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Authors

Moise, Nathalie
Wood, Dallas
Cheung, Ying Kuen K
et al.

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Patient preferences for Personalized (N-of-1) Trials: A conjoint analysis

Nathalie Moise, MD, MS[1], **Dallas Wood, PhD**[2], **Ying Kuen K Cheung, PhD**[1], **Naihua Duan, PhD**[1], **Tara St Onge**[1], **Joan Duer-Hefele**[1], **Tiffany Pu, MS, MBA**[3], **Karina W. Davidson, PhD, MASc**[1], **Ian M. Kronish, MD, MPH**[1], and **the members of the "Personalized Trial Collaboratory"**

[1]Columbia University Medical Center, New York, NY

[2]RTI International, Research Triangle Park, NC

[3]Nielson, Rochester, NY

Abstract

Objective—Despite their promise for increasing treatment precision, Personalized Trials (i.e., N-of-1 trials) have not been widely adopted. We aimed to ascertain patient preferences for Personalized Trials.

Study Design and Setting—We recruited 501 adults with ≥2 common chronic conditions from Harris Poll Online. We used Sawtooth Software to generate 45 plausible Personalized Trial designs comprised of combinations of 8 key attributes (treatment selection, treatment type, clinician involvement, blinding, time commitment, self-monitoring frequency, duration, cost) at different levels. Conditional logistic regression was used to assess relative importance of different attributes using a random utility maximization model.

Results—Overall, participants preferred Personalized Trials with no costs vs. $100 cost (utility difference 1.52 [standard error 0.07], p<0.001) and with less vs. more time commitment/day (0.16 [0.07], p<0.015), but did not hold preferences for the other 6 attributes. In subgroup analyses, participants ≥65 years, white, and with income ≤$50,000 were more averse to costs than their counterparts (p all <0.05).

Discussion—To optimize dissemination, Personalized Trial designers should seek to minimize out-of-pocket costs and time-burden of self-monitoring. They should also consider adaptive designs that can accommodate subgroup differences in design preferences.

Keywords

N-of-1 trials; conjoint analysis; multi-morbidity

Disclosures: none

Conflict of Interest
None to report.

Background

The age of personalized health and patient-centered care,[1] particularly as they relate to chronic disease management,[2] has ushered in a renewed interest in a decades old methodology – Personalized Trials (also known as N-of-1 trials or single-person trials).[3,4] Unlike parallel-group randomized controlled trials (RCTs) that randomly assign patients to different treatments to understand the effects of treatments in a population, Personalized Trials randomize treatments across time *within* each patient to determine the relative benefits and harms of the treatments for that one patient.[5] In this way, Personalized Trials are the foundational design for a truly patient-centered comparative effectiveness method.[6] In fact, a recent working group suggested that Personalized Trials may provide the strongest evidence in the hierarchy of evidence-based medicine for informing individual patients' treatment decisions.[7,8] Historically, in introducing evidence-based medicine, Guyatt and others described these Personalized Trials as the pinnacle of the evidence-based design pyramid.[9]

In prior research, Personalized Trials have led to valuable changes in treatment, cessation of treatment, or confirmation of the efficacy of the original treatment.[10–12] However, other than isolated pockets of activity, Personalized Trials are conducted infrequently in clinical practice.[8,13] [14] In post-mortem assessments as to why Personalized Trials never became standardly-employed designs, proponents concluded that they were insufficiently appealing to patients or clinicians to justify the cost and effort needed to design and implement them.[8,13] Personalized Trials design specifications are mostly driven by clinicians or researchers.[5] [14] Yet, there are a number of options for design features or design attributes (e.g., cost, blinding, duration) that could influence patient acceptability and demand.[5] A better understanding of the circumstances under which patients would be interested in conducting Personalized Trials could foster a wider adoption in the use of this methodology.[5,15]

Conjoint analysis is a well-established market research technique for assessing consumer preferences. It involves asking consumers to choose between hypothetical products that differ along a number of "attributes." Each of these attributes is defined by a set of characteristics called "levels." For example, a car can be described by attributes such as color and price. Levels for color can include black, white, and blue. The choices respondents make between hypothetical products can then be analyzed to determine how changes in these attributes can impact overall product acceptability.[16–18] We aimed to use conjoint analysis to elicit patient preferences for Personalized Trial designs and to understand the ways in which Personalized Trial attributes (e.g., cost, blinding, trial duration), contribute to the overall acceptability of these trials. The results would allow researchers and clinicians to incorporate patient preferences when designing the next generation of Personalized Trial prototypes such that they will be attractive to patients. Although conjoint analyses have been widely used in the fields of psychology, economics and marketing, and more recently in public health, they have infrequently been used to inform clinical trial design.[18]

Methods

Stakeholder engagement

An essential component of our methodology was the development of a ‘collaboratory’ or a networked format that includes social processes such as collaboration techniques, formal and informal communication, and agreement on norms, principles, values, and rules by a group of stakeholders relevant to the design and implementation of Personalized Trials in clinical practice.[19] The collaboratory’s 30-member team included patients with multiple comorbidities, clinicians with and without experience conducting N-of-1 trials, health care administrators, scientists, methodologists/statisticians, ethicists and experts in dissemination. Our collaboratory met quarterly from July 2014 to September 2017 to review study design, conduct, analysis, interpretation, and dissemination of findings. Collaboratory meetings were conducted by phone and in person, and were scheduled to maximize the availability of all participants. This allowed for a transparent process, and helped improve the relevance of the study design and approach.

Recruitment

We conducted a cross-sectional survey of 501 individuals with 2 or more chronic conditions. Participants were recruited from a general population panel maintained by the Harris Poll Online (HPOL), which includes several million online members. The panel was recruited from a multitude of sources (e.g., targeted emails sent by online partners, social media, news and telephone recruitment of targeted populations). Each recruitment source was carefully vetted through a rigorous interviewing and testing process and then monitored for response quality on an ongoing basis. For the current study, the HPOL panel was actively screened to identify a nationally-representative group of adults with two or more chronic conditions. These sampling procedures have been widely used and allow for rigorous, scientifically acceptable practice without spending considerable time and energy assembling large and comprehensive samples.[20]

Conjoint Survey Development

Choice-based conjoint surveys simulate the selection of a product (Personalized Trial) by presenting respondents with a set of products, here trial prototypes, composed of one level from each attribute, and asking the respondent to select which prototype they preferred (Figure 1). The first step in developing these conjoint survey questions is to determine which attributes will be used to describe the hypothetical Personalized Trial designs that respondents will be asked to choose between. Typically, the set of attributes describing the good or service in a conjoint survey includes all the major features that a respondent considers when making a decision about the service. The eight attributes we identified and the range of values that these attributes could take (i.e., their “levels”) are listed in Table 1.

These attributes and levels were identified as follows. First, we conducted focus groups with primary care providers (N=24) and patients with multiple chronic conditions (N= 54) to understand attitudes toward Personalized Trials and design features.[15] Second, we conducted a survey of individuals from HPOL with at least two chronic illnesses to identify a list of priority conditions that should be targeted by Personalized Trials. Hypertension,

hyperlipidemia, diabetes, depression, arthritis/joint pain, breathing problems/bronchitis/asthma, back pain, sleeping problems/insomnia were identified as the top priority conditions in this survey. In this survey, we also explored design features found in focus groups to be potential barriers or facilitators to participation (e.g., blinding, monitoring time, costs, duration, clinician input) in order to determine the range of acceptable levels for design attributes that should be used in those trials (e.g., patient chooses treatment options versus clinician chooses treatment options; self-monitoring once per day versus self-monitoring three times per day) (Table 1). For quantifiable options (e.g., self-monitoring frequency, time commitment per day), we relied on the interquartile ranges of survey responses that emerged from the formative survey. Not only was the cost of $100 the upper interquartile range in our survey, but aligned with prior literature.[5] Finally, we reviewed the literature to include Personalized Trial design attributes that could be informed by patient preferences (e.g., blinding, intensity of self-monitoring for treatment outcomes, extent of clinician involvement) and eliminated those that were essential to the validity, reliability and conduct of N-of-1 trials according to an AHRQ Report (e.g., randomization),[5] leaving 8 attributes.

Based on the attributes and levels listed in Table 1, there were 384 ($2 \times 3 \times 2 \times 2 \times 2 \times 2 \times 2 \times 2$) hypothetical conjoint tasks that could be created. However, one of the benefits of conjoint analysis is that only a small fraction of these need to be evaluated by respondents to determine their preferences, assuming that a statistically efficient design is created. As recommended by Carlsson and Martinsson (2003);[21] Hensher, Rose, and Greene (2005);[22] and others, an efficient design should incorporate the following features:

- Level Balance: levels of an attribute occur with equal frequency
- Orthogonality: the occurrences of any two levels of different attributes are uncorrelated
- Minimal Overlap: cases where attribute levels do not vary within a choice set should be minimized

We used Sawtooth Choice-Based Conjoint Software (Sawtooth, 2010) to generate an efficient design incorporating the above features. This design included 45 choice tasks that each included two Personalized Trial design prototypes (see Supplemental Material Table 1 for complete design).

In addition to conjoint questions, we collected data on participants' demographic characteristics. Based on input from our collaboratory members, we also assessed participant characteristics important to chronic disease management, including number of medications prescribed, satisfaction with current management (4 point Likert scale), and preferences for shared decision making based on the Control Preference Scale.[23] Types of treatment tried previously for the condition of interest were also ascertained, including prescription medications, complementary and alternative medicine (CAM), and lifestyle treatments (e.g., exercise, smoking-cessation, diet). Options for CAM were based on results of the 2012 National Health Interview Survey (NHIS) conducted among individuals with two or more chronic conditions.[24] The participant received a definition and examples of CAM as well as a description of how CAM differed from prescription and lifestyle options; participants could hover over "CAM" to access the definition throughout the questionnaire. Finally we

ascertained patient important outcomes (i.e., side-effects, quality of life/function, disease control, symptom control) for conducting Personalized Trials with response options based on our formative survey and focus groups.

The final survey was refined after being rigorously piloted amongst individuals with HPOL panelists with multiple chronic diseases. The survey was developed in English, then translated into Spanish with back translation into English to ensure comparability in both languages.

Study procedures

Panel members from the HPOL were eligible to complete our survey if they were 18 years or older, resided in the U.S., and reported two or more of six chronic diseases (hypertension, hyperlipidemia, diabetes, asthma, osteoporosis, or depression), which reflect chronic conditions considered amongst the most highly prevalent and burdensome in the U.S.[25,26]

Participants then entered and completed the survey utilizing a “least fill” quota system defined by pre-specified demographic criteria: age, gender, race, ethnicity, income and region. These demographic “bins” were developed to reflect a sample representative of NHIS participants with at least two chronic diseases.[27] If a “bin” was filled for a particular demographic, the participant was not prompted to continue the survey.

Respondents received a preamble, piloted in focus groups and in the first survey, describing how treatment selection takes place in routine clinical care or in traditional clinical trials, then described what takes place in Personalized Trials highlighting key differences, and concluded by providing a Personalized Trial pain management example to further clarify key features (Supplementary Material). Participants were then prompted to mark all chronic diseases for which they received a diagnosis (including diseases outside the inclusion criteria diseases) and to rate level of interest (4 point Likert scale) for participating in a Personalized Trial for each selected disease, after trials were appropriately described and illustrated. If participants selected one of the disease states deemed a chronic condition amenable to Personalized Trials in our formative data (i.e., hypertension, hyperlipidemia, diabetes, depression, arthritis/joint pain, breathing problems/bronchitis/asthma, back pain, sleeping problems/insomnia) and were at least minimally interested in conducting a Personalized Trial for one of their selected disease states, they were eligible to complete the full survey.

Final qualified participants were then shown consent language approved by an institutional review board (IRB) describing the conditions and details of the study. If the participant consented and agreed to the terms of the study, participants were then assigned to answer the rest of the survey (e.g., conjoint questions, preferred outcomes, trialed prior treatments, satisfaction) with respect to one of their chronic conditions that was amenable to Personalized Trials. For participants who were interested in Personalized Trials for more than just one condition, the condition of interest for the rest of the survey was randomly selected with preference weighting. Preference weighting was used to ensure that participants were randomized to their most preferred conditions and that equal numbers of participants completed discrete choice tasks for each condition. In total, there were 14 demographic questions and 18 conjoint questions. For conjoint questions, each participant

completed 15 short choice tasks (for practice) followed by 3 choice tasks, each of which consisted of a comparison between two design prototypes both comprised of a combination of all eight attributes; the respondents were prompted to select the preferred 8-attribute prototype within each task. (Figure 1). Prior to completing the conjoint tasks, participants received descriptions of all design attributes based on focus groups findings during which we elicited how best to communicate attributes to ensure patient comprehension. For example, we described blinding as "keeping the treatment hidden until the end of the trial to help patients more objectively evaluate the effects" (Supplementary Material). Participants on average spent 13 minutes completing the survey online. All participants provided e-signature informed consent. Study procedures and materials were approved by the Chesapeake IRB on February, 2017.

Statistical Analysis

The participant characteristics at baseline were summarized using descriptive statistics such as mean and standard deviation for continuous characteristics, and proportion for discrete characteristics.

To assess patient preferences for different attributes of Personalized Trials, we estimated a random utility maximization (RUM) model based on the choices that participants made between hypothetical Personalized Trials during the conjoint portion of the survey. The coefficient estimates for the RUM model can be interpreted as utility measures that reflect respondents' preferences for each attribute level. We considered the lower level of each attribute to be the baseline preference.

For the RUM model, we assumed that a respondent would select the option that provided the highest level of utility. In this case, the choice was between two hypothetical Personalized Trials. We defined the utility the respondent received from each trial design *j* by

$$u_j = v_j + \varepsilon_j, j = 1, \ldots, J, \quad (1)$$

where v_j was the observable component of utility that depended on the attribute levels. The term ε_j was a random error representing the component of utility that was unobservable from the perspective of the analyst but known to the respondent.

Under the assumption of utility maximization, the respondents chose trial design *j* over design *k* in a given choice task if $u_j \geq u_k$. Because total utility was unobserved by the analyst, this choice was random from the perspective of the model, and we could only state the probability that design *j* would be chosen. In general terms, this probability is given by

$$\Pr(u_j > u_k) = \text{pr}(v_j + \varepsilon_j > v_k + \varepsilon_k) = \text{pr}(\varepsilon_k - \varepsilon_j < v_j - v_k) \quad (2)$$

Estimation of the model proceeded using assumptions for the form of the deterministic component v and the error distribution. The deterministic component v was modeled as a linear function of the attribute levels.

To estimate the parameters of the model, we used a conditional logit model,[28] which assumed that the error term followed a Type I extreme-value distribution and used maximum-likelihood methods to estimate the parameters. Conditional logit is a computationally straightforward estimation approach that provides useful insights into the general pattern of participants' preferences, tradeoffs, and values. The specific form of the probability that design *j* was selected was given by the following equation and estimated using a conditional logit model.

$$pr\left(u_j \geq u_k\right) = \frac{\exp\left(v_j\right)}{\exp\left(v_k\right) + \exp\left(v_j\right)} \quad (3)$$

This analysis was performed in the overall sample to assess marginal utilities for the trial design attributes as main effects. Utilities in conjoint analyses are interval data (with an arbitrarily additive constant) so that preferences for levels within attributes are comparable. Marginal utilities were also converted to odds ratios (OR) (95% confidence intervals) by exponentiation of utilities. ORs corresponded to the odds of an individual preferring a Personalized Trial prototype with a given design prototype versus a comparator design prototype. Two-way interactions between attributes were explored systematically under the RUM model. With 8 attributes, we explored all 28 possible two-way interactions and tested significance using an omnibus likelihood ratio.

We also tested interactions between attributes with demographics (age, gender, race and income, dichotomized at median) and with chronic diseases. We assessed differences in design preferences across demographic groups using the following procedure. First, we conducted a likelihood ratio test to determine whether preferences were the same across subgroups. Second, if we rejected the null hypothesis that preferences were identical, then we investigated whether preferences differed between subgroups.

The sample size was determined according to the minimum sample size rule in Orme (2010).[29] Precisely, with three choice tasks, two choices per task, and a maximum of 3 levels of an attribute (treatment types), the minimum sample size was 250 for assessing the main effects, and 500 for assessing two-way interactions.

Results

Cohort

Overall, 15,883 potentially qualified individuals from the HPOL based on profile data (age, two or more chronic conditions) were invited to participate in the study via email, of whom 4,386 accessed the survey via a web link in their invitation email (excluding those who failed quality control tests such as accessing the study from the same IP address). Of these,

3,068 (69.9%) respondents did not meet eligibility criteria for the full survey [94.4% due to not having two qualifying chronic conditions; 0.4% age; 4.7% due to not being interested in Personalized Trials; 0.4% due to being randomized to a condition for which they did not want to complete a Personalized Trial], 82 (1.9%) respondents declined to participate, 601 (13.7%) did not complete the survey, 134 (3.1%) fell into demographic "bins" already filled, leaving 501 completed surveys.

Participant characteristics

The mean age (SD) was 57.2 (15.5) years; 55.6% were women; 13.0% black and 15.0% Hispanic or Latino; 74.2% had hypertension, 54.0% hyperlipidemia, 42.0% depression, 36.0% diabetes, 29.8% asthma/emphysema/chronic bronchitis (breathing problems), 43.0% arthritis/joint pain, 35.4% back pain, and 24.2% insomnia. Participants took a mean (SD) of 5.6 (4.5) medications daily; 24.8% were very satisfied with the current care of their condition; and 51.4% preferred to share decision making with their clinician (Table 2; Supplementary Table 2). Overall, most participants had previously used CAM (92.2%) and lifestyle treatments (82.0%) for their respective disease state. The most commonly used CAM treatments for the disease of interest were deep breathing (31.6%), multivitamins (29.0%) and prayer (28.2%) (Supplementary Table 2).

Overall, 88.8% were moderately or very interested in participating in a Personalized Trial to learn if one treatment was better than other, 82.6% to learn if a new treatment was better than an older treatment, and 84.0% to determine if one of the current treatments could be stopped without worsening a condition. With respect to the treatment effects that could be measured as part of Personalized Trials, most participants were moderately/very interested in monitoring disease control (93.6%), side effects (92.8%), ability to perform usual activities (90.8%), and symptoms related to the disease (92.7%). When prompted to discuss what they hoped to gain from participating in a Personalized Trial, top reasons included finding the best treatment for them (37.8%), improving functional status (25.0%) and improving the condition/symptoms of interest (23.0%) (Supplementary Table 2).

Marginal Utilities

We found (Table 3) that participants preferred trials that had no cost over trials that cost $100 (difference in utility 1.52 [standard error 0.07], $p<0.001$) and trials that only required 5 minutes instead of 30 minute of tracking time commitment/day (0.16 [0.07], $p=0.015$). No other attribute had a significant effect on utility (Figure 2; Table 3; Supplementary Table 3). As such, preference for no cost (1.52) was stronger than preference for shorter time commitment (0.16).

We found that preferences for Personalized Trial attributes differed across several demographic characteristics (Table 4; Supplementary Tables 4–6). Likelihood ratio test results indicated that patient preferences differed significantly by age ($p=0.001$), race ($p=0.009$), and income ($p<0.001$), but not gender ($p=0.18$). Compared to younger adults (18–65 years old), older adults (≥ 65 years) had stronger preferences for trials with no cost over $100 cost (1.99 [0.14] vs. 1.33 [0.08], $p<0.001$). Compared to nonwhite respondents, white respondents had a significantly stronger preference for trials with no cost (1.67 [0.08]

vs. 1.14 [0.14], p<0.001). Compared to higher earning participants (≥ $50,000 per year), lower earning participants (< $50,000 per year) had a significantly stronger preference for trials that had no cost (2.05 [0.12] vs. 1.18 [0.09], p<0.001). We found no other significant differences in preferences by age, race or income.

We also found that preferences for Personalized Trial attributes differed among patients with different chronic diseases. Specifically, likelihood ratio test results indicated that patient preferences differed significantly for patients with arthritis vs. without arthritis (p=0.03). Individuals with arthritis had a stronger preference for trials that had no cost than individuals without arthritis (2.53 [0.31] vs. 1.43 [0.07], p=0.001) (Supplementary Table 7).

Odds Ratios

We further provided odds ratios of the results to elucidate how including certain attributes affected the odds of a patient selecting a particular prototype. Participants had greater odds of selecting Personalized Trial prototypes that had no cost over prototypes that cost $100 (OR=4.58 95% CI 4.01–5.24, p<0.001) and those with shorter time commitment of 5 minutes/day vs. 30 minutes/day (OR=1.18, 95% CI 1.03–1.35, p=0.015). Odds ratios for all of the subgroup and exploratory analyses are included in the Supplementary Material Tables 2–8.

Discussion

In a nationally representative sample of patients with two or more chronic conditions, we found that the Personalized Trial prototype preferred by the majority of respondents would involve no cost and be conducted in an efficient manner such that the total amount of time spent tracking treatment outcomes would be less than 5 minutes per day. Other attributes such as blinding, treatment options, trial duration, and clinician involvement did not appear to influence preferences for Personalized Trial prototypes. In addition, we found signals for differences in preferences by subgroup, with particular aversion to cost amongst white, lower income and older participants compared to their counterparts. Preferences were remarkably similar across chronic conditions, with the only difference in attribute preferences among patients with versus without arthritis who had stronger preferences for no cost N-of-1 trials.

To our knowledge, this is the first study to elicit patient preferences for Personalized Trial design features using conjoint methodology, [5,18] thus providing a roadmap for Personalized Trial designers seeking to market and create patient-centered prototypes. Although there has been excitement about Personalized Trials from the evidence-based practice community, widespread implementation has been hindered, in part, from a lack of understanding of the circumstances under which patients would engage in this methodology. Conjoint analyses allow us to quantify the degree to which including an attribute decreases participation in a Personalized Trial prototype. For example, participants had a 18% greater odds of preferring a trial that required 5 minutes as opposed to 30 minutes of monitoring daily. In addition, the preferred prototype differs from what an expert in Personalized Trials (N-of-1) methods might design (e.g., more time commitment to collect and monitor data on treatment effects and out-of-pocket costs for staff, pharmacists, blinding, monitoring, and

travel).[8] Finally, our survey also demonstrates that nearly 90% of our participants were interested in participating to compare whether one treatment is more effective than another, further providing a roadmap for marketing Personalized Trials.

The strongest deterrent to participation appeared to be out-of-pocket costs, which is to be expected in our cohort of patients with multiple chronic conditions who are likely already spending larger shares of their income on out-of-pocket medical expenses.[30] Most notably, groups with disproportionately high out-of-pocket expenses, specifically older, lower income, and white individuals[30] as well as those with costly conditions such as arthritis appeared to be particularly averse to paying out-of-pocket for Personalized Trials. Estimates for fixed and variable costs to patients (drawn mostly from research studies which included costs for development of protocols, creation of data collection instruments, blinding protocols, trial design, recruitment, and analyses) range from $32 for 6 months to $876 for 12 months.[5] Participants in our study were particularly averse to paying $100, which was the upper limit of the interquartile range of out-of-pocket costs that individuals in our prior formative survey were willing to pay. Our findings argue that widespread uptake of Personalized Trials may hinge on building a value proposition and achieving a sustainable business plan for Personalized Trial designs, which has eluded prior efforts.[8]

First, marketing efforts should consider emphasizing preferred attributes (e.g., low time commitment and cost) and outcomes (e.g., finding the best treatment for you; minimizing side effects) elicited in our survey. This will also require careful description of trials to mitigate concerns should less desirable attributes be needed to ensure Personalized Trials' rigor.[31] Second, further research is needed to confirm the cost-effectiveness of Personalized Trials, particularly as they relate to reducing adverse events or resulting in long-term use of less expensive but equally efficacious drugs. Finally, creating a value proposition may require aligning with nationwide agendas around individualized medicine and leveraging the innovative strengths of the biomedical research community.[32]

The second strongest preference after costs related to shorter daily time requirements for performing Personalized Trial study activities. With the advent of smartphones, wearable devices, and other advances in mobile health technology, frequent but brief assessments can be achieved, substantially lowering the burden of collecting data for Personalized Trials. Smartphone applications can be used to scale the tools needed to collect and visualize patient data.[33,34] Mobile devices for collecting data have the greatest potential to facilitate more data while reducing time spent daily and potentially reducing costs given the widespread ownership of smart devices.[35]

In contrast with cost and time commitment, our results suggest that patients do not have strong preferences around several additional attributes key to conducting rigorous Personalized Trials (i.e., a blinded trial with prescription medications to allow for placebo comparison, longer duration to account for washout period and multiple treatment repetitions). In fact, our findings suggest that Personalized Trial designers can select the most robust use cases without being overly concerned about discouraging participation with certain attributes.

Finally, our findings have implications for disseminating Personalized Trials, which have largely been conducted in academic settings or through grant funded research, in clinical settings. Interestingly, there remain few if any centralized locations, “apps” or websites for conducting, managing and analyzing Personalized Trials. Healthcare experts have increasingly suggested that personalized healthcare may be achieved by leveraging information technology, creating defined patient profiles and applying “mass customization’ strategies, which are used in business sectors to better connect products to specific customer needs.[36] Some have posited that elucidating options for Personalized Trial design *a priori* would allow patients and clinicians to more quickly design and implement their own trials, and would guide the development of successful Personalized Trial services and mobile health technologies that facilitate N-of-1 trials, and importantly, minimize costs. Given our finding that there were differences in preferred Personalized Trial designs depending on demographic characteristics and disease states, one would surmise that there may be substantial individual differences in design preferences as well. Our results also suggest that it will be essential for those interested in developing a Personalized Trial platform to develop flexible designs that can be customized according to patient preference. Thus, a Personalized Trial service that delivers custom built trial prototypes, facilitates data collection, and analyses might best reduce logistic and cost barriers to widespread implementation.

While this study is the first to assess patient preferences for Personalized Trial design features by employing sophisticated conjoint methodology, there were several limitations. Limiting eligibility for the survey to those with two or more pre-defined chronic conditions may have limited the generalizability of our findings, though we sought to include both symptomatic and asymptomatic conditions deemed to be amongst the highest contributors to chronic disease burden worldwide. In addition, the list of Personalized Trial amenable conditions was created after extensive focus groups and a national survey. Because we did not ask participants to report their likelihood in engaging in the personalized prototypes, we were unable to ascertain the extent to which the preferred designs would lead to actual participation in Personalized Trials. Nonetheless, fewer than 5% of individuals were “not at all interested” in participating in a Personalized Trial, and our methods allowed us to ascertain the trade-offs patients make in deciding among trial prototypes. Future research might also ascertain the average probability of acceptance per increase in utility. In addition, the HPOL survey methods, though widely used, may have biased the sample towards those with online access and who could self-report symptoms related to their chronic illnesses. Nevertheless, our final cohort demonstrated geographic, socioeconomic, and racial/ethnic diversity representative of the U.S. adults with multiple chronic conditions. In addition, the sample size was predicated on non-adjusted but pre-specified analyses, and while this adheres to conventional approaches, we may have been underpowered for subgroup analyses. Nearly 12% of participants did not complete the survey, also suggesting some concern for survey comprehension, though our survey was extensively piloted, took on average less than 15 minutes to complete and adhered to rigorous Nielson quality checks. Relatedly, the low response rate amongst potentially qualified individuals who accessed the survey may have led to non-response bias. Additionally, despite our use of previously piloted descriptions and rationales for design attributes, like blinding and frequent monitoring, it is possible that participants did not fully understand the drawbacks or utility

of some attributes. Finally, while conjoint methods allow one to ascertain preferences for product attributes and have been widely used in marketing and psychology fields, an inherent limitation is that they are merely a proxy for final patient decisions.

In conclusion, our study provides patient preferences for multiple potential Personalized Trial designs. Designing Personalized Trials that appeal to patients will be key to improving the dissemination of Personalized Trial methods. Specifically, it appears that avoiding cost and limiting patient time spent monitoring treatment effects are key features of future Personalized Trials. Future research should focus on testing whether including these design features does in fact increase patient engagement and build a business case for Personalized Trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This is the first study to use conjoint methodology to assess preferences for Personalized (i.e., N-of-1) trial designs.
- This is one of the first studies to focus explicitly on treatment and trial design preferences for patients with multiple chronic conditions.
- Most individuals prefer a personalized trial that limits out-of-pocket costs and is short in duration.
- Personalized trial designers and public health officials should consider ways to limit out-of-pocket costs associated with Personalized trials and consider facilitating short duration trials with mHealth.

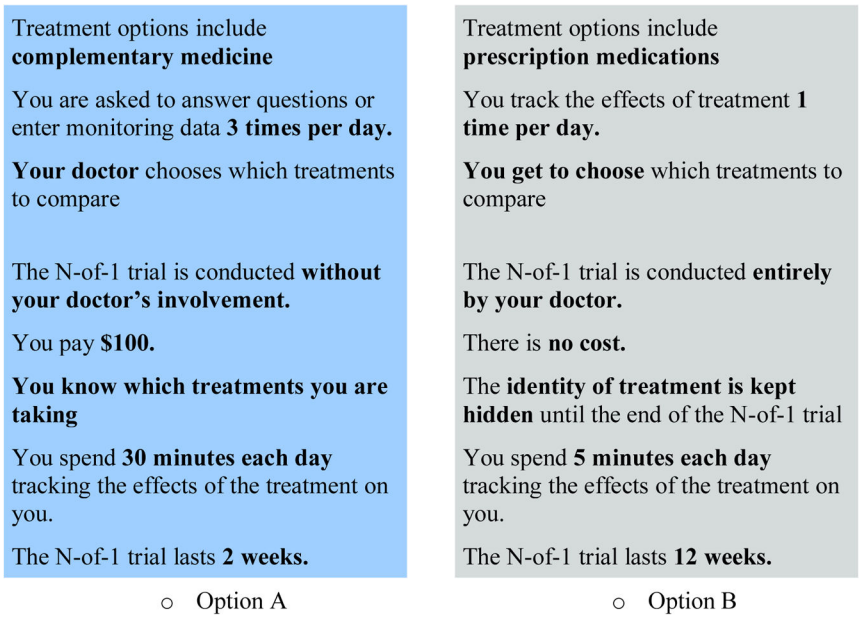

Figure 1.
Example of choice task for Personalized Trial design prototypes

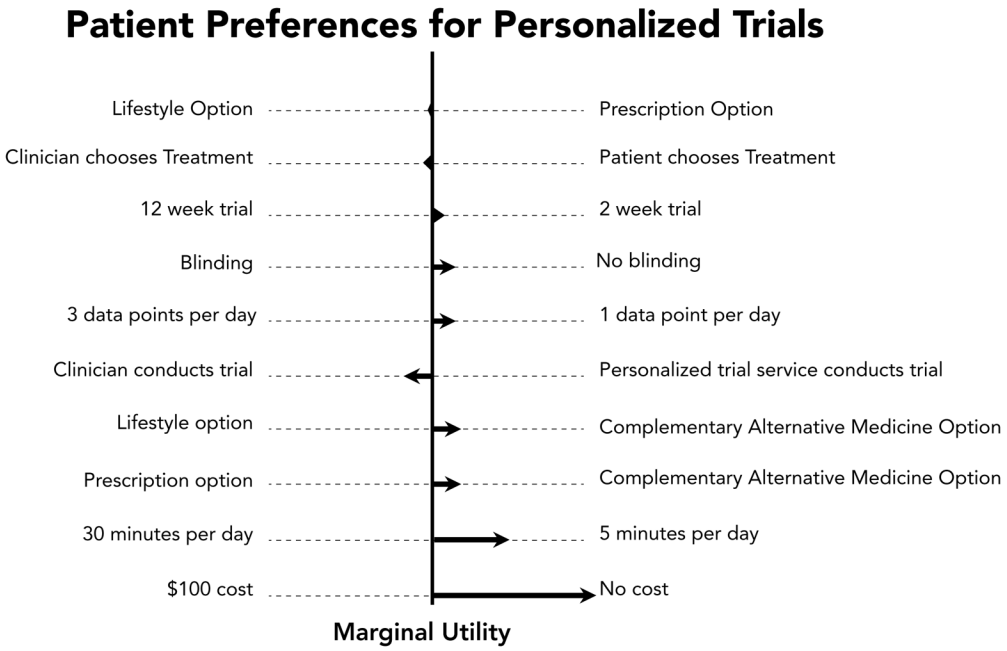

Figure 2.
Patient preferences for Personalized Trials

Table 1

N-of-1 design attributes

Attribute Name	Levels*
Treatment Selection	• Patient gets to choose treatments to compare in N- of-1 trial • Doctor chooses treatments to compare in N-of-1 trial
Treatment Type	• Lifestyle Change • Prescription Medication • Complementary Alternative Medicine
Doctor Involvement	• Study is conducted without doctor involvement (N of 1 service) • Study is conducted with doctor involvement
Blinding	• Not Blinded • Blinded
Time Commitment	• 5 minutes per day • 30 minutes per day
Self-Monitoring Frequency	• 1 times per day • 3 times per day
Study Duration	• 2 weeks • 12 weeks
Out-of-Pocket Cost	• No cost (all costs including travel are covered) • $100

* Lower levels were considered the baseline level in all analyses

Table 2

Characteristics of participants with multiple chronic diseases recruited from the Harris Poll Online (N=501)

Participant Characteristics	Frequency (%)
Age, mean, SD	57.2, (15.5)
Female	278 (55.6%)
Race/Ethnicity	
Black	65 (13%)
Hispanic or Latino	75 (15%)
Asian	26 (5.2%)
High school diploma/GED or less	86 (13.6%)
Not employed	52 (10.4%)
Health insurance status	
Medicare Insured	253 (50.6%)
Medicaid Insured	71 (14.2%)
Chronic Conditions Amenable to Personalized Trials	
Hypertension	371 (74.2%)
Hyperlipidemia	270 (54.0%)
Arthritis/Joint Pain	215 (43.0%)
Depression	210 (42.0%)
Diabetes	180 (36.0%)
Back Pain	177 (35.4%)
Breathing Problems/Asthma/Bronchitis	149 (29.8%)
Insomnia/Sleeping Problems	121 (24.2%)
Number of current prescription medications (Mean, SD)	5.6 (4.5)

Data are presented as N (%) unless otherwise specified.

Table 3

Overall Marginal Utilities for Personalized Trial Attributes

"Utility Gained When…"	**Utility Gained (Std. Err.)**	**P-values**	**Interpretation**
Study has no cost instead of costing $100	1.52 (0.07)	<0.001	No cost > $100
Study requires 5 minute time commitment instead of 30 minute time commitment	0.16 (0.07)	0.015	5 min > 30 min
Study is not blinded instead of blinded	0.08 (0.07)	0.212	Blinded = Not Blinded
Study collects data 1 times per day instead of 3 time per day	0.08 (0.07)	0.256	1 time = 3 times
Study lasts 2 weeks instead of 12 weeks	0.05 (0.07)	0.494	2 weeks = 12 weeks
Treatment is lifestyle instead of prescription medication	0.02 (0.10)	0.856	Lifestyle = Rx
Patient required to choose own treatment instead of letting doctor choose	−0.03 (0.07)	0.634	Patient chooses = Clinician
Study is conducted without doctor involvement instead of with doctor involvement	−0.11 (0.07)	0.098	Conducted by Personalized Trial service = Conducted by your doctor
Treatment is lifestyle change instead of Complementary Alternative Medicine	−0.13 (0.09)	0.157	Rx = CAM
Treatment is prescription medication instead of Complementary Alternative Medicine	−0.15 (0.10)	0.123	Lifestyle = CAM

Table 4

Preferred Personalized Trial Designs by Age, Race, and Income

Attribute	<65 years*	≥65 years*	White*	Nonwhite*	Income <50K*	Income≥50K*
Treatment Selection	No Preference	No Preference	No Preference	No Preference	No Preference	No Preference
Prescription vs. CAM	No Preference	No Preference	No Preference	No Preference	**CAM***	No Preference
Lifestyle vs. CAM	No Preference	No Preference	No Preference	No Preference	No Preference	No Preference
N of 1 service vs. Clinician conducted	No Preference	**Clinician conducted***	No Preference	No Preference	**Clinician conducted***	No Preference
Blinding	No Preference	No Blinding	No Preference	No Preference	No Preference	No Preference
5 or 30-minute time commitment/day	No Preference	**5 minutes/day***	**5 minutes/day***	No Preference	No Preference	**5 minutes/day***
1 or 3 data points/day	No Preference	No Preference	No Preference	No Preference	No preference	**1 time/day***
2 or 12-week Study duration	No Preference	No Preference	No Preference	No Preference	No Preference	No Preference
No or $100 study cost	**No Cost***	**No Cost****	**No Cost****	**No Cost***	**No Cost****	**No Cost***

* significant effect within subgroup at p<0.05.

Red font= Significant interaction at p <0.05

** Stronger preference