

ORIGINAL RESEARCH

How to enhance recruitment of individuals at risk of rheumatoid arthritis into trials aimed at prevention: understanding the barriers and facilitators

Laurette van Boheemen ¹, Marieke M ter Wee,^{2,3} Bart Seppen,¹
Dirkjan van Schaardenburg ^{1,4}

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¹Rheumatology, Reade, Amsterdam Rheumatology and Immunology Center, Amsterdam, North Holland, The Netherlands

²Epidemiology and Data Science, Amsterdam Public Health, Amsterdam UMC Location VUmc, Amsterdam, The Netherlands

³Rheumatology and immunology, AI&I, Amsterdam UMC Location VUmc, Amsterdam, The Netherlands

⁴Rheumatology, Amsterdam UMC Location AMC, Amsterdam, The Netherlands

Correspondence to

Dr Laurette van Boheemen;
l.vanboheemen@
amsterdamumc.nl

ABSTRACT

Objectives Several trials to test the efficacy of a pharmacological intervention aimed at primary prevention of rheumatoid arthritis (RA) are ongoing or have recently been completed. A common issue in these trials is the severe difficulty with patient recruitment. In order to enhance recruitment, this qualitative study identified barriers and facilitators of individuals at risk of RA to participate in a prevention trial.

Methods Individuals at risk of developing RA (ie, arthralgia with anticitrullinated protein antibodies and/or rheumatoid factor without arthritis), who had previously been asked to participate in a prevention trial, participated in focus group discussions (n=18) exploring their facilitators and barriers for trial participation. Thematic analysis identified factors that were important in at-risk individuals' decision about trial participation.

Results The prospect of personal benefit, the acknowledgement of one's symptoms and the desire to contribute to society facilitated trial participation. In contrast, misconception about what it means to be at risk, or about the aim of the prevention trial, negative views on trial medication, and a low perceived urgency to act on the possibility of developing RA versus a high perceived burden of participating in a trial discouraged participation.

Conclusions To enhance inclusion in trials aimed to prevent RA, the results suggest to use strategies such as optimising education about RA, personal risk, trial aim and trial medication, explicitly addressing misconceptions and concerns, using tools to improve information provision, limiting study burden in trial design and encouraging physicians to mention trial participation.

INTRODUCTION

Early diagnosis and rapid intervention improve clinical outcomes in patients with rheumatoid arthritis (RA). This has led to the initiation of RA treatment in ever earlier phases.^{1 2} Moreover, the recognition of a preclinical or at-risk phase of RA provides an

Key messages**What is already known about this subject?**

- ▶ Several clinical trials to prevent rheumatoid arthritis (RA) in high-risk individuals have been performed or are ongoing. A common theme in these prevention trials is that they encounter(ed) severe difficulties in achieving their recruitment aims.

What does this study add?

- ▶ This study identifies facilitators and barriers for prevention of trial participation in persons at risk of RA.

How might this impact on clinical practice?

- ▶ Strategies to enhance recruitment should focus on optimising education about RA, personal risk, trial aim and trial medication, using tools to improve information provision, limiting study burden in trial design and encouraging physicians to mention trial participation.
- ▶ Improved recruitment of individuals at risk of RA into trials aimed to prevent RA onset may eventually help to reduce the overall RA disease burden.

opportunity for pharmacological intervention before clinical arthritis onset, aimed at primary prevention.³ The at-risk phase is a period of disease development before clinical arthritis onset, where characteristic symptoms and biomarkers are often already present.⁴ Using such characteristics, high-risk individuals can be identified for preventive intervention trials.^{5 6}

Several trials to test the efficacy of a pharmacological intervention aimed at primary prevention are ongoing or have recently been completed.⁷⁻¹³ A common theme in these trials is that they experience severe difficulties with patient inclusion and need(ed) up to 5 years to achieve their recruitment aims, or

failed to reach recruitment aims mainly due to an unwillingness to participate. Yet, successful completion of these trials is pivotal to advance in the field of primary prevention of RA. Therefore, recruitment difficulties have been placed on the research agenda by the recently convened EULAR taskforce on conducting clinical trials and observational studies in individuals at risk of RA (manuscript in preparation). The difficulty to include at-risk individuals in RA prevention trials seems in contrast with the large numbers of participants included in relatively short time periods in early RA trials.^{14–17} It may be that at-risk individuals' perceived urgency and preferences regarding treatment are not fully addressed in the current prevention trials. Previous research reported that at-risk individuals' willingness to use preventive treatment was influenced by medication effectiveness and potential side effects,^{18–24} which can be taken into account when selecting a treatment to be tested. In addressing issues of trial recruitment, previous research has tried to identify barriers to patient participation,^{25–26} such as the possibility to be randomised to a placebo, potential side effects of the investigational product and treatment discontinuation at the end of the trial. However, these studies have been performed in patients with RA, and motives and barriers may differ considerably from healthy individuals at risk of RA. It is necessary to better understand the motives of at-risk individuals when making a decision about trial participation. In order to help overcome barriers for participation in prevention trials, this qualitative study identified barriers and facilitators of individuals at risk of RA to participate in a trial for medication to prevent RA.

METHODS

Participants and study design

Individuals at risk of developing RA who had previously been asked to participate in a clinical trial of medication to prevent RA were asked to participate in a focus group discussion (FGD) exploring their facilitators and barriers for trial participation. At-risk individuals were patients with arthralgia ≥ 18 years old with anticitrullinated protein antibodies (ACPAs) $>3\times$ the upper limit of normal or both ACPA and rheumatoid factor (RF), with no history of clinically diagnosed arthritis. Their risk was calculated as 55% risk of RA within 3 years.²⁷ Between November 2015 and January 2019, they were asked to participate in one of two prevention trials: the STATins to Prevent Rheumatoid Arthritis (STAPRA) trial,¹⁰ and the Arthritis Prevention In the Pre-clinical Phase of RA with abatacept (APIPPRA) trial.⁷ In case of being eligible for both trials, patients were first offered the STAPRA. Both trials were a multicentre, randomised, double-blind, placebo-controlled clinical trial to study the effect of temporary use of medication on RA prevention. The STAPRA trial investigated atorvastatin 40 mg daily for 3 years, and the APIPPRA study investigated subcutaneous abatacept 125 mg weekly during 1 year. Participant eligibility criteria were the same for both trials. All individuals

who participated in a prevention trial (n=60) and all individuals who declined trial participation but consented to registration of their contact information (n=63) were invited by email to participate in the focus groups. FGD participants were scheduled for the FGDs in order of first availability and data were gathered until saturation was reached, meaning no new themes or explanations emerged. Each focus group included individuals who had participated as well as individuals who had declined participation in one of the trials. The focus groups were moderated by a senior researcher experienced in qualitative research (MMtW). Two researchers (LvB and BS), both with experience in rheumatology research and clinical trials, were present to take notes, but did not engage in the discussion. The discussions were taped and anonymously transcribed. The FGD structure is shown in [box 1](#). In short, several open-ended questions were asked about facilitators and barriers for trial participation and participants discussed their view while the moderator asked in-depth questions for clarification.

Statistical analyses

Thematic analysis was chosen to identify and interpret patterns of meaning across datasets.²⁸ The primary aim was to uncover opinions, motivations and barriers of at-risk individuals to participate in a clinical trial aimed at primary prevention of RA. An inductive approach was applied where code development for themes was directed by the content of the data. Two researchers (LvB and BS)

Box 1 Basic structure of the focus group discussions

General introduction: explanation of the structure and the goal of the focus group discussion and introduction of the researchers involved.

Opening questions

1. Could you introduce yourself and tell us when your joint symptoms first started?
2. How are your symptoms now, compared with when you were approached to participate in the prevention trial? Has there been any change?

Follow-up questions

3. What made you choose to participate or to decline participation in the prevention trial for which you were approached?
4. If we look at all the reasons listed, do you think there are any more reasons missing?

Break

Follow-up questions

5. What do you think of all the reasons mentioned for participating or declining participation in prevention trials? Are there certain reasons that are more important to you than others?
6. Additionally, we would also like to explicate what you, as a patient, need to participate in a prevention trial. What do you think is necessary to ensure that you or others participate in a rheumatoid arthritis prevention trial?

Conclusion of the focus group discussion.

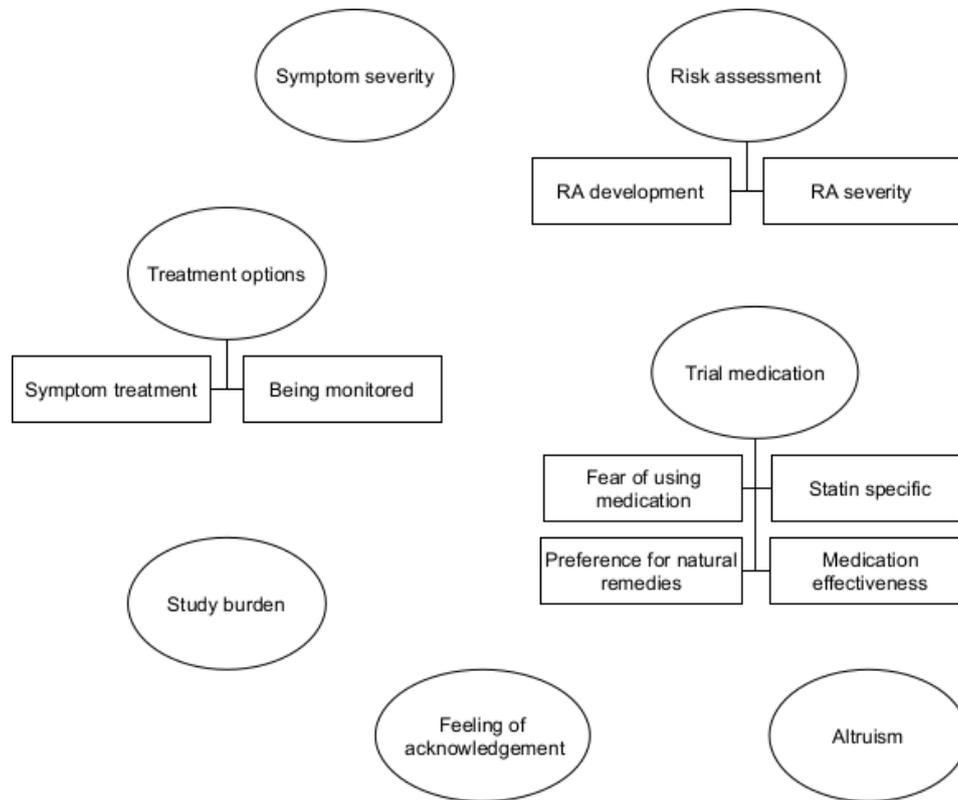


Figure 1 Focus group discussion thematic map. RA, rheumatoid arthritis.

systematically and independently analysed the transcripts to identify relevant themes and subsequently agreed to the same set of major themes during a consensus meeting. Any differences in views were resolved by discussion among the researchers.

RESULTS

One hundred and twenty-two individuals who had been asked to participate in a prevention trial were approached to participate in the FGDs, of whom 33 consented to participate. However, after three focus groups including 18 individuals (six per FGD), data saturation was reached and inclusion was stopped. Of the FGD participants, nine took part in a randomised controlled trial (eight in STAPRA, one in APIPPRA) and nine had declined participation (seven for STAPRA, two for APIPPRA). Mean age was 59 (SD 9) years, and 56% were women. The mean known duration of their antibody positivity was 4 years; 61% were RF positive and 100% were ACPA positive.

Thematic analysis identified seven major themes that were important in at-risk individuals' decision whether or not to participate in a prevention trial: (1) symptom severity, (2) own risk assessment, (3) treatment options, (4) trial medication, (5) study burden, (6) feeling of acknowledgement and (7) altruism. The thematic map is presented in [figure 1](#). [Table 1](#) summarises the themes and the number of quotes per theme and [table 2](#) shows the full quotes.

1. Symptom severity

Many individuals mentioned that the severity of their symptoms played a role in their decision whether or not to participate in a prevention trial. Having no or minor symptoms was considered a barrier since, without symptoms, there would be no personal benefit to trial participation (Q1, Q2). In contrast, severe symptoms were considered a facilitator because individuals hoped that the study medication would resolve their symptoms (Q3, Q4).

2. Risk assessment

Perceived severity of personal risk to develop RA and of RA as a disease played a role in trial rejection or participation.

a. Risk of RA development

A low estimated risk of RA development was considered a barrier for trial participation, while a high estimated risk was considered a facilitator (Q5). Personal risk was estimated to be low in case the overall chances of RA development were considered small or the possibility of being diagnosed with RA seemed a long way off (Q6). Most individuals had difficulty estimating a minimum risk required to participate in a prevention trial. Numbers varied from 60% to 100% (Q7, Q8).

b. Severity of RA

In addition to personal risk of RA development, the estimated severity of RA as a disease played a role in at-risk individuals' decision. Especially those who had nearby experience with RA, for example in family members, considered it to be a serious

Table 1 Overview of the focus group discussion themes

Themes	Examples of reasons mentioned	No of quotes
Trial medication	Fear of medication Preference for natural remedies, for example, supplements or diet Bad image of statins Incomprehension about statin use in RA context Expectations about medication effectiveness	84
Own risk assessment	Estimated risk of imminent RA development and severity of RA	50
Symptom severity	Pain and physical limitations	37
Altruism	Opportunity to contribute to society Preventing others from developing similar symptoms	34
Treatment options	Search for symptom treatment Safety of close monitoring Rapid access to medical care	21
Study burden	Too time-consuming Objectionable study actions	11
Feeling of acknowledgement	Symptoms are taken seriously	7

RA, rheumatoid arthritis.

disease and were more motivated to participate (Q9). Additionally, the way in which individuals were informed about RA (risk) determined how severe they assessed their situation (Q10).

3. Treatment options

Two subthemes on treatment options emerged.

a. Treatment of symptoms

The hope that the trial medication would resolve symptoms was a facilitator for participation. In some cases, trial participation was seen as the final option to treat (pain) symptoms (Q11).

b. Feeling of being monitored

The feeling of being closely monitored by health-care professionals through study visits was seen as a facilitator for trial participation. In case of symptoms progression, appropriate action could be taken, and in contrast to long waiting lists in regular care, trial participation would provide rapid access to expert medical care (Q12, Q13).

4. Trial medication

A negative view on medication, ranging from an overall aversion to medication, to a preference not to use medication unless strictly necessary, was a barrier for trial participation. Four subthemes emerged.

a. Fear of using medication

Some individuals regarded medication in general, or excessive use of medication, as toxic (Q14, Q15). For them to use medication, they needed to be certain of its necessity and effectiveness, and the use of trial medication that still needed to be proven effective was undesirable (Q16). Additionally, individuals mentioned that they did not want to risk having side effects.

b. Preference for natural remedies

Many individuals who viewed the use of study medication as a barrier would rather use natural options,

such as nutritional supplements (Q17). Specifically, in all focus groups there was great interest in the effect of certain diets on RA development and some had personal experience with its beneficial effect on their symptoms (Q18).

c. Statin specific

The main statin-specific barrier was their bad image, causing a reluctance to use them (Q19).²⁹ Additionally, not understanding the rationale for statin use in the context of RA development, resulting in a low expectation of its effectiveness, was a barrier (Q20). Also, the effects of statins on normal cholesterol levels were unclear, leading to a fear that cholesterol levels could become dangerously low (Q21).

d. Medication effectiveness

In contrast, a belief that the study medication could prevent RA development was a facilitator for trial participation (Q22). Some mentioned that they would still participate despite a small probability of efficacy, since they had little to lose (Q23).

5. Study burden

The burden of trial participation was mentioned as a barrier. The main issues were the time investment required to attend all study visits and undergoing certain study procedures, such as venipuncture (Q24).

6. Feeling of acknowledgement

Participation in a prevention trial meant that at-risk individuals' symptoms and worries were taken seriously, which was a facilitator (Q25). Taking part in a clinical trial would justify their symptoms towards themselves and their surroundings (Q26).

7. Altruism

Individuals frequently mentioned altruism as a reason for trial participation. Participation was an opportunity to contribute to society in general (Q27).

Table 2 Focus group discussion participants' quotes

Quote number	Quote	Participant
Q1	'You don't really have a physical reason to do it, because you don't have the pain and you don't have the symptoms.'	3.3
Q2	'Why put something in my body when it's not necessary? With me, it also plays a role that the development [of symptoms] is fairly stable.'	2.2
Q3	Interviewer: 'But I'm just curious, because you have made that choice [to participate in the RCT].' Participant: 'Yeah, because I was in so much pain, I was willing to try anything.'	3.4
Q4	'The chance that I would do it would increase hand over hand if I had severe pain.'	3.2
Q5	'Of course, that plays a role, the chance of getting it. If there is a good chance of getting it, then maybe that's a reason to... [participate in the RCT].'	2.2
Q6	'Yeah, I looked it [information about RA] up online, and yes, then you see how bad it can get, and I think, well, I'm not that far along yet.'	2.2
Q7	'At a risk of 60%, and it running in my family, yes then I probably would have [participated in the RCT].'	2.2
Q8	'It's got to be really, really sure it is necessary (to start preventive medication).'	2.4
Q9	'RA is in my family unfortunately. My mother, my grandmother, they're both gone (...). And the fact that I participate in the medication trial is just like, yes, I've seen what RA can do.'	1.4
Q10	'I really got it as a bad news announcement, you know. And yeah, I thought that it was a pretty intense message. It was also brought like 'You have a serious problem'.'	2.5
Q11	'Yeah, I just wanted to get rid of the pain you know. That's been my motive [to participate in the trial] (...) I had symptoms. You go see a doctor, they can't find anything, but you keep having pain, so you go back to your doctor. You go to the rheumatologist, yeah okay, one [autoantibody] factor then. Well, you keep having pain so you go to an internist, you keep going. The internist does blood tests again and then you're a year further along but you keep having pain. Then you think, okay, now what?'	1.2
Q12	'Well, I actually participated because then I would be closely monitored and I thought to myself, that's a good thing for me too.'	3.5
Q13	'And, of course, what also matters is the accessibility. I mean, if I have pain and I call my GP who refers me to the rheumatologist, I have to wait 6 to 12 weeks and by that time, I'm doing a lot better. So by the time I get to see someone there's nothing left (of my symptoms). Whereas during a trial, I can come right away and someone will see me and that's the only way to get diagnosed.'	3.3
Q14	'I wanted to participate [in the study] but I just didn't dare to take extra medication.'	2.1
Q15	'I already use medication, should I then use extra on top of that? Your liver still has to be able to process it all.'	3.3
Q16	'One reason not to participate is that I find it a little scary to take something when I'm not sure if it even helps.'	1.5
Q17	'If a study were to start tomorrow with natural medication, for example aloe vera, put me at the top of the list! I want to know what effect that has.'	2.4
Q18	'I went for diet. I radically broke with everything I ate before and focused on fruit, nuts, vegetables, fish. No more caffeine, then, bread, white rice, pasta, potatoes. I left all that stuff five years ago. And in 2 months, the rheumatism went away.'	1.3
Q19	'My dad used statins when it hadn't been in the news yet that is was that bad. And when it did get in the news, he quit and he's doing a lot better now.'	2.4
Q20	'Why would I take a cholesterol-lowering drug if I don't have high cholesterol?'	2.2

Continued

Table 2 Continued

Quote number	Quote	Participant
Q21	'I didn't participate because I have low cholesterol levels. Your body doesn't make cholesterol for nothing. So I don't think it's necessary to further decrease it with medication (...). Then there won't be anything left.'	3.3
Q22	'That is the difficulty of research in prevention: what is the chance, that it will be effective? If you say, well, we have to test it but we're fairly sure it works, there is more reason to participate.'	2.2
Q23	'You're always going to get worse if you don't do something.'	2.5
Q24	'Because I am very afraid of needles, so in terms of blood tests, that was very scary. Sometimes eleven, twelve tubes of blood and then I sat there and I thought: gosh, what am I doing?'	3.1
Q25	'I found it very pleasant that attention was paid to me and attention was paid to my feelings of powerlessness about the disease, so to speak.'	1.1
Q26	'I appreciate coming here. And yes, whatever comes out of the test, it's also towards my surroundings: I have something. (...) I've sometimes indicated: Yes, I would like to walk, but I just can't do it today. "Nonsense, you have to move" [they say]. So for me, if I come here, there's something going on. That doesn't mean that I can't move or anything but that I just get a little more recognition for, yeah...'	1.2
Q27	'I participated in the trial because maybe the next generation can benefit from it. So I'm actually helping people for later. It's a matter of attitude.'	1.4
Q28	'Rheumatism is in my family unfortunately. I've seen what it can do. I don't want anyone to have to go through that.'	1.4
Q29	'The rheumatologist already explained a little about the study before I came here.(...)I was able to ask him some questions and he was enthusiastic about it himself. I immediately said yes.'	3.6
Q30	'The chance of me doing it would increase hand over hand if I'm well-informed.'	3.2

Information on participants: 3.3 (F, 55 years, declined STAPRA); 2.2 (M, 57 years, declined STAPRA); 3.4 (F, 58 years, declined STAPRA); 3.2 (M, 54 years, declined STAPRA); 2.4 (F, 43 years, declined STAPRA); 1.4 (F, 58 years, participated in STAPRA); 2.5 (M, 68 years, participated in STAPRA); 1.2 (M, 63 years, participated in STAPRA); 3.5 (F, 52 years, participated in STAPRA); 2.1 (M, 64 years, declined APIPPRA); 1.5 (M, 72 years, declined STAPRA); 1.3 (M, 47 years, declined STAPRA); 3.1 (F, 73 years, participated in APIPPRA); 1.1 (F, 70 years, participated in STAPRA); 3.6 (M, 61 years, participated in STAPRA).

APIPPRA, Arthritis Prevention In the Pre-clinical Phase of RA with abatacept; GP, general practitioner; RA, rheumatoid arthritis; RCT, randomised controlled trial; STAPRA, STATins to Prevent Rheumatoid Arthritis.

Others more specifically wanted to help in preventing others from having to experience similar symptoms (Q28).

Contributing factors

Two additional factors that could not be categorised under any of the themes played a role in the decision whether or not to participate in a prevention trial.

1. Attitude of the physician

The mention of the trial by the individual's own physician inspired confidence and encouraged participation. This also applied to the physician's enthusiasm about scientific research (either the prevention trial specifically or research in general) (Q29).

2. Being well informed

Being well informed about the study encouraged participation. Receiving detailed information about the medication, including possible side effects and anticipated effects on RA development, and about pros and cons of trial participation would help individuals decide to participate (Q30).

DISCUSSION

This study is the first to qualitatively evaluate facilitators and barriers for prevention trial participation in patients with seropositive arthralgia at risk of developing RA. The study revealed several factors that might play a key role in the decision about trial participation, including perceived risk, symptom severity, treatment options and trial medication.

Appropriate recording and reporting of recruitment difficulties can help to understand the challenge and to devise strategies to overcome this problem. The present study identifies several barriers and facilitators in at-risk individuals for participating in RA prevention trials. What stood out in all FGDs was a general reluctance to use medication. Concerns about the general toxicity of medication and about specific side effects of trial medication were prominent. Possible side effects had also been reported by patients with RA as a barrier for participation in trials with novel RA therapies.²⁶ However, in the early RA setting, the perceived necessity of medication

use might outweigh any concerns about potential side effects, while in the at-risk setting, this balance is different, requiring extra attention to be paid to these concerns. Furthermore, in our FGDs there was a strong preference for natural remedies, which is in line with the increasing use of complementary medicine throughout the Western world.^{30 31} In contrast, trial medication was also viewed as a possible treatment for current symptoms, which was a motivator for trial participation. This is in line with research in patients with early inflammatory arthritis, reporting that the prospect of direct medical benefit is a facilitator for prevention trial participation.²⁵ These results emphasise the importance of extensively informing potential participants about the study medication rationale in prevention trials and its potential effects and side effects, taking people's current co-medication into the discussion.

Many participants regarded participation in a trial mostly as receiving treatment for their symptoms rather than a possible treatment to inhibit RA progression. This is interesting since the possibility to reduce personal RA risk was a motivator for trial participation, also in absence of severe symptoms. Considering this, it is critical that people understand the aim of prevention trials, and what it means to be at risk. Research shows that people find it difficult to assess risks and that perceptions of risk differ between individuals based on demographic characteristics, as well as personal experiences with the disease.²⁰ Therefore, it is important to optimise education of at-risk individuals about interpreting personal disease risk in the trial setting.^{23 32} Additionally, the motivation to participate was strengthened by a good understanding of the severity of RA as a disease and what it means to have RA, making this another focus point for education.

Despite the benefit of being monitored, the time commitment of trial participation and undergoing certain study procedures was defined as a barrier, which is in line with previous reports on clinical trial participation.³³ Especially without a perceived urgency for action, as might be the case in the at-risk phase, these objections may impair prevention trial recruitment. Therefore, in designing future trials, it is important to condense study visits and limit invasive procedures. Additionally, the mention of trial participation and a positive attitude towards research by the individuals' own physician can have a positive impact on participation.

Finally, the way information on the study is provided is a point of attention. Despite being informed multiple times both verbally and in writing about the STAPRA or APIPPRA trial, the FGD participants indicated that there was uncertainty about the study aim, study protocol and trial medication, and there was a need for more information before they could make the decision to participate. Previous research on clinical trial recruitment showed that improvement in the way candidates for participation are informed about the study may help trial recruitment.^{21 34} Possible solutions in this setting can be to use visual tools displaying the research aim, study medication

information and study flowchart, as well as repeatedly and actively asking about uncertainties and asking individuals to give a summary of the provided information.

A strength of our study is the inclusion of individuals who were actually approached about prevention trial participation, which may result in more realistic considerations than if prevention trial participation were a hypothetical scenario for the FGD participants. Furthermore, inclusion of both at-risk individuals who chose to participate and who declined participation in one of two prevention trials ensured as much diversified opinion as possible. A limitation is the relatively small group of participants, potentially inducing selection bias and limiting generalisability. However, each focus group had enough participants to ensure an in-depth discussion and after three groups, data saturation was reached and therefore no further FGDs were conducted.

CONCLUSION

Given the tendency to treat RA very early, sometimes even before definitive RA diagnosis, the importance of prevention trials will increase. Therefore, it is crucial to better understand at-risk individuals' motives in order to improve recruitment into preventive trials. The current qualitative study identified several factors that influence the decision about involvement in a prevention trial, such as the prospect of personal benefit, the acknowledgement of symptoms and the desire to contribute to society stimulated trial participation. In contrast, misconception about the aim of the prevention trial or about being at risk, negative views on trial medication, and a low perceived urgency to act versus a high perceived burden of trial participation discouraged participation.

Our results suggest that inclusion of RA-risk individuals can be improved by implementing strategies such as optimising education about personal risk, trial aim and trial medication, explicitly addressing potential participants' misconceptions and concerns, using tools to improve information provision, limiting study burden by condensed trial design and encouraging physicians to mention trial participation. Addressing these factors could facilitate inclusion in trials aimed to prevent RA onset, potentially improving prognosis and reducing overall RA disease burden.

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Patient consent for publication Not required.

Ethics approval The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Ethical Review Board of the VU Medical Center and Reade stated that the focus group discussion (FGD) study was not subjected to the Medical Research Involving Human Subjects Act. All participants signed informed consent before the start of the FGD.

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ORCID iDs

Laurette van Boheemen <http://orcid.org/0000-0003-3168-548X>

Dirkjan van Schaardenburg <http://orcid.org/0000-0003-4006-3762>

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