

# Identifying physician-perceived barriers to a pragmatic treatment trial in rheumatoid arthritis

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## Abstract

**Objective:** The aim of this qualitative research was to identify physician-perceived patient and clinic barriers to patient recruitment in a rheumatoid arthritis (RA) pragmatic trial of anti-tumor necrosis factor (TNF) biologic versus non-TNF biologic/Janus-Kinase inhibitor initiation after an inadequate response to methotrexate.

**Methods:** Semistructured telephone interviews were conducted with 26 rheumatologists in March 2019. An exploratory thematic analysis approach was used to analyze the interview data.

**Results:** Physician perceived patient barriers to the implementation of an RA pragmatic trial. This theme covers three subthemes: (1) patients' personal barriers, (2) patients' treatment-related factors, and (3) trial-related factors (eg, patient recruitment, side effects, mode of use, etc). Physicians perceived clinic barriers interfered with the pragmatic trial enrollment from the clinic or the healthcare system perspective. This theme covered four subthemes: (1) clinic-related factors, (2) patient-related factors, (3) research personnel, and (4) facilitators (positive factors of the clinic).

**Conclusion:** Our results from the inductive thematic analysis will help researchers understand the key patient and clinic/system factors/barriers that may influence pragmatic RA trial implementation. The themes suggest there are factors that can be modified (eg, coordinator effort needed, effective patient recruitment during clinic visits, provider engagement) and challenges to overcome (patient insurance status, busy clinic flow, and space issues including limited number of patient rooms). In summary, these themes provide a basis for our and other research teams to develop clinic-centered and patient-centered strategies to implement a pragmatic RA trial.

**Keywords:** Pragmatic trial, rheumatoid arthritis, barriers

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## Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory autoimmune arthritis.<sup>1,2</sup> Randomized controlled trials (RCTs) comparing new disease-modifying antirheumatic drugs (DMARDs) with placebos have established their efficacy in RA. RCTs are often criticized for limited external validity.<sup>3</sup> Pragmatic studies that assess comparative effectiveness of treatments can provide critical information on how these medications can be used in the real world. Therefore, we need pragmatic studies in heterogeneous patient populations to estimate the treatment effectiveness of DMARDs in RA.<sup>4</sup> Although a few pragmatic trials are conducted since the recognition of this knowledge gap yet more are needed.<sup>5</sup>

Methotrexate (MTX) improves joint pain, swelling, function, quality of life, and prevents progressive joint damage in patients with RA.<sup>6-8</sup> MTX is the first-line therapy in RA. A significant proportion of RA patients show inadequate or no response to methotrexate or have an adverse event (MTX-IR/failure) and need to add or switch to other DMARDs including Janus-kinase inhibitors (targeted synthetic DMARDs) and biologics that either target tumor necrosis factor (TNF) or non-TNF pathways.<sup>9</sup> Pragmatic trials that compared these options to each other after MTX failure are lacking. This critical evidence is needed so that patients and physicians can make treatment decisions among DMARDs including biologics.<sup>10</sup> We aimed to fill this evidence gap by designing a pragmatic trial to compare choices after MTX-IR/failure. For example, a recent pragmatic RA trial showed that among previously treated patients with anti-TNF biologics with inadequate response, a non-TNF biologic was more effective than a second anti-TNF biologic in achieving a good or moderate RA disease activity response.<sup>11</sup> With a focus on patient-reported outcomes including function, fatigue, anxiety, depression, and sleep,<sup>12-14</sup> we designed an RA pragmatic trial of the initiation of TNF biologic versus non-TNF biologic/Jak Kinase inhibitors in RA after MTX-IR/failure. The goal of this qualitative research was to identify physician-perceived patient and clinic barriers to patient recruitment in this RA pragmatic trial.

## Methods

### Sample

We examined a nonprobabilistic purposeful sample of 26 rheumatologists, from clinics across the United States. We used the maximum variation sampling method to understand the patient recruitment barriers from participants with different types of practice, regions, specialty, and clinic characteristics.<sup>15</sup> All participants provided verbal informed consent for the interview, permission to record the interview, and analyze the results at an aggregate level. The Institutional Review Board at the University of Alabama at Birmingham (UAB) approved this study.

### Data collection

Semistructured telephone interviews were conducted by the principal investigator (J.A.S.) with 26 rheumatologists in March 2019.<sup>16</sup> We obtained the clinic and patient characteristics, and trial protocol-related questions (eg, lab monitoring, feasibility of the study, interest in the trial) using multiple-choice or open-ended questions. The key interview questions included "What do you see as the top three patient barriers for enrollment in an RA pragmatic trial of TNF biologic versus non-TNF biologic/Jak Kinase initiation in an RA patient who has failed MTX?" "What do you see as the top three clinic or systems barriers to patient enrollment in the trial mentioned above?" and "Which of these key clinic/patient/system barriers are insurmountable in your opinion?" Each interview lasted about 45 minutes and was recorded and transcribed verbatim.

### Analytic approach

We used an exploratory thematic analysis approach to analyze the interviews. This inductive content-driven approach emphasizes themes and subthemes emerged from the data.<sup>17,18</sup> Researchers with qualitative expertise carefully read transcripts multiple times to gain an overall understanding of the interviews and listened to the audio recordings to verify transcripts by the interviewee. The second step was to generate initial codes using the QSR NVivo 12 Plus (Burlington, MA). Field notes and memos were previously recorded by hand during the transcription verification process and were used to identify the main themes in the coding process. A codebook was developed after coding of first three transcripts independently by two coders. Differences were reconciled through mutual agreement. The average intercoder agreement (Cohen's Kappa) was above 0.90 between the two independent coders.<sup>18,19</sup> The third step was to search for a theme by triangulation. It reduces the information volume, systemically organizes the findings into themes from specific to general, and identifies data patterns and meanings.<sup>17,18</sup> Codes were then developed based on the main thematic areas. Subthemes were organized to reflect concepts and topics pertaining to each of the main themes. Each main theme contained at least one subtheme.<sup>17</sup> In step 4, researchers reviewed themes to discuss any discrepancies until consensus was reached. The research team defined and named themes in step 5.<sup>18</sup>

## Results

Table 1 shows the clinic, patient, and rheumatologists' characteristics, as well as responses to trial-related questions. Among 26 clinics, 58% were general rheumatology (42% had separate RA clinics), 69% were academic-center clinics. The median number of rheumatologists at each potential trial site was 10 with a support staff of 6. The median number of RA patients seen in one clinic per year was 1000 with a median of 10 RA patients per day. The median rheumatologist age was 45 years. Half of the rheumatologists had 6-10 years of clinical practice experience since completing their rheumatology fellowship.

All participants indicated interest in participating in this pragmatic trial. About 77% clinics performed at least one lab monitoring for RA patients. Most participants (73%) thought the plan for the 8-month trial with 28 joint counts was feasible, and 23 participants (88.5%) indicated that there were no other critical barriers than discussed below (Table 1).

In terms of patient-reported outcomes measures, three participants (11%) indicated that

they were satisfied with standard RA measures without additional suggestions. Other suggestions for RA measures are listed in Table 2.

Two main themes were coded, consistent with the research questions identified and included patient and clinic barriers (Figure 1).

### Theme 1: Patient barriers

Physician-perceived patient barriers offer challenges to an RA pragmatic trial. This theme covered three subthemes: (1) patients' personal barriers, (2) patients' treatment-related factors, and (3) trial-related factors (eg, patient recruitment, side effects, mode of use).

#### *Patients' personal factors*

Patients' personal factors, the largest subtheme, included insurance status, language barriers, and travel-related factors. Insurance status and plan was the biggest factor thought to influence patients' medication affordability and thus, trial participation. Seventeen out of 26 (65%) physicians mentioned health insurance as one of the top three patient barriers. Different insurance plans (ie, private commercial plan, Medicare, Medicaid) have different rules for RA medication-switch, when the MTX did not work. This may limit physicians to prescribe only the insurance-preferred new medication. Dr. D stated "let's say they start on one TNF (tumor necrosis factor) and they want to crossover, but their insurance only allows them another TNF, so, they usually make us do two TNFs before being able to move on. ... we have Medicare which is probably about 30-35% of our population." Insurance plans have restrictions and requirements on crossover medications and have different co-pays. Medicare patients accounted for about 30-35% patient population in some clinics, but the medication coverage rules also differed by the region. Dr. Y said, "it can vary according to Medicare secondary. If it is straight Medicare, they are going to an 80/20 split, with that 80/20 split, the cost of the TNF is much less than say Actemra, where it is a much higher, so 20% of you know, I am just going to throw out, it's not \$40 000 but I mean 20% of a \$2000 infusion versus 20% of a \$1000 is more out of pocket for them." Medicaid has restrictions too. Dr. Y explained, "Medicaid doesn't let us have; some insurance companies may let you have it."

Patients with limited English proficiency have communication barriers, which limit trial participation. Clinics across the country serve a different population, such as Hispanic and Asian population in California, and Hispanic population in Texas. Dr. L said, "We do have a

### Main Points

- Successful implementation of rheumatoid arthritis pragmatic trials need to address patient, provider, and clinic-level implementation barriers. Our study identified two main physician perceived themes: patient and clinic barriers. Each with three or four sub-themes.
- Physician-perceived patient and clinic level barriers included health insurance status and type, patient recruitment, patient unwillingness to participate, lost to follow-up, patient preference for one versus alternate treatment, access to clinic and language barriers, and restrictions on medication by health insurance.
- Additional clinic barriers included research coordinator efforts over multiple clinical trial management, budget, the stressed clinical environment and provider engagement in trial.

**Table 1.** Clinic, rheumatoid arthritis provider, patient characteristics, and trial-related questions (N = 26).

Clinic characteristics	N (%)
Clinic characteristic*	
General rheumatology	15 (57.7)
RA specialty	3 (11.5)
Practice characteristic*	
Academic	18 (69.2)
Private	3 (11.5)
Community	1 (3.8)
Region	
Northeast	8 (30.8)
South	8 (30.8)
West	7 (26.9)
Midwest	3 (11.5)
Number of rooms for RA in clinic, median (IQR)	19 (5, 12)
Number of support staff, median (IQR)	6 (4, 10)
Total number of RA physicians, median (IQR)	10 (5, 12)
Total RA patients per year, median (IQR)	1,000 (400, 2,000)
Number of RA patients per day, median (IQR)	10 (8, 20)
Number of RA patients newly started on MTX per month in clinic, median (IQR)	3 (2, 7)
Number of RA patients newly started on MTX per month in entire practice, median (IQR)	10 (5, 21)
Patient characteristics	N (%)
Average patient age (estimate)*	
45-54	10 (38.5)
55-65	8 (30.8)
Patient race/ethnicity*	
White	13 (50.0)
Black	3 (11.5)
Hispanic	5 (19.2)
Asian	2 (7.7)
Patient education*	
≤High school	10 (38.5)
College	11 (42.3)
Patient income (estimate)*	
<\$25k	4 (15.4)
\$26k-\$50k	8 (30.8)
\$51 K-\$100k	7 (26.9)
>\$100k	1 (3.8)
Patient health literacy*	
Low	5 (19.2)
Medium	15 (57.7)
High	2 (7.7)
Patient missed appointment rate*	
Low	15 (57.7)
Medium	8 (30.8)
High	1 (3.8)
Patient satisfaction with care*	
Medium	3 (11.5)
High	20 (76.9)
Patient-physician communication*	
Medium	6 (23.1)
High	17 (65.4)
Patient involvement in decision-making*	
Low	0 (0.0)
Medium	8 (30.8)
High	14 (53.8)
Number of inpatient/number of urgent RA visit*	
Rare	15 (57.7)
Moderate	5 (19.2)

large number of patients that are Spanish speaking. We do have bilingual coordinators, also bilingual physicians but, you know, they may or may not be attracted to (the trial), but we would obviously need to get consent form and other materials in Spanish."

Physicians were also concerned about the travel time for patients. A longer distance from home to clinic might limit patients from visiting clinic regularly. Dr. X stated, "Distance from home to visit us, sometimes they don't want to come as often as we would like."

#### Treatment-related factors

The second subtheme was treatment-related factors, including patients' medical condition and complexity, comorbidities, treatment, and patient outcomes. Patients differ by types and numbers of current medications, and their behavioral and physical health conditions. These factors provided additional challenges for physicians when they identify patients for pharmaceutical trials. Dr. O explained, "Sometimes patients are started on dual therapy, MTX (methotrexate) +HCQ (hydroxy-chloroquine), for a physician not to push dose higher, triple therapy in 25% of my patients." Patients on single therapy are optimal for the pragmatic trial. This makes physicians easy to examine the effects of the medication and adjust another medication if it failed. Dr. K said, "If they have another serious infection with one type of drug, then switch to another drug." Some physicians were concerned that infections lead to discontinuation. Dr. M asked, "If they have infection, can they cross-over to the other arm sooner? They can also drop out, if the other arm has a similar contraindication." Other physicians had different opinions about the comorbidities and thought serious infections are uncommon, "Comorbidities shouldn't be an issue (Dr. L)." One physician was concerned about the influence of some biologics on patients' outcome. Dr. B asked, "If DAS28 (Disease Activity Score in 28 joints) is the outcome measure, how do you measure the outcomes with IL-6 drugs (tocilizumab) that are very effective against C-reactive protein and compare outcomes across groups?"

#### Trial-related Factors

The third large subtheme was trial-related factors and included patient recruitment, preferences, burden, and side effects. Almost all physicians reported patient recruitment as one of the top three patient barriers, including few eligible RA patients (eg, new RA patients), unwillingness in trial participation, patients from different cities, patient identification, other competing study in the clinic limiting

**Table 1.** Clinic, rheumatoid arthritis provider, patient characteristics, and trial-related questions (N = 26). (Continued)

Clinic characteristics	N (%)
High	1 (3.8)
Rheumatologist characteristics	N (%)
Average provider age, median (IQR)	45 (40.5, 50)
Years since Rheumatology Fellowship*	
6-10 years	13 (50.0)
>10 years	9 (34.6)
Number of male versus female physicians*	
Male > Female	7 (26.9)
Male < Female	12 (46.2)
Male = Female	4 (15.4)
Perceived usefulness of shared decision device*	
Low	1 (3.8)
Medium	7 (26.9)
High	3 (11.5)
Trial-related questions	N (%)
Insurmountable barriers*	
No	9 (34.6)
Yes	15 (57.7)
Regular laboratory monitoring of inflammation marker*	
None	1 (3.8)
ESR	1 (3.8)
CRP	3 (11.5)
Both ESR and CRP	16 (61.5)
Feasibility of 8-month trial with 28 joint counts*	
Not feasible or challenge	6 (23.1)
Feasible	19 (73.1)
Recruitment of one patient per month for 28 months*	
No	2 (7.7)
Yes	11 (42.3)
Other critical barriers*	
No	23 (88.5)
Yes	2 (7.7)
Interested in participation of this trial	
Yes, very interested	22 (84.6)
Yes, moderately interested	4 (15.4)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; RA, rheumatoid arthritis.

\*The sum of the percentages is not equal to 100% because of missing values.

patient availability. Dr. R explained, "A lot of time research visits are on nonclinic days, interestingly, even for studies that I am doing it's hard to stop and identify patients in the middle of a busy clinic."

Patient preferences also play an important role in recruitment, such as unwillingness to be randomized, research participation, or strong patient preference for oral therapy versus injection or vice versa. Dr. G said, "Patient preference - They have a strong choice, based on what they want, either the drug or the route." There are different patients, some patients are willing to join the clinical trial. Dr. W explained, "for a lot of people placebo-based trials, it is going to be more, you know people who may not have insurance that are willing to get on a

trial. Since it is a pragmatic trial, they are eligible for any of the biologics is my assumption."

Physicians also reported concern about patient attrition from the study. Patient burden of completing the questionnaire and extra time added to their usual clinic visit time was a perceived barrier. However, some physicians thought committing extra time during usual clinic visits will increase patient participation. Dr. A stated, "Well, it depends on patient not wanting to commit the extra time, they may not see what's in for them."

Medication side effects were also a concern, including gastrointestinal (GI) side effects, upper respiratory infection (URI), and injection site reaction. However, there were mixed opinions on side effects. Some physicians

were worried about the side effects, while, other physicians did not expect too much side effects from the medications in RA pragmatic trial. One physician suggested a solution to cope with side effects. Dr. P explained, "GI side effects, viral URIs are the most common issues with these drugs, hold it for one dose. If Jak kinase, hold for 5 days."

In summary, physicians' perceived patient barriers reflected concerns about insurer requirement, patient preferences and recruitment, trial-related factors, treatment and comorbidities, and available resources to work with patients.

## Theme 2: Clinic barriers

Physician-perceived clinic barriers from the clinic or the healthcare system perspective to RA pragmatic trial enrollment. This theme covered four subthemes: (1) clinic-related factors, (2) patient-related factors, (3) research personnel, and (4) facilitators (positive factors of the clinic) (Table 2).

### Clinic-Related Factors

The clinic-related factors include patient/clinic flow, lack of resources (eg, patient room, infrastructure, and time), ethics committee approval, competing trial/studies, clinical equipoise, and recent changes to a new health care record system (eg, Erosion Productivity Impact Calculator (EPIC)).

A big concern among clinic-related factors was the patient/clinic flow. "Hard to integrate clinical research into the routine clinic flow, not to say it cannot be done, we see patients pretty quickly, in the real world, 20-minute follow-up visit, it will take a little bit more for the patient" (Dr. R). Lack of resources was a close second, including inadequate resources for adequate coordinator time, room and time to do the study, technology, and logistics. Dr. S stated, "Logistics, how it is set up in the clinic. If you had a small shop, it might be a problem for those sites." Within the lack of resources subtheme, the number of rooms for RA patients remained a concern for four participants although the median number of patient rooms in the clinic was 10 (Table 1).

Institution review board (IRB) application and other ongoing studies in the clinic were considered as other clinic barriers. Five participants reported delay in IRB application approval as a barrier to their trial participation. Dr. X said, "We may have competition from another study. Easy to deal with our own IRB. Central IRB was difficult." Participants thought that other trials that they were conducting might compete with the pragmatic trial for

**Table 2.** Suggestions of patient-reported outcomes measures for RA patients.

Measures	N (%)	Measurement scales
CDAI (Clinical Disease Activity Index)	6 (23.1)	Use CDAI instead of Disease Activity Score 28 (DAS-28) (4, 15.4%) or RAPID (Routine Assessment of Patient Index Data) (1, 3.8%)
PROMIS (Patient-Reported Outcomes Measurement Information System)	4 (15.4)	
Pain assessment	4 (15.4)	eg, Catastrophizing pain questionnaire, VAS (Visual Analogue Scale), Widespread pain at baseline.
Depression/anxiety	2 (7.7)	PHQ8 (Patient Health Questionnaire depression scale), Fibromyalgia Impact Questionnaire (FIQ) for patients with Fibromyalgia)
HAQ (Health Assessment Questionnaire)	2 (7.7)	
Short Form 36	2 (7.7)	
Adherence	2 (7.7)	Medication adherence, self-reported measure pill counts for the coordinator.
Mental health assessment	1 (3.8)	No suggestion for a specific assessment
Erosion Productivity Impact Calculator (EPIC)	1 (3.8)	

CDAI, Clinical Disease Activity Index.

patient recruitment. Dr. Y explained, “I have another study that is a bit of a conflict because everybody wants patients with methotrexate exposed and not anything else.”

Clinical equipoise was also considered a clinic barrier. Participants were concerned about the clinical equipoise for patients who will participate in the trial. Dr. P said, “Whole issue of equipoise is we don’t realize that we do not know. Worry that if they are being randomized, they may be harmed by not getting the ‘preferred treatment.’” Two participants reported that recent changes to their electronic health record system (EHR), EPIC, raised some challenges for them to recruit patients, however, other two participants thought the changes would help patient recruitment in this trial. For example, Dr. Y explained, “We had used RAPID-3 (Routine Assessment of Patient Index Data with 3 measures), we have now switched to EPIC and we only got the upgrade to use CDAI (Clinical Disease Activity Index).” However, Dr. T held the opposite opinion and said, “Getting EPIC implemented this weekend, that should be a big plus.”

#### Patient-related factors

Among all patient-related factors, insurance was considered as the key clinic barrier by 12 (46%) participants, including 7(27%) participants who thought that insurance was a barrier for both clinic and patients. As mentioned early in the section of patient barriers, different insurance plans have different requirements or restrictions on the TNF versus Non-TNF biologic versus Jak-kinase inhibitor initiation for RA patients who experienced MTX failure. The variation in patient insurance plans by geography poses different levels of challenges to the clinics. Dr. J, one of the seven participants who

considered insurance as both clinic- and patient-level barrier, explained “Underinsured, probably, I think, 35%-40% of our patients. Medicare would probably be, overall, 60%. Commercial 10%-15%. That is going to be a problem.”

Another patient-related factor was clinic-level recruitment, which was mentioned by 8 (31%) participants, including 4(15%) participants who treated patient recruitment as both clinic- and patient-level barriers. Participants were concerned about patient recruitment because they saw few early or new RA patients, for example, Dr. N said, “Typically, these are early RA patients, very few, not common.” Participants thought that patient randomization might be problematic. Dr. P explained, “Can keep track of who is enrolled in the study but cannot be randomized.” Multiple sites of the clinic might be a barrier to implement the trial. Dr. W said, “We have obviously patients coming from many different sites, so I would have to think about where we would maximize our personnel to be at the site that sees the most of these patients, right?”

#### Research personnel

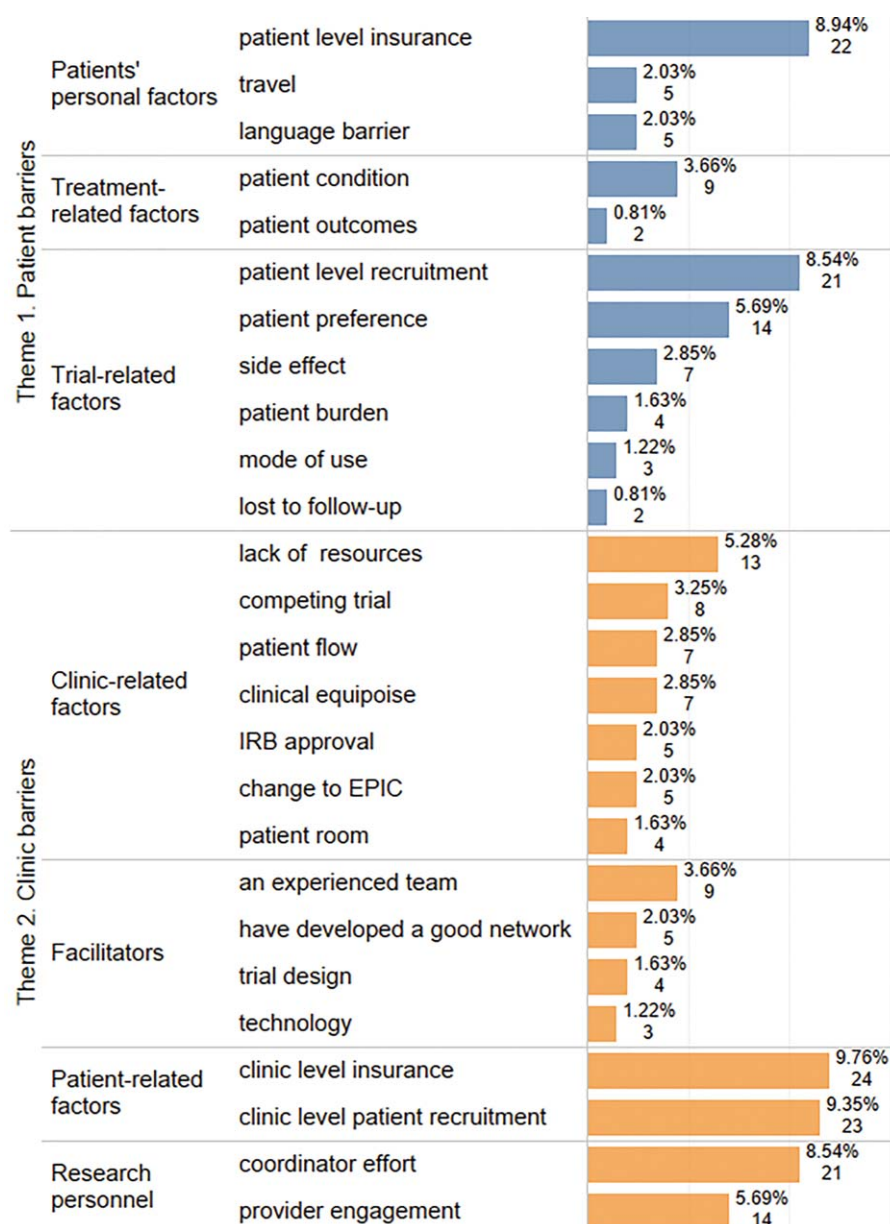
Research personnel was the third subtheme under the clinic barrier theme, including coordinator efforts and provider engagement. Nearly half of participants (46%) reported that coordinator effort was a concern, including a decision on full time versus part-time coordinator, budget for a new coordinator, and coordinators were stretched between several studies. Dr. M explained, “would need coordinator to help with all the paperwork and keeping on track with you guys, that would be my concern. ‘Dr. Y said,’ ...the problem for us is most of the bureaucracy of clinical trials

because we do not have a dedicated clinical trial coordinator.” Another concern was rheumatologist engagement mentioned by 10 participants (38.5%) because they thought that every physician has a busy schedule. Dr. S explained, “I just think everyone is overwhelmed in the clinic, you know, gotten harder and harder to make a living in rheumatology and so, people are squeezing more patients in, so the rate limit taking the time to begin that discussion, we have a clinical research center, your budget is not going to be what we are used to.”

#### Facilitators (Positive Factors)

Although the goal of the interviews was to identify factors that contributed to the patient recruitment in the pragmatic trial, many participants pointed out some positive factors that may facilitate patient recruitment. These positive factors include (1) having an experienced research team, (2) having developed a good network, (3) having technology support, and (4) the trial design rigor. Seven participants were confident that they had an experienced research team, including pharmacists and nurses. Dr. F explained, “We have done 100 clinical trials, we have a full support of our nursing team.” Five participants reported that they have developed a good network of research that can help in trial implementation. Dr. O stated, “in recent years, no RA studies, patient pool is larger and less fatigued than before, mostly PsA (psoriatic arthritis) studies. They trust our coordinators and our research teams.”

In summary, physicians perceived clinic barriers reflect concerns in insurance (eg, proportion of patients with Medicare and Medicaid), influence on clinic routine, coordinator efforts, and provider engagement, and patient



**Figure 1.** Patient barriers and clinic barriers.

recruitment. In addition to barriers, participants also reported some facilitators for trial implementation.

#### Insurmountable barriers

After discussing the top three patient barriers and top three clinic/system barriers, participants were asked which barriers were insurmountable. Nine (35%) participants said there were no insurmountable barriers at their clinic. Fifteen (58%) participants pointed out that 28 barriers were insurmountable, including clinic-related barriers (ie, clinic flow, change to EPIC, IRB), patient-related barriers (ie, insurance, patient recruitment, patient stipend, provider engagement, patient language barriers, and coordinator effort). Among all insurmountable barriers, the leading barrier was patient insurance (7 out of 15 participants, 47%), followed

by patient interest/recruitment (6 of 15, 40%), patient stipend (3 of 15, 20%), provider engagement (3 of 15, 20%), patient language barriers (2 of 15, 13%), coordinator effort (2 of 15, 13%), clinic flow (2 of 15, 13%), change to EPIC (7%), and the IRB (7%).

#### Discussion

Pragmatic trials address the limitations of the traditional RCTs in terms of participants and intervention types.<sup>20</sup> Pragmatic trials have broad eligibility criteria and use simplified data-collection and protocol (eg, crossover, nonadherence, and loss of follow-up).<sup>21,22</sup> The design characteristics make pragmatic trials similar to routine care delivery. Patients are recruited from traditional care settings.<sup>20</sup> Therefore, patient, provider, and clinic factors are all important to successfully implement an

RA pragmatic trial. Our data revealed themes on key perceived barriers for implementing an RA pragmatic trial. Insurance status and type were reported as both patient-level and clinical barriers. Medicaid, Medicare, and private insurance plans had different restrictions on medication changes. RA medication restriction differed by each insurance plan, by geography, and by patient populations. Some participants expressed concern over their large (30%-50%) Medicare or Medicaid patient population in addition to uninsured patients which may pose a challenge for patient recruitment.

Patient recruitment was also reported as both patient-level (eg, patient identification and randomization, culture, patient stipend, lost follow-up, patient knowledge/awareness) and clinic-level barriers (eg, few RA patients targeted for this protocol, multiple offices, research visits being on nonclinic days for some practices for pharmaceutical trials). Patient unwillingness for clinical trial participation, strong patient preference for one versus alternate treatment, preference for oral versus injectable medication, long distance from home to clinic, commitment of extra visit time, and loss of follow-up were additional barriers. Patient conditions, current treatments, and potential side effects of medications were also considered as potential barriers. At the clinic level, some participants reported that they had very few RA patients, had early RA patients, or RA patients visited the clinic not very often. Another barrier was patient fatigue due to enrollment in too many RA studies. Some participants mentioned that they had several clinics sites with 1 hour (or 5-15 miles) travel distance between satellite clinics, and no disease specific clinics. One participant mentioned that a lot of times research visits were on nonclinic days. He further explained that it was hard to stop and identify patients in the middle of a busy clinic. This indicated that a pragmatic RA trial needs to be both rigorous and feasible.

Participants from a clinic with more minority patients considered language as a key barrier hindering communication between providers and patients. This indicates hiring bilingual (eg, Hispanic-English, Chinese-English) coordinators and providing materials with translations in Spanish, Chinese, or other languages for limited English-speaking populations.

Research personnel including coordinator effort and provider engagement were reported as a key clinic barrier. Many participants indicated that coordinators play a key role in identifying and recruiting patients and managing trial activities. Budget for

supporting appropriate coordinator effort was key per participants, since it would be impossible to implement a trial without coordinators. Provider engagement was another key clinic barrier due to providers' busy schedule or due to their involvement in other research trials. Some participants suggested engaging junior physicians for trial implementation, which may help their academic career development.

Although the purpose of the interviews was to identify physician-perceived patient and clinic barriers to implement a pragmatic RA trial, participants reported some facilitators (eg, an experienced team, a developed network, available technology, and the well-designed trial) that would be helpful. The participants indicated they had an experienced team, had support from nurses and pharmacist on their team. In contrast to the participants who were concerned about patient recruitment, some participants were very confident in patient identification and recruitment because they were part of a research-based facility and had an established research network with their RA patients. These facilitators suggest we have a good opportunity to implement the trial successfully.

## Conclusion

Our results from the inductive thematic analysis will help researchers understand the key patient and clinic/system factors/barriers that may influence pragmatic RA trial implementation. The themes suggest the factors that can be modified (eg, coordinator efforts, patient recruitment, provider engagement) and the challenges to overcome (patient insurance status and types, limited patient rooms, busy clinic flow). In summary, these themes provide a basis for our and other research teams to develop clinic-centered and patient-centered strategies to implement a pragmatic RA trial.

**Ethics Committee Approval:** The University of Alabama at Birmingham's Institutional Review Board approved this study and all investigations were conducted in conformity with ethical principles of research (UAB X120207004).

**Informed Consent:** No individual person's data were presented in any form in this study and therefore no consent to publish is required.

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## Appendix 1. Codebook: Qualitative analyses of interview data.

Subtheme Node	Description	Illustrative quotes
<b>Theme 1: Patient barriers</b>		
<b>Patients' personal factors</b>		
Patient-level insurance	Patient insurance plan	"Let's say they start on one TNF (tumor necrosis factor) and they want to crossover, but their insurance only allows them another TNF, so, they usually make us do two TNFs before being able to move on..."—Dr. D
Language barrier	Non-English-speaking patients have language difficulty	"Large Asian populations, that do not speak English, although we have interpreters, can be a barrier."—Dr. G
Travel	Long distance b/w patient home to clinic	"Geographic pull is quite extensive; travel distance is one—we are not seeing these patients."—Dr. F
<b>Treatment-related factors</b>		
Patient condition	Treatment, related issues	Sometimes patients are started on dual therapy, MTX (methotrexate) +HCQ (hydroxychloroquine), for a physician not to push dose higher, triple therapy in 25% of my patients."—Dr. O
Patient outcome	Patient outcome and measures	"I think they all work about the same, but safety data and longer safety data with TNF than with some others, and there are obviously some monitoring differences in terms of is the outcome measure"—Dr. B
<b>Trial-related factors</b>		
Patient recruitment	Patient-level recruitment barriers	"Culture/ethnicity bias/barrier African American (AA) difficult to recruit in the trials."—Dr. F
Patient preference	Patient preference re. trial, randomization, mode	"Patient preference—if they have a strong choice, based on what they want, either the drug or the route."—Dr. G
Patient burden	Extra time, questionnaire	"Well, it depends on patient not wanting to commit the extra time"—Dr. A
Side effect	Side effects related to drug in trial	"GI side effects, viral URIs are the most common issues with these drugs"—Dr. P
<b>Theme 2: Clinic barriers</b>		
<b>Patient-related factors</b>		
Clinic-level insurance	Proportion of patients with different insurance plans	"Depending on the patient insurance plan, have to fail a TNF-biologic, before they get the TNF; large access population, Medicaid 40%; Medicare 25%; private, 25%,"—Dr. L
Clinic-level patient recruitment	Issues-related recruitment in clinic	"Being able to bring the patient back to clinic; there may not be any openings."—Dr. A
<b>Clinic-related factors</b>		
Patient flow	Clinic flow, patient flow, clinic routine-related issues	Hard to integrate clinical research into the routine clinic flow, not to say it can't be done, we see patients pretty quickly, in the real world, 20-min follow-up visit, it will take a little bit more for the patient"—Dr. R
Lack of resources	Time, patient rooms, technologies, logistics, reimbursement	"Time involved, taking clinic space."—Dr. Y
Clinical equipoise	Clinical equipoise b/w drugs	"...triple therapy they won't be comfortable with the choice. I personally feel that there would be more equipoise between TNF versus non-TNF is an excellent trial that needs to happen."—Dr. O
Change to EPIC	Issues related to switching current health care record system to EPIC	"Changed to EPIC, have to build specific searching criteria"—Dr. X
Competing trial	Other trials or studies that were currently conducted	"XXX study is competitive; much more involved; five people randomized 1.5-2 years."—Dr. Y
IRB approval	Issues-related IRB application	"My experience is that it takes to work out the organizational issues to get everything lined up for a study like this, rather than doing the study itself. Such as IRB etc"—Dr. G
<b>Research personnel</b>		
Coordinator effort	Issues related to coordinator	"Study coordinator may be stretched too thin, not a half-day clinic study."—Dr. U
Provider engagement	Engage RA providers in the trial	"Engaging the provider before the visit, before they are engaged in a discussion."—Dr. B

**Appendix 1.** Codebook: Qualitative analyses of interview data. (Continued)

Subtheme Node	Description	Illustrative quotes
<b>Facilitators</b>		
Have an experienced team	Research team members with different background and experience in clinical trials	"We have done 100 clinical trials; we have a full support of our nursing team."—Dr. F
Have developed a good network	Current Network with RA providers and patients	"Some faculty are research-based, so not a problem for their patients getting in the study."—Dr. G
Technology	Factors-related tech support	"We are changing medical records to EPIC, may be that will help."—Dr. F
Trial design	Factors related to trial design	"The beauty of the design, this is what the patients do that in the practice."—Dr. K
<b>Theme 3: Insurmountable barriers</b>		
<b>Clinic-related barriers</b>		
Clinic flow	Clinic flow, patient flow, clinic routine-related issues	"Clinic flow issues"—Dr. Z
Changes of EPIC	Issues related to switching current measure tool to EPIC	"Getting EPIC implemented this weekend. Capture all CDAI in our EHR."—Dr. T
IRB	Issues-related IRB application	"We have many trials; local IRB is pretty tough."—Dr. V
<b>Patient-related barriers</b>		
Insurance	Patient insurance status and plan, proportion of patients with different insurance plans	"Insurance and patient preference are the biggest barriers."—Dr. E
Patient recruitment	Issues-related patient recruitment	"Patient preference are the biggest barriers."—Dr. E
Patient stipend	Patient stipend for participating in the trial	"Sometimes we have to offer \$25 gas money, that helps."—Dr. F
Language barrier	Non-English-speaking patients have language difficulty	"Worst barrier that is challenging is the language barrier for us."—Dr. G
Coordinator effort	Issues related to coordinator	"I would say, you know we don't have a good steady coordinator, it will be difficult for me to keep at, to get screening 5 or 6 to get 1 a month."—Dr. W
Provider engagement	Engage RA providers in the trial	"Research studies have got pharma studies are incredibly hard and almost impossible for the credible level of frustration right now."—Dr. E