially in any way, you know, in order to want to participate.* [Excerpt 8994; female, younger focus group]

In point of fact, insurers, managed care organizations, and other payers might have a much greater stake in n-of-1 trials than manufacturers; although we did not specifically probe,

patients raised no misgivings on the payer side. When asked in broad terms about the factors that might dissuade them from participating in an n-of-1 trial, patients were also largely silent about an issue that seemed especially troubling to doctors: the notion that such trials might make therapeutic uncertainty more explicit and disrupt the traditional doctor–patient relationship.

Patients' *clinical* concerns showed remarkable congruence with themes sounded by doctors, with a heavy emphasis on safety. Questions about potential hazards of the n-of-1 approach were posed by patients in all three focus groups. One participant in the middle-aged group balked at the cross-over design, which could promote adverse drug interactions: *That could be scary because you're mixing two different types of medications that are both experimental, so there could be even more side effects when you're going back and forth and switching them.* [Excerpt 8868] In contrast, members of the older patient focus group worried about the consequences of receiving suboptimal treatment for an extended period of time, whether a result of taking placebo, taking the less effective therapy, or taking nothing during a washout period. As one woman put it, *I wouldn't want to be taking one that didn't work for very long, because the risk of stroke is too high.* [Excerpt 9066] Another added, *You would have to be sure that your system could tolerate a wash out period.* [Excerpt 9078]

Finally, one man in the younger-aged focus group wondered about the adequacy of standards to ensure safe preparation of active and placebo capsules for use in n-of-1 trials: *I mean if there's some guy who's having to make special drugs for huge groups of people in these n-of-1 trials, it just sounds like more room for error this way — way more.* [Excerpt 9014]

Like physicians, patients had their own *logistical* concerns about how n-of-1 trials would fit into modern clinical care. Two patients from the middle-aged focus group worried that doctors are too busy: *They've got tons of patients.* [Excerpt 8895, male] *They don't have the time.* [Excerpt 8893; female] Another woman from the same focus group commented: *I would think it would be much more costly.* [Excerpt 8865]. A woman in the younger patient focus group questioned patients' tolerance for prolonged crossover trials: *…at some point, you're going to be like, 'I think I already know which one I'm better [on], and I don't want to go through eight months.* [Excerpt 8997] As one middle-aged woman summarized, organizers of n-of-1 trials need to keep it simple: *You're going to have to make it really easy for them.* [Excerpt 8895]

### 2.4. Clinical, social, and contextual influences

Although we identified a few unabashed n-of-1 enthusiasts among physicians and patients, most participants were circumspect, carefully detailing conditions under which they would (or would not) be likely to participate. These contingencies fell into three broad categories related to the medical condition, the patient, and the trial. While both physicians and patients suggested specific conditions that might be especially well-suited for n-of-1 trials (with substantial agreement on chronically painful conditions), physicians also offered some general principles (Table 2). Physicians and patients were remarkably congruent in their assessment of patient characteristics making for the best n-of-1 trial candidates: proactive, cognitively intact, reliable, and motivated to experiment by dint of poor results with standard treatment. Both also noted the importance of a trusting physician–patient relationship (Table 2). When discussing trial characteristics they would find attractive, physicians emphasized the importance of minimizing

**Table 2**
Clinical, social, and contextual influences favoring adoption.

| Theme/subtheme | Heard from physicians | Heard from patients |
|---|---|---|
| Medical conditions | | |
| General characteristics | Easily monitored; unresponsive to standard therapy; relatively quick response to treatment | [No pertinent material] |
| Specific conditions | Hypertension, high cholesterol, depression, fibromyalgia, chronic pain, diabetes | Allergies, chronic pain, neuropathy |
| Patient characteristics | | |
| Attitudes | Motivated to take active role in care; interested and inquisitive; responsible; serenely persistent (not searching for "quick fix"); open to novelty (not put off by prospect of being a "guinea pig") | Proactive; diligent and responsible (e.g., "able to take medication on time and the way you're supposed to"); optimistic; open to experimentation |
| Knowledge, skills, and resources | Medically sophisticated; articulate; able to follow-up (including transportation); no language barriers | Know own body; no memory problems; accurate observer and reporter |
| Clinical situation | Frustrated with usual care ("willing to try pretty much anything"); struggling to keep condition under control; sensitive to or anxious about medication side effects: | "Searching" for relief; serious condition requiring frequent physician visits (to facilitate monitoring) |
| Relationship with physician | Established relationship, leading to "comfort and confidence" | Comfortable with doctor; trusting of the health care system |
| Trial characteristics | | |
| Treatment under study | [No pertinent material] | Solid track record in parallel group and other n-of-1 studies |
| Demands on time | Follow-up frequency reasonable (not much beyond what is necessary for good clinical care); rationale that is quick and easy to explain to patients; minimal paperwork | Short term trials (days to a few weeks) preferable to longer ones |
| Adequacy of support | Ample guidance on trial design and measures; pharmacist to prepare active drug and placebo, if necessary; clinical research assistance to collect and monitor outcomes data; protected time and/or other forms of financial support | Access to personal outcomes data, particular laboratory results; financial reimbursement |

demands on their time and maximizing logistical support, whereas patients mentioned the treatment's prior track record, the need to keep trials short, and the desirability of financial reimbursement (Table 2).

## 3. Discussion

Though widely touted as a rigorous approach to individualization of therapy, n-of-1 trials have struggled to gain traction with physicians and patients [16]. We conducted this study to gain insight into perceived benefits and drawbacks of n-of-1 trials from the perspectives of physicians and the public. We learned that most physicians and patients readily grasp the logic of n-of-1 trials and appreciate their potential for personalizing care. However, both groups expressed reservations along scientific, relational, and clinical lines. In addition, physicians were particularly apprehensive about potential demands on time and resources.

Recent efforts by the National Institute of Health to support clinical and translational science have stressed the importance of community engagement, which emphasizes conducting research in settings that are more directly relevant to end-users [21]. However, recruiting and retaining community practitioners and patients for clinical and translational research remains a challenge [22–25]. One reason is that patients and their physicians may see little personal value in participating in clinical trials and worry about being assigned to the wrong treatment; "weak altruism" (a term coined by Canvin and Jacoby [26] to denote unwillingness to accept more than minimal personal risk for the sake of communal benefit) may be insufficient to sway participation [26–28]. N-of-1 studies theoretically overcome these objections by focusing on benefit for the individual patient, using patient-centered outcomes measures, deploying in familiar settings, and relying on financing by non-pharmaceutical industry sources. In this light, the failure of n-of-1 trials to gain widespread implementation defies easy explanation. The results of the current study not only help to explain why the n-of-1 movement has failed to gel but also suggest ways in which such trials might be more successfully marketed to physicians and patients.

Before discussing stakeholders' reservations about n-of-1 trials, it is worth highlighting areas of enthusiasm. Both physicians and patients found n-of-1 trials logical — a more systematic way to evaluate therapy. Both appreciated the emphasis on finding the best treatment for the patient at hand. And both liked the idea that n-of-1 trials could encourage more assiduous clinical monitoring and help cement the patient–physician relationship. In addition, physicians appreciated the prospect that patients engaged in n-of-1 trials would share in decision making, participate more actively in their own care, and develop a more realistic understanding of physicians' capabilities and limitations. Patients noted that, unlike placebo-controlled parallel group trials, n-of-1 trials afford access to at least one active treatment during the course of the study and possibly more. In recognition of these issues, education and marketing campaigns promoting n-of-1 trials might emphasize their inherent logic, opportunities for improved clinical care through careful monitoring of symptoms and reinforcement of existing patient–physician relationships, and the ability, in most cases, to stay on active treatment while contributing to new knowledge about "me." [29]

On the other hand, we identified a number of perceived problems with n-of-1 trials. These perceptions limited focus group participants' enthusiasm for the n-of-1 enterprise, and if not adequately addressed, could undermine recruitment to future n-of-1 trials. Both patients and physicians raised questions about the validity and safety of trials involving repeated cross-overs; investigators contemplating such designs will need to explain themselves carefully. In addition, some physicians seemed to misunderstand the scientific basis of n-of-1 trials, raising issues of sample size and "statistical validity." This suggests the need for ongoing efforts to explain the scientific underpinnings of the n-of-1 approach, especially in academia where opinion leaders are concentrated and where attachment to time-worn research paradigms may be most deeply entrenched. Some physicians were also concerned about cloaking the traditional healing role in the mantle of science, "taking away the doctor's doctoring." These clinicians need reassurance in the form of data as well as testimonials that n-of-1 trials enhance rather than subvert the clinical relationship. Finally, both physicians and patients worried about the logistical demands of single patient trials. For n-of-1 enthusiasts, this means creating systems that minimize the burdens on physicians and being flexible about selected elements of n-of-1 design, particularly randomization and blinding.

Creating the needed infrastructure to "make it really easy for them" will require funding. Potential funders include both payers (who may be motivated by the opportunity to identify the most cost-effective therapies for the individual patient) and pharmaceutical manufacturers (for whom n-of-1 trials may be an attractive alternative to blanket non-coverage or stepped care) [30]. Before these private funders can be expected to step forward, however, additional demonstration projects will need to show that "if you build it," consumers and practitioners will come. In addition, more research is needed on the tradeoffs between rigor, validity, and appeal in single patient trials.

These conclusions are tentative, based on feedback from a paid convenience sample of 21 physicians and 32 patient volunteers, most from Northern California. Physician and patient participants in this study were largely homogenous. Many physicians in our sample had academic affiliations, and patients were mostly white and highly educated. Patient groups were not segmented by decision-making status (parent versus adult patient) nor by disease type, which may have slanted the discussion in the direction of generalities rather than specifics. It is possible that probes from interview questions or other group interview participants prompted both physicians and patients to voice opinions they would not have generated spontaneously. Although we used reproducible methods to recruit and interview subjects and analyze the data, the results cannot be generalized to all populations of physicians and patient where n-of-1 trials might be made available, as experiences with chronic illness or its treatment and interest in study participation might differ from site to site.

Nevertheless, the results reported her provide a preliminary sense of the range, breadth and depth of reactions likely to be encountered during "start-up" for any new n-of-1 trial

enterprise. The face validity and everyday logic apparent in the concerns and observations of our sample are clearly relevant more broadly. As such, the results should be useful to a multitude of stakeholders whose interests might be served by establishing n-of-1 trial services [4,13,31,32], including academic investigators, entrepreneurs, integrated health plans, and health care payers.

In summary, n-of-1 trials hold tremendous promise for individualizing therapy and are potentially appealing to both physicians and patients. However, in focus groups with physicians and patients, a number of scientific, relational, clinical, and logistical concerns constrain enthusiasm for involvement. Researchers interested in expanding the appeal of n-of-1 trials as an implement of enhanced therapeutic precision will need to attend to these concerns by carefully explaining the approach, perhaps developing educational materials and training programs emphasizing the benefits, and minimizing the effort required of doctors and patients. Further investigation into the potential facilitators and barriers related to n-of-1 trial acceptability and dissemination could take the form of large-scale survey research, making use of the concepts generated by our formative research endeavor as a basis for survey construction.

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## Appendix A

Guiding questions for physician and patient interviews

Involvement in & awareness of clinical trials

- Have any of you been involved in a clinical trial? Probe for reasons related to involvement or noninvolvement.
- Based on what you know about clinical trials, would you consider participating in a clinical trial if it were offered?
- In what ways might clinical trial involvement influence the way you practice (physicians) / experience (patients) medicine?
- In what ways might clinical trials change patient outcomes?

*Educate physicians/patients on the n-of-1 trial*

*Introduction of clinical trials*: Most clinical trials are typically conducted by enrolling a large number of patients. Investigators assign each patient to one of two or more groups. Each group gets a different treatment. In the end, success is measured by looking at how the different treatment groups responded to the different treatments. These trials are closely monitored to ensure the safety and comfort of all patients. The results can help doctors decide which treatment works for most people.

*Introduction of n-of-1 trials*: A different approach that has sometimes been used is called an "n-of-1" clinical trial. In an "n-of-1" trial, an individual patient is assigned to receive a sequence of treatments in a random order. For example, a patient will receive treatment A for 2 weeks, followed by treatment B for 2 weeks, then by a random sequence of treatments A and B. Often, both the patient and the doctor are blinded to the treatment that the patient is receiving. Throughout the trial, the patient is closely monitored and at the end of the trial, the treatment "code" is broken and the patient and doctor jointly review the results to see if the patient did better with A or B.

Does anyone have any questions before we go on to discuss n-of-1 trials?

*Involvement in n-of-1 trials*

- Could you imagine participating in an n-of-1 trial? Probe for reasons related to interest in involvement or desire for noninvolvement.
- What do you perceive as the benefits/barrier of your participating in this type of trial with your patients (physicians)/doctor (patients)?
- In a practice like yours (physicians)/for a condition like yours, do you think n-of-1 trials would be particular applicable? (Follow-up for physicians: for what kinds of conditions do you see n-of-1 trials to be the most useful?)

  Have you ever tried (or would you consider trying) an n-of-1 trial with your patients (physicians)/doctor (patients)? Probe for reasons related to willingness or lack of willingness to try n-of-1.

| *Physicians* | *Patients* |
|---|---|
| Imagine that there is a new medication on the market (for heartburn), the clinical trials literature is favorable, but you are unsure whether it would be helpful for a particular patient. | If you had a symptom that was not going away and you were not sure if your medication was having an effect, would you like to try an n-of-1 trial? |
| Would you consider approaching the patient with an n-of-1 trial? Why or why not? | If you have tried two different medications, but you weren't sure which one worked better, would you like to try this type of trial? |

- Now that you know more about these trials, do you think that this is something you would encourage your patients (physicians)/doctor (patient) to consider? Why or why not?

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