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Preferences and Insights for Participation in a Rheumatoid Arthritis Clinical Prevention Trial: A Mixed-Methods Study

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Objective. In rheumatoid arthritis (RA), anti–citrullinated protein antibodies (ACPA) can be elevated prior to inflammatory arthritis (IA). The potential to intervene in people with ACPA positivity underpins the development of prevention trials in RA. The Research Participation Influences Study examined factors influencing the decisions of individuals who are ACPA(+) to participate in a prevention trial using qualitative and quantitative methods.

Methods. Individuals with ACPA positivity without IA were provided information regarding their risk for future RA, were provided a description of a clinical prevention trial using hydroxychloroquine, and were asked if they would participate in the trial. After agreeing to or declining participation, they were surveyed on what influenced their decision using Likert scales and open-response questions.

Results. Thirty-nine individuals who agreed to trial participation (enrollees) and 31 individuals who declined (nonenrollees) completed surveys. Enrollees expressed greater perceived risk for RA and greater perception of benefit to themselves or others than nonenrollees. Nonenrollees expressed greater concern about medication effects and less personal or family experience with RA than enrollees. There was a higher proportion of first-degree relatives (FDRs) of people with RA in enrollees versus nonenrollees (54% vs. 23%, $P = 0.01$).

Conclusion. Enrollees were more likely than nonenrollees to be FDRs, exhibit stronger concern for personal risk for RA, and have less concern about adverse effects. Further exploration is needed to determine why these differences were present, including exploration of symptoms and the role of family history. Understanding these issues will better inform researchers and individuals who are candidates for prevention.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease that results in increased morbidity and mortality, typically requires lifelong therapy, and results in high personal and societal costs (1). There is a preclinical phase of RA in which autoantibodies such as anti–citrullinated protein antibodies (ACPA) can be elevated in the blood and are predictive of the future onset of clinically apparent inflammatory arthritis (IA) and classifiable RA (1). Based on knowledge of this preclinical phase, there are now a number of completed, ongoing, or developing clinical trials to prevent or delay the future onset of IA and RA in individuals who exhibit ACPA and/or other features (2–8). These trials identify risk differently among their populations (including various combinations of factors such as symptoms and different patterns of ACPA and rheumatoid factor elevation and, in some studies, imaging abnormalities), but most participants were required to be free of IA as determined in physical examination and were enrolled in placebo-controlled trials using interventions such as abatacept, atorvastatin, corticosteroids, methotrexate and rituximab.

A critically important part of these trials is the identification of individuals who are at high risk for future RA due to ACPA positivity or other factors given that these individuals may not readily present to clinical care or research (1). It is also challenging to enroll individuals who are at risk for future RA into clinical prevention trials. Indeed, an RA clinical prevention trial based in Europe using atorvastatin was prematurely halted because of difficulty in identifying individuals who were willing to participate in the study (4).

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The factors that influence a decision to participate in medical research are often multifaceted. In addition, the decision to take medication to prevent a future disease may be more complex, especially among populations who show minimal to no symptoms and signs of clinical disease yet who may be at high risk of disease onset in the future. Trials of RA prevention are a good example of this context. To date, published research in this area has focused on perceptions of risk and willingness to engage in preventive treatments being studied among those at risk in Canada and Western European countries (9–14). In addition, these studies have often used hypothetical decisions to reveal preferences, although one study has evaluated individuals who were directly asked to participate in a clinical trial (13).

Some concepts that have emerged from these studies that support participation in prevention include an opportunity to reduce risk for disease, whereas concepts that have been identified for not participating include a potential lack of understanding of RA as a disease and personal risk for future RA and reluctance to take the study medication, primarily because of the uncertain benefit and potential side effects and risks. However, further research is needed to understand what motivates people to participate in trials of preventive treatments for RA to support trial design, implementation, and enrollment, as well as ultimately for delivery of preventive interventions in clinical care. Therefore, we performed the Research Participation Influences (RPI) study to evaluate the decision-making strategies and considerations that led people to either agree or decline to participate in a real-life clinical trial of prevention of RA.

PATIENTS AND METHODS

Study context. We developed a mixed-methods survey to collect decision-making influences from individuals who were eligible for a double-blind placebo-controlled clinical prevention trial for RA of hydroxychloroquine (HCQ). The prevention trial was conducted at University of Colorado and multiple study sites within the United States (Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis [StopRA]; ClinicalTrials.gov identifier NCT02603146; sponsor National Institutes of Health and the National Institute of Allergy and Infectious Diseases) (6). Study randomization ended November 2021. Individuals were screened for this trial in rheumatology clinics and health fairs; in addition, we offered screening to individuals who were first-degree relatives (FDRs) of patients with established RA. All participants consented for initial testing for a version of ACPA anti–cyclic citrullinated peptide (anti-CCP3) (Inova Diagnostics Inc.). Following testing, individuals who were positive for anti-CCP3 at two or more times the normal cutoff (ie, ≥40 units) without IA and who otherwise met inclusion criteria were eligible to participate in the clinical prevention trial.

Study population. The RPI study was conducted at the University of Colorado site to harnesses the unique opportunity to learn about preferences regarding preventive clinical trials and interventions from those who were eligible by being directly at risk for developing RA. The individuals who participated in the RPI study had already decided whether or not to participate in a clinical prevention trial (StopRA) after being informed that they were anti-CCP–positive and had undergone a process of informed consent for the prevention trial that included a description of their estimated risk for future RA (for the trial, >50% risk of developing RA within 3 years) (6), the study design and intervention (HCQ versus placebo for 1 year, with 2 years of follow-up after that for a total duration of ∼11 in-person visits over 3 years and additional intermittent telephone assessments, with compensation provided for in-person visits), risks and potential benefits of the intervention, and other aspects of the study (eg, blood draws). After each individual underwent the consent process and agreed ("enrollees") or declined ("nonenrollees") to participate in the clinical prevention trial, they were invited to participate in the separate RPI study, which explored the reasons for their decision. Furthermore, all individuals who agreed to participate in the RPI study provided either written or verbal informed consent that was specific for the RPI study (a waiver of written consent was granted by the Colorado Multiple Institutional Review Board for participation over the phone), which included a description of the study and participation requirements. The RPI study began enrolling in 2016 and ended when the last participant was randomized for the clinical trial.

Study assessments. The RPI survey collected limited demographic information (age, sex, education, household income) with no personal identifying characteristics and a series of Likert scale questions that asked participants to rate 11 potential influences on decision-making (0 = not at all; 4 = very much). These potential influences, identified from a literature review of influences on participation in other prevention trials and refined in a pilot phase of this study, revolved around benefit to self and others, time, education, feelings of morality, risk, and study medication. The survey differed in how these Likert scales and the follow-up questions were framed; for enrollees, the questions were framed as influences in the "decision to participate" in the trial, and for nonenrollees, the questions were framed as influences in the "decision not to participate" in the trial. The survey also asked two open-ended questions; one asked individuals to explain why they decided to get their blood tested for anti-CCP, and another asked if they wished to list a reason that was not covered by the Likert scales that most influenced their decision on clinical trial enrollment. Surveys were completed in person, over the phone, or via online survey software (15). When completed over the phone, study staff would record the participant's words verbatim, without paraphrasing or substituting. Of note, there was an initial version of the survey that

was provided to the first 10 RPI participants (six enrollees, four nonenrollees); however, after early review, the Likert scale questions were revised to better capture responses, although the open-ended questions were not changed; as such, for quantitative analyses of the Likert scale responses, these initial 10 participants' responses were excluded. A copy of the survey is included as Supplementary Figures 1 and 2.

Ethical considerations. The RPI study was approved by the Colorado Multiple Institute Review Board (COMIRB #15-2295).

Statistical analyses. Comparisons between the enrollee and nonenrollee groups by their demographics were made using chi-square tests and *t*-tests, as appropriate. Differences in Likert scale responses by enrollees and nonenrollees and FDRs and non-FDRs were assessed using chi-square tests or Fisher's exact tests when group size was less than five. We also compared the Likert responses by FDR status, regardless of enrollment status, using logistic regression to allow evaluation of what specific factors might be different between FDRs and non-FDRS and potentially associated with higher enrollment among FDRs. Likert scale responses were assessed as dichotomous variables comparing any influence (survey responses of "a little," "somewhat," and "very much") to no influence (survey responses of "not at all" and "no opinion"). Analyses were performed using SAS 9.4 (SAS Institute, Inc.).

Qualitative analysis. Open-ended responses were transcribed, and content analysis was conducted, in which initial categories were developed by one author (CF) and then narrowed through continuous review of the responses and discussion among the research team. After developing, organizing, and assigning categories among the text into more generalized themes, meaning units were specified and counted; one meaning unit is counted as one instance of that category being mentioned (16). Meaning units were quantified to allow for the use of descriptive statistics of occurrences. Any discrete line of text can have a number of categories identified and thus multiple meaning units assigned.

RESULTS

Seventy individuals (39 enrollees and 31 nonenrollees) consented to the RPI study and completed a survey. A comparison of the characteristics of the participants is shown in Table 1. There were no statistically significant differences in age, sex, education, or income between enrollee and nonenrollee groups; however, a higher proportion of enrollees reported having an FDR with RA compared with the nonenrollees (54% vs. 23%, $P = 0.01$).

There were several significant differences between enrollees and nonenrollees in quantitative analyses of Likert responses (Figure 1). Enrollees were more likely than nonenrollees to endorse the following factors as influential to their decision to participate in the clinical trial: 1) benefits to the individual (themselves and their health), their family, and others; 2) their personal risk of developing RA; 3) potential positive effects of trial medication; and 4) a desire to learn about RA. In contrast, nonenrollees were more likely than enrollees to endorse the potential adverse effects of the trial medication as an influence in their decision to participate in the trial. There were no significant differences between enrollees and nonenrollees in how issues of "time to participate" and "compensation offered" influenced the decision to participate. We found similar results when we evaluated the dichotomous Likert responses in regression analyses (Supplementary Figure 3).

Because FDRs were significantly more likely than non-FDRs to enroll in the clinical trial (Table 1), we compared the Likert responses by FDR status, regardless of enrollment, to evaluate if these two populations (FDRs vs. non-FDRs) reported different influences (Figure 2). In these analyses, there was a significantly smaller proportion of FDRs who endorsed being influenced by the potential adverse side effects to the study drug compared to non-FDRs (52% vs 81%, $P = 0.01$). In addition, although not statistically significant, there was a larger proportion of FDRs who indicated they were influenced by the potential benefit to family compared to non-FDRs (83% vs. 46%, $P = 0.06$) and a smaller proportion of FDRs who indicated they were influenced by the potential to be assigned a placebo compared to non-FDRs (27% vs. 62%, $P = 0.09$). However, these differences became significant in regression analyses assessing dichotomous Likert variables (Supplementary Figure 4).

Specific meaning units, which are single occurrences of a category, are listed in order of highest frequency to lowest in Table 2 for the question pertaining to why a participant underwent anti-CCP testing and in Table 3 for the question pertaining to additional factors not included in the Likert questions that influenced participation in the clinical trial. A list of the relevant themes from the analysis of open-ended quetsions is shown in Table 4.

Regarding the responses to the question pertaining to why a participant underwent anti-CCP testing (Table 2), among the enrollees, there were prominent themes of "support for research and RA prevention," acknowledgment of "personal risk of RA," and a "family history or familiarity" with RA. In contrast, in the nonenrollees, there were prominent themes of "convenience/ease" of getting tested and the desire for monitoring of "joint symptoms and obtaining access to care." Of the 31 nonenrollees, 11 participants (36%) mentioned initially taking the test because it was free and/or offered to them conveniently while they were already having their blood drawn for other health tests.

Participants in both groups mentioned "perceived risk of RA high" themes among their influences for getting tested (Table 2), but only the nonenrollees displayed a theme of "perceived risk of

Table 1. RPI study participants

Characteristic	Enrollees	Nonenrollees	*P*
Number of participants	39	31	
Age, mean ± SD	52.0 ± 13.8	57.8 ± 14.2	0.09
Female, n (%)	29 (74.4)	25 (80.7)	0.53
Any educational degree (includes associate's, bachelor's, master's, doctorate), n (%)	29 (74.4)	21 (67.7)	0.54
Annual income >$50,000, n (%)	21 (63.6)	15 (75.0)	0.55
First-degree relative with RA, n (%)	21 (53.9)	7 (22.6)	0.01

Note: Seventeen participants did not complete income data.
Abbreviations: RA, rheumatoid arthritis; RPI, Research Participations Influences; SD, standard deviation.

RA low" in their responses to the question of what influenced them to enroll or decline prevention trial participation (Table 3). The theme of "aversion to taking medication or worry of medication side effects" only occurred among nonenrollees; furthermore, a preference for natural remedies or diet changes was mentioned more frequently by nonenrollees.

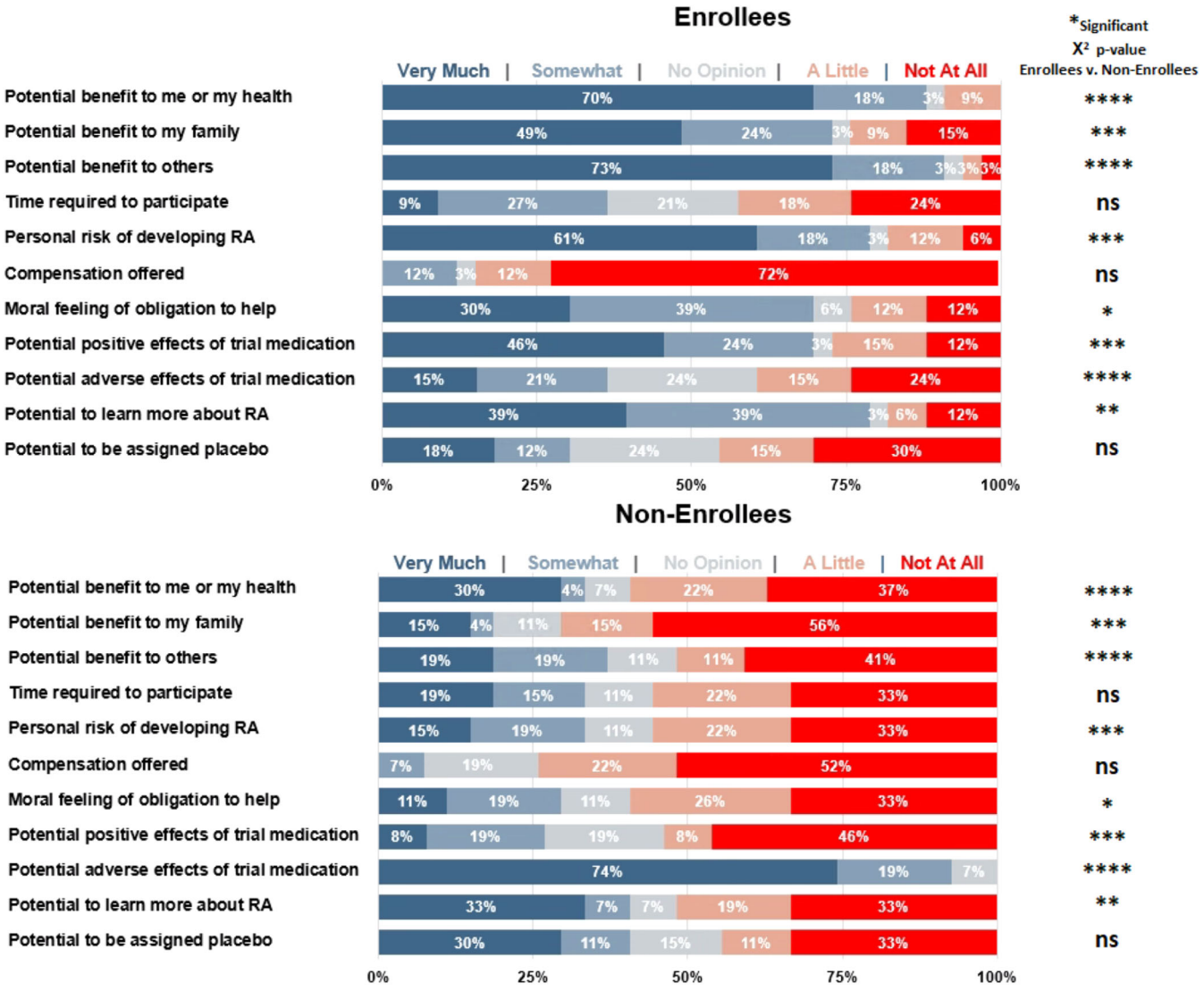

Figure 1. Likert question responses among enrollees and nonenrollees. Percentages of enrollees' and nonenrollees' indicated influence for given Likert scale questions are shown in stacked bars. Asterisks denote a significant difference in the proportion of enrollees' compared to nonenrollees' degree of influence for the given Likert scale questions as follows: ns (nonsignificant), *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$. RA, rheumatoid arthritis.

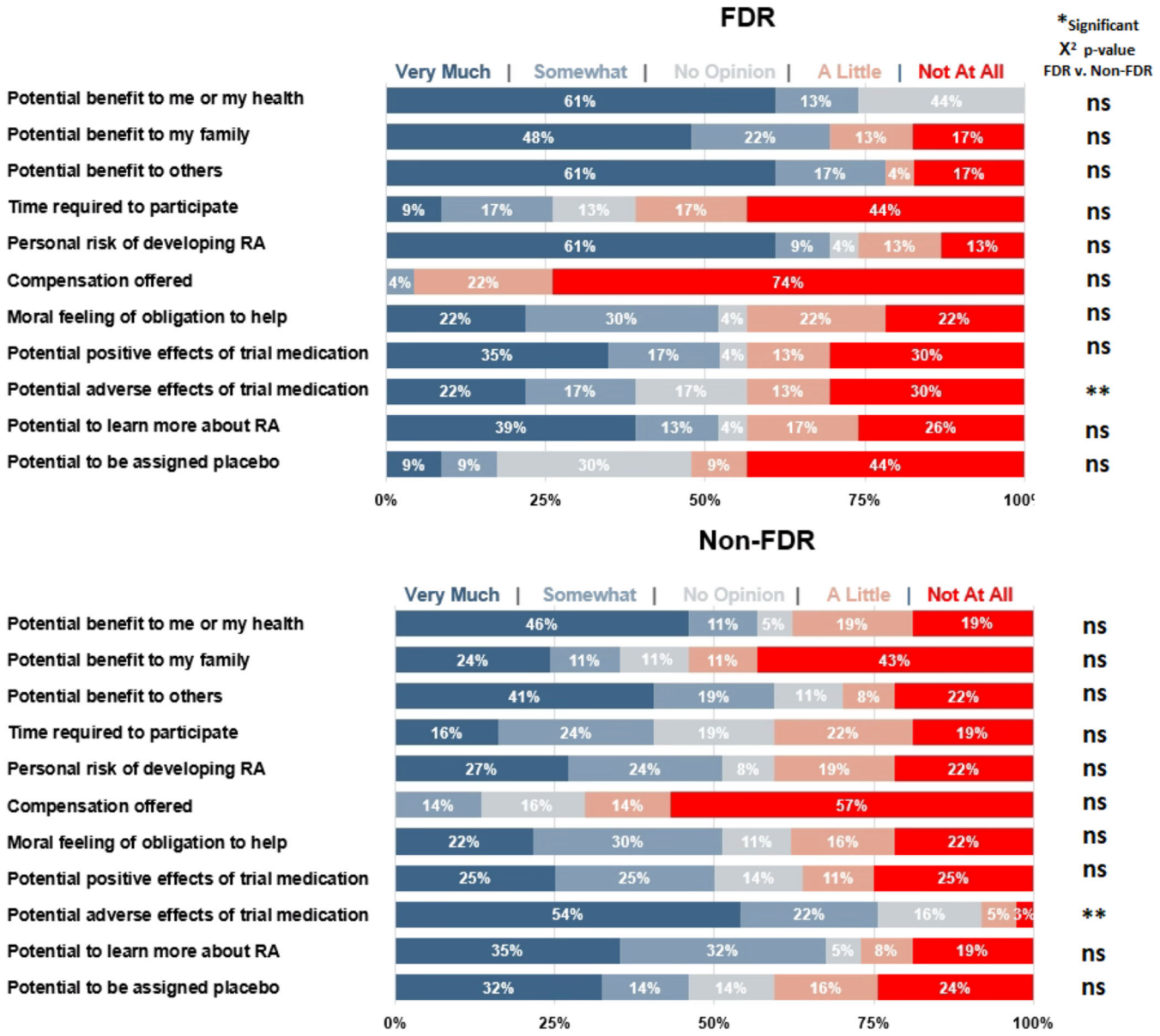

Figure 2. Likert question responses of first-degree relatives (FDRs) and non-FDRs. Percentages of FDRs' and non-FDRs' indicated influence for given Likert scale questions are shown in stacked bars. Asterisks denote a significant difference in the proportion of FDRs' compared to non-FDRs' degree of influence for the given Likert scale questions as follows: ns (nonsignificant), *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$. FDRs are less likely to be influenced by the potential adverse effects of the trial medication ($P = 0.01$). RA, rheumatoid arthritis.

In comparing responses to both open-ended questions, the theme of wanting access to care or monitoring of potential symptoms contributed as a motivator for getting initial blood testing but was not indicated for enrolling in the clinical trial. In contrast, although individuals reported a trust and familiarity with research and wanting to support RA research through participation, these influences were diminished by apprehension relating to study medication or a potential vulnerability associated with becoming a research participant. Multiple enrollees pointed to their awareness for developing RA based on anti-CCP positivity as a significant reason for enrollment in a clinical prevention trial, yet multiple nonenrollees noted that they felt fine otherwise.

When open-ended responses were evaluated in the context of FDR status, there were only mentions of family history playing a role in their participation decision among enrollees. In addition, mentions of FDR status co-occurred frequently among enrollees with mentions of first-hand experience with RA. These categories co-occurred enough that they were placed into the same theme of "family history or experience with RA" and could include terms such as "really bad" or "suffered" and were often mentioned in the same sentence with the "support research or prevent RA"

Table 2. Content analysis from survey question: "In your own words, why did you decide to come here today to be screened and have your blood tested?"

Themes	Enrollees n = 39	Nonenrollees n = 31	Total meaning units
Support research or prevent RA	18	6	24
Personal risk of RA	13	4	17
Family history or experience with RA	11	2	13
Trust, familiarity, or physician recommendation	8	9	17
Convenience or ease	7	13	20
Joint symptoms or care access	6	11	17
Perceived risk of RA high	6	5	11
Learn more or increase awareness	6	3	9
Other autoimmunity or health concern	3	0	3
Perceived risk of RA low	0	5	5
Aversion to medication or worried about side effects	0	4	4
Natural remedies preferred	0	1	1
Vulnerability or inconvenience	0	0	0
Distrust or negative research experience	0	0	0

Abbreviation: RA, rheumatoid arthritis.

theme. Furthermore, "family history or experience with RA" produced 11 meaning units among the enrollee responses as they explained why they initially had their blood tested for anti-CCP (Table 2). All six nonenrollees who reported being FDRs stated reasons for not enrolling, which in general related to concerns about the impact of treatment on their mental or physical health or a dislike of taking a medication that they either did not like or did not feel they needed (Table 4).

DISCUSSION

The RPI study has provided insights into the preferences for participation in a prevention trial for RA in individuals who are known to be positive for anti-CCP and who have been presented with the opportunity to participate in a clinical prevention trial.

We have identified that being an FDR of someone with known RA can have a significant influence on the decision-making process about enrolling in a trial of preventive treatment, and indeed there were significantly more FDRs among those agreeing to participate in the clinical trial. This may be due to an FDR being more aware of what RA is and its potential complications, including potential side effects of the medications. FDR status may also influence an individual's perception of their personal risk for RA as well as the risk for other members of their family, making participation in prevention trials more likely. In addition, from the open-ended questions, it also appeared that if someone knew about RA from a personal experience, even if they were not an FDR, this positively influenced their decision to participate. These findings are in line with other published work in which FDRs express interest in assessing their personal risk for RA (17) as well as an awareness of both the impact of RA and treatments (18). These issues will need further investigation but raise the point that to optimize enrollment in RA prevention studies, an important target participant group will be FDRs. Furthermore, these findings also

Table 3. Content analysis from survey question: "Is there a reason not listed in the chart above that most influenced your decision to decline/participate in the clinical trial?"

Themes	Enrollees n = 39	Nonenrollees n = 31	Total meaning units
Support research or prevent RA	6	1	7
Trust, familiarity, or physician recommendation	6	1	7
Perceived risk of RA high	2	1	3
Personal risk of RA	1	1	2
Family history or experience with RA	1	1	2
Convenience or ease	1	0	1
Learn more or increase awareness	1	0	1
Aversion to medication or worried about side effects	0	18	18
Perceived risk of RA low	0	6	6
Vulnerability or inconvenience	0	6	6
Natural remedies preferred	0	4	4
Distrust or negative research experience	0	3	3
Other autoimmunity or health concern	0	1	1
Joint symptoms or care access	0	0	0

Abbreviation: RA, rheumatoid arthritis.

Table 4. Themes derived from open responses to Q5 and Q7a

Theme	Description	Significant statements
Trust or familiarity or physician recommendations	Anti-CCP testing or study enrollment recommended by health provider, previous positive research relationship, general familiarity with clinical trial research or institution	"Doctor recommended the study" "Have been coming in to the…study for 15+ years" "was doing a lot of clinical trials on campus"
Distrust or negative research experience	Previous negative research experience, mistrust of institution or maker of trial medication	"I was offered a placebo trial in college and it was poorly handled"
Learn more or increase awareness of RA	Seeking an inside look or deeper understanding of RA or emerging research and treatment options	"to learn more about RA prevention" "was just curious about the CCP test and the study" "to see if this is normal or not"
Family history or experience with RA	Having a direct relative, friend, or other person in their lives with RA; witnessing someone suffering with RA; recognizing symptoms of RA; other personal experience with RA	"I understand RA is a difficult disease" "my mother had severe RA" "relatives with RA so I know a bit about it"
Joint symptoms or care access	Favor access to care or monitoring of joint symptoms via research, having joint pain influenced decision, opportunity to learn more about their own health	"this was an opportunity to monitor (pain in my knees)" "concerned about my health" "was having some symptoms…and didn't know if I had RA"
Support research or prevent RA	Support the prevention, treatment, or cure for RA; want to prevent others from suffering with RA	"happy to assist in advancing knowledge to help others in the future" "if I can help prevent (RA) for me or others"
Other autoimmunity or health concerns	Existing autoimmunity or other health complications that take priority	"…screened for CCP because I have Sjogren's" "I have type 1 diabetes"
Convenience or ease	Easy, convenient, free to get tested or enroll; asked at health fair to add on to existing blood draw	"at health fair, I was in line…asked if I would be willing to do a RA blood test" "so I just thought, well why not"
Vulnerability or inconvenience	Unwillingness to be a research subject or don't have time in life to participate	"I live 4 hours away" "didn't want to be a guinea pig"
Aversion to medication or side effects	Negative perception of trial medication; indication that they don't know enough about it, worried about adverse side effects or taking medication unnecessarily	"I don't want to take meds" "adverse effects of the trial medication were the biggest factor for me" "don't want to take a medication for something that I don't have"
Natural remedies	Prefer use of supplements, diet changes, exercise to lower Anti-CCP levels or otherwise reduce risk of RA	"would rather be able to control it myself with changes to diet and exercise" "prefer holistic"
Weighing personal risk of RA	Worried about risk of RA based on family history, chose to get screened based on family history, want to prevent damage or health decline within themselves	"I am at high risk for developing RA" "history of RA has always been a worry in the back of my mind" "want to be proactive in monitoring my RA possibility"
Weighing risk based on anti-CCP test results		
Perceived risk high	Unexpected anti-CCP test results and worried about associated risk, want to take action	"since (CCP) was three times normal limit I was willing to enroll"
Perceived risk low	Willing to wait to see if anti-CCP level lowers without medication intervention	"didn't want to take it unless I was sure I was going to get RA"

Abbreviations: CCP, anti-cyclic citrullinated peptide antibody; RA, rheumatoid arthritis.

suggest that educating individuals about RA as a disease and its impacts on daily life, as well as the specifics of a trial including the potential risks and benefits of a specific intervention, may be a critical part of the implementation of prevention trials in RA, especially if individuals who may not have personal knowledge RA are recruited.

The perception of personal risk for RA was an important factor in deciding to participate in the clinical trial. Importantly, an additional theme identified was that the presence of existing joint symptoms influenced decisions to participate in the clinical trial, with some participants mentioning declining participation in the clinical trial because they "felt well." These findings are in part similar to what has been seen in prior studies; however, symptoms in RA development are complex (19). They may indicate that an individual is closer to developing clinically apparent RA, with some models finding that the presence and degree of symptoms plus autoantibodies is associated with the highest risks for imminent progression to clinically apparent IA and RA (20,21). In addition, an individual's symptoms may also drive their perception of their risk for future RA as well as drive their willingness, even if in the context of a clinical trial, to take a medication to reduce risk or improve their symptoms (13). However, the absence of joint

symptoms may not indicate that an individual is not still at risk for future IA or RA, especially if other risks, such as autoantibodies, are present. With these issues in mind, recruitment approaches for clinical prevention trials in RA will need to address education needs of participants about the best estimates for their personal risk for future RA. Given the importance of current joint symptoms in individuals' decisions to participate in a clinical prevention trial found herein as well as in published work (13), education should also include explanation of how symptoms may influence risk for RA and how those symptoms may be addressed within a clinical trial. Furthermore, there may need to be an opportunity for individuals to reconsider decisions to participate in prevention studies. Moreover, because some responses identified in the RPI study indicated that individuals were using their personal levels of anti-CCP to make their decisions (eg, if an anti-CCP level went down, a participant used that as rationale to decline participation in the trial), education, when possible, should include a discussion of specific anti-CCP levels and personalized risk for RA with this following published work in which individualized personal risk disclosures and education led to increased motivation to change health behaviors (14).

We also noted an aversion to taking a trial medication among those who declined enrollment. This issue appeared to relate to the potential toxicity of a medication as well as a balance of risk–benefit in which some individuals may have been more willing to take a medication if they had a higher risk for future RA—a finding that is similar to other published work in assessing individuals' preferences for participation in RA prevention (11). The issue of how to address individuals who are averse to a pharmacologic intervention is complex and includes their perception of their personal risk of disease as well as risks and benefits of a potential intervention. Furthermore, there are ethical standards to uphold in fully disclosing potential risks and benefits of an intervention, with these discussions being challenging in prevention trials in which the full risk of future disease is not known and neither is the benefit of the preventive intervention in mitigating this risk. This will need further study to find the right balance to optimize recruitment into prevention trials, but at the least it will need to be addressed by careful and balanced education of participants—a factor that can also address issues around the importance in decision-making of trust in the investigators as well as the research institution, which also emerged from our investigations herein. In addition, it may be that in the broader scope of RA prevention, there should be multiple offerings for at-risk individuals that can include pharmacologic as well as potential lifestyle interventions to meet the needs of the greatest number of at-risk individuals.

Notably, the open-ended questions provided participants the opportunity to explain why they initially underwent testing for anti-CCP, and what additional factors may have influenced their decision to participate in the clinical trial. An important finding that emerged from the nonenrollees was that there were initial motivations to get tested for anti-CCP, such as convenience of testing and potential access to joint symptom monitoring, but then other factors, such as perception of low personal risk for future RA as well as aversion to pharmacologic therapy, impacted their decision to not participate in the clinical trial. Understanding the issues around initial assessment of risk for future RA and then actual participation in a clinical trial will be important to explore more deeply in the future to optimize both initial testing to identify risk and participation in the actual clinical intervention trials.

There are some limitations with the RPI study. First, we used a survey to assess influences on participation as opposed to a semistructured interview; we took this approach to gather a broad range of responses, but in the future, a semistructured interview may produce additional detail on decision-making processes, and these types of approaches are planned for the future. Second, this was a single-center study, and in the future, assessing a broader range of individuals may provide additional insights into preferences for participation in a prevention trial. Third, there were likely some details missed by using a Likert scale rating rather than an interview, but we felt this limitation was less negatively impactful than the burden of a full interview on an individual who had just been told of their risk for RA and who simultaneously had to make a decision on participation in a prevention trial. Fourth, because the parent trial recruitment in part focused on FDRs because of their elevated risk for RA, it is possible that there was a bias toward a higher number of FDRs agreeing to the trial and to the RPI study. Finally, as discussed above, the degree of symptoms and actual anti-CCP levels may have an association with personal perceptions of risks of RA, benefits of participation in a trial, and ultimately enrollment and nonenrollment, and these will need to be explored more in future studies.

In conclusion, these findings provide useful information around individuals' decision-making around participation in a clinical prevention trial in RA, with particular identification of the importance of FDR status in decision-making. Given that the area of prevention is growing in RA as well as other autoimmune diseases, including systemic lupus erythematosus and type 1 diabetes (22,23), these findings can inform developing trials as well as serve as basis for future studies that can learn more about the influences on decision-making in participation in clinical prevention trials.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Deane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Fleischer, Bemis, Deane, Harrison, Striebich.

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