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Transparency, trust and minimizing burden to increase recruitment and retention in trials: a systematic review

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Abstract

Objective: To describe patient perspectives on recruitment and retention in clinical trials.

Study Design and Setting: Systematic review of qualitative studies that reported the perspective of adult patients with any health condition who accepted or declined to participate in clinical trials.

Results: Sixty-three articles involving 1681 adult patients were included. Six themes were identified. Four themes reflected barriers: *ambiguity of context and benefit* – patients were unaware of the research question and felt pressured in making decisions; *lacking awareness of opportunities* – some believed health professionals obscured trials opportunities, or felt confused because of language barriers; *wary of added burden* – patients were without capacity because of sickness or competing priorities; and *skepticism, fear and mistrust* – patients feared loss of privacy, were suspicious of doctor's motivation, afraid of being a guinea pig, and disengaged from not knowing outcomes. Two themes captured facilitators: *building confidence* – patients hoped for better treatment, were supported from family members and trusted medical staff; and *social gains and belonging to the community* – altruism, a sense of belonging and peer encouragement motivated participation in trials.

Conclusion: Improving the visibility and transparency of trials, supporting informed decision making, minimizing burden, and ensuring confidence and trust may improve patient participation in trials.

Keywords: Patient recruitment; Patient retention; Clinical trials; Research; Barriers; Strategies

What is new?

- The barriers and facilitators to trial participation from the patient perspectives are captured in the themes of ambiguity of context and benefit, lacking awareness of opportunity, wary of added burden, skepticism, fear and mistrust, building confidence, and social gains and belonging to the community.
- Trials were perceived as an opportunity for some patients to access free and high-quality healthcare, whilst fear of discrimination and inequities in accessing healthcare, particularly among patients from vulnerable ethnic minority groups, discouraged participation in trials.
- Specific data on patient perspectives on participating in novel trial designs, including registry-based, pragmatic and adaptive trials, are needed.

1. Introduction

Low rates of recruitment and retention in trials can undermine the reliability of results, increase statistical uncertainty, limit generalizability of the findings, increase cost

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and resource waste, and ultimately impede access to potentially effective treatments [1–8]. It is estimated that about half of trials in patients with various health conditions achieve the target sample size [8–10], and the retention rate is 80% [11,12]. Studies have shown that vulnerable groups including women, elderly, rural and ethnic minorities are less likely to be recruited in trials [13–15], and this can perpetuate inequities in trial participation.

Previous systematic reviews and recent qualitative studies of patients' perspectives on recruitment and retention in trials have identified barriers. For example, patients may be unwilling to be randomized, feel confused by complex study protocols, worry about side effects of the interventions; while altruism, potential benefits in terms of quality of life, access to clinical follow-up support trial participation. However, the existing systematic reviews had a restricted time frame, and some patient populations were excluded from these studies [16–18]. Challenges to trial recruitment include a lack of awareness and knowledge about trials aims and outcomes among patients, limited funding, participant burden, and mistrust about doctors' motivations for promoting participation in clinical trials [19–24]. Various strategies have been used to increase trial participation and retention rates, such as engaging the target population in developing participant information, sending reminders after the initial invitation and offering financial incentives. However the effectiveness of these strategies is variable and remains substantially uncertain [9,25,26]. Also, it is unclear if the range of strategies explicitly integrates patient priorities and concerns regarding trial participation.

A synthesis of evidence from multiple qualitative studies on patient perspectives on recruitment and retention in clinical trials can provide more comprehensive and detailed insights across settings, strategies and populations. The aim of this systematic review was to describe the patient perspectives in participation in trials, elucidating the gap among settings, populations and clinical conditions, to inform strategies to maximize recruitment and retention to improve trial-based evidence for decision making.

2. Methods

2.1. Selection Criteria

Qualitative studies that described the perspective of patients aged 18 years and over, with any health condition that either accepted or declined to participate in clinical trials were eligible. We used the term "clinical trials" as defined by World Health Organization as "any type of research that studies new tests and treatments and evaluates their effects on human health outcomes… including medical interventions, drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments and preventive care [27]. Studies on prevention on healthy individuals were excluded. There were no restrictions by setting or year of publication. Articles were excluded if they used structured questionnaires and reported only quantitative data. For broader transferability of concepts, we included only studies that described patient perspectives on recruitment and retention in clinical trials in general. Studies were eligible if they included perspectives of participants who had agreed/declined to participate in one or more trials in general, and where perspectives on recruitment and retention pertained to clinical trials in general terms, rather to participation in a specific trial. Studies that reported perspectives with reference to a specific trial were excluded. Studies which reported perspectives of patients focused on a specific clinical trial (eg, if authors reported reasons why participants agreed/declined to take part in an intervention-specific content or to assess participant perspective after the completion of a prespecified trial) were excluded. Observational epidemiologic studies, editorials, and review articles were also excluded. Non-English articles were excluded to prevent misinterpretation in translation.

2.2. Data, Sources and Searches

We searched MEDLINE, Embase, PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from inception to December 11, 2019. Reference lists of relevant articles and Google Scholar were searched. The full search strategy is provided in Table S1. PN and AT independently screened the search results and excluded those that did not meet the inclusion criteria. Full texts of potentially relevant articles were assessed for eligibility.

2.3. Data Extraction and Quality Assessment

Four authors (PN, VS, MR, AMG) independently assessed the comprehensiveness of reporting of each primary study using an adapted Consolidated Criteria for Reporting Qualitative Health Research (COREQ) framework, which included items specific to research team, study methods, study setting, analysis, and interpretations [28]. The COREQ tool can help readers ascertain the rigor of the studies. Any disagreement was resolved by discussion.

2.4. Data Analysis

We used the thematic synthesis to synthesize the findings from each study. Thematic synthesis uses an explicit and systematic process to generate new insights (for example a new framework of themes) that reflect participant perspectives across different populations, settings and context [29,30]. All participants quotations and text in the "results/findings" or "discussion/conclusion" section from each article were imported into the software HyperRESEARCH (Research Ware Inc., version 4.5.0) [31] for data management. PN performed line-by-line coding of the primary studies, inductively identified preliminary themes and

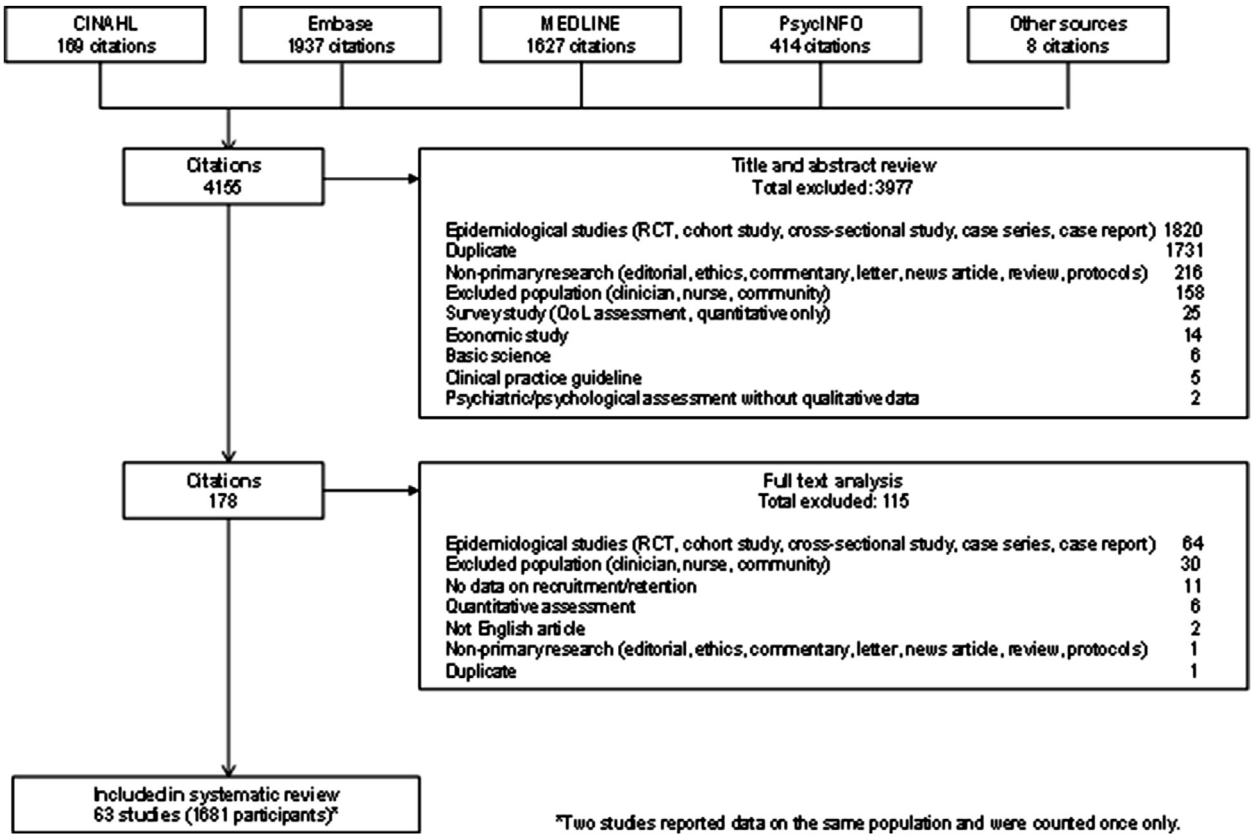

Fig. 1. Search results.

similar concepts were grouped into subthemes. The preliminary analyses were reviewed and discussed by the research team to ensure that the full range and depth of data were included. We developed a thematic schema to identified relationship among themes.

3. Results

3.1. Literature Search and Study Description

We included 63 articles, performed in clinical setting, involving 1,681 patients aged from 18 to 90 years, 31% males, from 12 countries including Australia, Brazil, Canada, China, Denmark, Germany, Japan, Russia, Singapore, Sweden, the United Kingdom and the United States. In total, 790 (47%) patients had participated in clinical trials. The search process is shown in Fig 1. Data were collected using interviews, focus groups, and questionnaire with open-ended questions. The study characteristics are provided in Tables 1 and S2.

3.2. Comprehensiveness of Reporting

Studies reported on six to 19 reporting items based on the COREQ framework (Table 2). The sampling strategy was reported in 51 (81%) studies and the sample size was reported in all studies. Audio recording and transcription was stated in 54 (86%) studies, investigator triangulation was reported in 50 (79%) studies, and participant quotations to support the findings were available in 59 (94%) studies.

3.3. Synthesis

We identified six themes. Some of the themes that reflected patient perspective on recruitment and retention in clinical trials were related to trust/mistrust. The themes of ambiguity of context and benefit, lacking awareness of opportunities, wary of added burden, skepticism, fear and mistrust were barriers to participating in trials, whilst building confidence, and social gains and belonging to the community motivated or supported participation in trials. The respective themes are described below with concepts specific to demographic or clinical characteristics reported accordingly. Selected participant quotations to support each theme are provided in Table 3. An analytical schema depicting the relationships among the themes is shown in Fig 2.

Table 1. Summary characteristics of the included studies

Characteristics	Number (%) of studies
Demographics	
Age, years (range)	18–90
Male (n, %)	528 (31)
Number of participants	
1–10	9 (14)
11–20	15 (24)
21–30	18 (29)
31–40	9 (14)
41–50	7 (11)
51–60	2 (3)
More than 60	3 (5)
Country	
United States	32 (51)
United Kingdom	12 (19)
Australia	5 (8)
Canada	5 (8)
Japan	2 (3)
Other[I]	7 (11)
Previous participation in trials	
Patients who participated	790 (47)
Patient who declined/never participated	891 (53)
Conditions	
Cancer	37 (59)
Chronic conditions[II]	9 (14)
HIV	3 (5)
Cardiovascular diseases	2 (3)
Other[III]	12 (19)
Method of data collection	
Semistructured interview	41 (65)
Focus group[IV]	21 (33)
Open-ended interview/survey	1 (2)

[I] "Other" included one study from Brazil, China, Denmark, Germany, Russia, Singapore, and Sweden.

[II] Chronic conditions included cardiovascular, autoimmune, neurodegenerative, motor neuron, gynecological, erectile, metabolic disease, systemic, cancer, respiratory, gastric, mood, and genetic disorders.

[III] "Other" included acute illness (n = 1), chronic kidney disease stages 1-5D (n = 1), cystic fibrosis (n = 1), general medicine (n = 1), patients admitted to the emergency department (n= 1), patients undergoing haematopoietic stem cell transplantation (n = 1), patients without a clear clinical condition (n = 1), pelvic floor disorders (n = 1), postmenopausal women taking combination hormone therapy (n = 1), primary care ward (n =1), systemic lupus erythematosus (n = 1) and type 2 diabetes (n = 1).

[IV] Focus group included face-to-face focus groups (n = 20) and an online focus group (n = 1).

4. Ambiguity of context and benefit

4.1. Indistinct from routine clinical care

Some patients could not distinguish the difference between standard clinical procedure and experimental treatment – "Because there didn't seem a great deal of difference in a lot of [clinical trials]…it's just different drugs" [32]. The term "clinical" led people to suppose it was a test, scan or procedure which took place in the clinic to diagnose a patient [33].

4.2. Only as a last resort

Some believed that trials were conducted to cure "rare types or unknown diseases" [34] or were the "last chance for someone who has no hope" [34]. Some patients in early stages of cancer or with curable illness declined to participate in trials because they considered themselves "healthier than others" [35] who were at risk of "imminent death" [34].

4.3. Risk of being in a lottery

Patients compared randomization to "lottery numbers" [36], "tossing coins" [37], or "Russian roulette" [38], where the "computer picks what you're going to get" [36]. They were aware that neither themselves nor the "doctor can influence the choice of treatment" [39]. Some patients felt cheated if they were allocated to the control arm because "the new [drug could be] much better than the known one" [37]. While placebo was considered "harmless pill" [40], some felt they missed out on the optimal treatment and they would not benefit from participating in the trial.

4.4. Unaware of research question

Patients reported that general practitioners had little time to explain the trial, including the aim and as such "[patients] just do what the doctor is recommending" [41]. Some patients felt intimidated and embarrassed to ask questions. One patient commented: "I didn't think it was my job to understand it all…" [34]. Without knowing the research question, some were unsure if participation in trials was "the right thing" [42] to do. Some searched for further information in news and online media, and from other patients and clinicians.

4.5. Pressure of making decision

Some patients with cancer stated they were informed about trials during their first clinical appointment when they "had no idea what was going on" [43], and felt "bombarded with it at an emotional time" [42] when they were not able to make such a decision. Some felt "put on the spot" [44] and pressured to decide immediately [43]. Others made the decision hastily because they "didn't want to have to travel back down and go through more tests" [45]. Patients wanted time to make decisions, to be able to take the information and consent form home and "call doctors on [their] time and ask questions" [46].

Table 2. Comprehensiveness of reporting in included studies

Item	Studies reporting each item (references)	Number of studies
Researcher characteristics		
Interviewer/facilitator identified	[32–35,39,40,43,44,46,48,49,53–55,57–62,96–123]	48
Occupation	[32,34,35,39,43,53–55,58,61,96,97,100,101, 104,105,107–109,111,112,114,117,118,120]	25
Experience or training in qualitative research	[32–35,43,46,48,53–55,58,59,62,96,100–102,104–106,108,109,114,116,118,122]	26
Relationship with participants		
Relationship established prior to study commencement	[32,34,35,37,43,57,60,62,96,103,105,108,114,118, 120,122,124]	17
Participant Selection		
Sampling strategy *(eg, snowball, purposive, convenience)*	[32–37,39,40,42,43–49,51,53,55,56,58,60–62,96,97,99,100,102–119,121–125]	51
Method of approach or recruitment	[27,32–42,44,46–51,53–55,58,59,61,62,96,97,99–106,108–115,117–124,126]	53
Sample size	[27,32–62,96–126]	63
Number and/or reasons for non-participation	[32,34,36–40,42,47,52,53,56,57,59,60,62,96,103, 104,106,107,110,112,113,115,117,118,120,122]	29
Setting		
Venue of data collection	[32–38,40–46,48,50–53,56–59,61,96,97,100,101, 103–115,117,120–122,124–126]	47
Presence of nonparticipants	[32,35,38,39,46,62,96,97,102,104,105,106,110,112]	14
Description of the sample	[27,32–62,96,98–126]	61
Data Collection		
Questions, prompts or topic guide	[32–36,38–45,47–53,55,56,57,59–62,96–107,109–117,120,121,123–125]	53
Repeat interviews /observations	[56,97,117,119,126]	5
Audio/visual recording	[32–39,40,42–45,47,48,50–53,55–61,62,96,98–109,112–121,123–125]	54
Field notes	[33,34,37,38,43,46,53,55,97,98,100–104,107,108,111,112,121,123,125]	22
Duration of data collection *(interview or focus group)*	[32–37,39–45,47,49,51,54,56,57,58,61,62,96,99–103,105–108,110–113,115,117–120,122,124,125]	44
Translation and interpretation *(NA if English)*	[27,33,41,44,49,53,56,97,98,101,119,121,123]	13
Transcription	[48,50,58,96,109,119]	6
Data or theoretical saturation	[32,34–38,43,44,46,53,55,57,58,60,61,62,99, 102,105,107,116–118,123,124]	25
Data Analysis		
Researcher/expert triangulation *(multiple researchers involved in coding and analysis)*	[27,32–39,42–45,47,48,50,51,53,55,57–62,96,98,101–111,113–124]]	50
Translation *(specifies language in which analysis was done – NA if English)*	[33,53,56,101,119]	5
Derivation of themes or findings *(eg, inductive, constant comparison)*	[27,32–40,42,43,45,47–51,53,55,57,58,60–62,96,97,99,100–109,111–125]	53
Use of software	[27,32,34,35,37,43,45,47,48,50–53,58,62,96,99, 100,103,104,106,108,113,114,116,117,119,121,126]	29
Participant feedback on findings	[50,57,59,61,98,105,119,122]	8
Reporting		
Participant quotations or raw data provided *(picture, diary entries)*	[27,32–58,60–62,96,98–103,105–111,113–126]	59
Range and depth of insight into participant perspectives of recruitment/retention in clinical trials *(thick description provided)*	[32–53,55–58,60–62,96,98–109,111,113–126]	57

Table 3. Illustrative quotations

Theme	Quotations	Sources
Ambiguity of context and benefit		
Indistinct from routine clinical care	"I was in a clinical trial, but I do not really know what it means; I could not explain it to anyone" [33].	[32–34,48,59,97,99,106,114,126]
	"During my treatment I had to have several scans, I think in some ways this is like a clinical trial because they were a test which took place in the clinic" [33].	
Only as a last resort	"If I am in an early stage and curable, why would I try a new drug?" [53]	[34,35,53]
	Even though Madeline was offered a clinical trial that day, she said that she declined it because she considered herself healthier than other cancer patients and "just wanted to get out of there" [35].	
Risk of being in a lottery	"They put your information in the computer...and it decides which one would be best for you... initially I thought I wanted to do that, but then I was like no I didn't want to be experimented on…because I couldn't choose myself" [36].	[34,36,37–40,42,46,48,51,53,55,103,104,108,114,115,119,120,126]
	"It would take good nerves to say YES to a drawing of lots, and then having to accept to be treated with the traditional treatment and at the same time thinking, that the new one is better...I would feel cheated, definitely" [37].	
Unaware of research question	"When explaining clinical trials, one can explain the benefits of the drug, aim of study, and side effects of the drugs, explain in more detail, explain clearer to patients and make the patients less worried, then the participants will feel more comfortable to join the clinical trials and have more confidence in the treatment" [56].	[27,32–34,37–39,41,42,44,46,50,51,53–57,59–62,98,99,101,102,104,106,111,113,118,120,122,125,126]
	"I want to know how much I'm getting, and what it's for, and how it's going to be used. That part they never seem to tell you" [120].	
Pressure of making decision	"It's not that I don't want to talk with a doctor, but I want to see information presented to me in writing because I can then sit down at a quiet time at home and make sure that I understand that" [99].	[32,37,38,42–46,49,51,55,60,62,98,99,106]
	"I could call after work and talk to somebody…without feeling that I was being pressured into doing something" [46].	
Lacking awareness of opportunities		
Obscured by health professionals	"We were also never told that you couldn't you couldn't go in any other clinical trials. Now those are options that to me just blare out negligence. If the doctor doesn't tell you those things, how would you know that?" [126]	[35,36,42–45,47,48,50,53,57,98–100,119,120,121,126]
	"I had to bring information to my doctor and I was kind of disappointed in that. But, you know, she also protects you, too…not protects you from trials, but I'm sure timing is everything and you have to be at a certain stage or certain place. You know, trials aren't for everybody" [43].	
Confused because of language barriers	"There was quite a lot to read, and I think sometimes that can be off-putting…So it would be nice to have it in a like condensed way, with like the summary, which I think would be better, instead of pages and pages of information which sometimes people don't have the time to go through…" [48].	[33,39,40,42,44,48,49,50,51,54,55,97,100,113,119,121]
	"I think, maybe in his medical lingo he did a good job, I am not a physician, I didn't understand a word" [51].	

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Table 3 (*continued*)

Theme	Quotations	Sources
Wary of added burden		
Competing priorities	"We live on a small farm, so the hassle – and we have a 15-year-old son, so our challenge is, well [our son] being the priority, you know, be least disruptive to his life and then who is going to take care of the animals?" [45]	[34,35,38,39,44–47,49,50,52,53,55,56,57,60,97–100,104,106,107,111,114,124]
	"They invited me up for further research a few years later, I declined because I couldn't take any further time off from my employment" [57].	
Without capacity because of sickness	"And the lack of concentration, I've had that happen. What were we talking about? We're joking, but you're right. How do people participate when, that's the million dollar question" [50].	[32,36,42,43,50,51,53,57,61,114,124]
	"My brain wouldn't seem to cope because so much had happened to me in the last month, my brain still hasn't adjusted to what has happened to me and I didn't want anything further to think about" [42].	
Skepticism, fear, and mistrust		
Fear of loss of privacy	"Probably the confidentiality factor due to fact that most of the time you all probably have computers and stuff like that…anybody could have access to that computer…even though you say it's secured" [98].	[50,54,61,98,100,104,120]
	"The confidentiality of it. I mean it's easy to say that the information won't go someplace else but, nowadays information gets dropped all the time someplace…you don't want everybody to know what you're doing" [120].	
Suspicion of motivation	"Just because they're independent of the sponsor, that doesn't mean they don't know the sponsor at all. You can still be getting paid off by them" [102].	[39,44,49,54,55,99,101–103,106,111,113,114,120,125]
	"Well you have to sign this informed…I think that's where the risk comes in. That's when I'll start thinking, 'Is there something that this person's not telling me?'" [44]	
Afraid of being a guinea pig	"They want to take me into a clinic and use me as a test specimen or something…all thoughts and animal thoughts. Guinea pig" [98].	[32–34,36–40,42,46,47,50–53,55,56,61,62,96–99,103–105,106,108,113,114,115,117,119,120,122,123,124]
	"And I didn't really want to try to add that to what I was already taken because I was having enough problems just taking the medications I was given so I back away for a minute" [120].	
Vulnerable to discrimination	"There was an Asian woman who couldn't speak English and I could see she was treated differently. Not only just by the staff, also the other patients. She was a friendly person and everything, so yes people do treat differently if you don't speak the language" [44,49].	[41,44,49,55,62,100,101,103,104,113,125]
	"You have all these barriers and stuff. When you say race, you think that racism is over, but then it's not" [113].	
Disappointment, isolation and abandonment	"You are sort of in this cocoon really and suddenly you are cast aside, we have finished with you know, off you go." [57]	[27,34,37,52,56,57,105,107,122,123]
	"Now the trial I participated in is finished. But they say that in September a new trial will start. I told that I would like to participate. I like that in any moment, if I need anything, medical help will be provided to me" [123].	
Disengaged from not knowing outcomes	"I don't even know if mine is over yet, the study I was in, if they're still doing it, but I would love to get, as a member of the study, when the study results are done, get notification of the outcome of the study. What's going on? I volunteered and then they shut you out" [106].	[34,48,50,57,106,122]

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Table 3 (*continued*)

Theme	Quotations	Sources
	"It will be nice [if researchers] let you know [if] it did a certain amount of good…it would make you feel a bit better and you think oh well somebody got something out of it" [122].	
Building confidence		
Hope for an answer and better treatment	"Yes, hope! During the conversation and several days after, when I experienced everything here, with all the people, I really have to say, I thought it was great [to take part in the study] and it also gave me hope, definitely" [51].	[32–35,37,38,40,41,43,44,47,48,51–53,55,56,57,58,59,61,62,96,99–101,103,106,107,109–117,124,126]
	"And I'm a very religious person and I feel strongly that God had a hand in that. I was one of the lucky ones. I did go on the trial…From a selfish point of view, it was more important for me to get this extra drug, because to my mind it was an extra bite of the cherry" [48].	
Opportunity to access treatment	"I feel a bit special, because I have had the chance to be on it. Plus you think you are getting this extra attention. I think because it's a study you know you are going to have the best really, rather than just being one of the others" [52].	[34,37,38,39,40,46,48,52,53,55,56,58,59,60,62,104,107,115,117,120,122,123,126]
	"The biggest gain is, I'm really lucky, I can know [the disease progression] earlier, I can realize that earlier, but not wait till my condition has become very bad, then I won't even know what happened to me. I feel this is the biggest gain, to know earlier" [56].	
Safety and reassurance	"There is no worry about leaving the trial; you just need to let the doctors or nurse know. This was very comforting" [59].	[37,39,40,48,51,53,55,56,59,102,109,111,115,120,122–124]
	"During the research, I was more assessed than I normally be in an outpatient care. I performed more tests, and if there was anything more serious, I would have been informed" [40].	
Support from family members	"My friends and family are very informed and aware of what is going on with me. Always want to come to the hospital and they all do their own research…It's great, I am very supported" [96].	[27,33–36,41,43–45,48,49,51,53,55,57,58–62,96,99,101,104,106,107,111,118,119,121,122,124]
	"After much discussion in the family, thinking about the impact on the children, and if all these side effects did materialize what impact that would have on us as a family with no extended family to call upon, I thought it was too selfish of me to ask for that. But my children said, 'Look, Mum, we'd put our lives on hold for a year if it means that you're going to be better at the end, if you've got a better chance of survival.' And I said, 'Well, it's a chance I've got to take'" [48,58].	
Trusting medical staff	"[The physician] knows my body now and he knows what will work. I have complete faith in him that he will come up with the best that is there. Not just because it's a study that's out there and he wants to put me in it just to, you know, get my name in a study and do it. He's trying to pick the best that will work for me" [116].	[27,32–34,36,37,41,44–53,55,56,57,58,60,61,96,100,101,105,112,114,116–120,122–124]
	"When I walk into the clinic I feel like I' am in heaven. When you sit down and talk to your doctor and they tell you I have something new to tell you. That's why I love my doctor. There are not too many of them that are really good and dedicated. But they are angels and they know their patients" [120].	

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Table 3 (*continued*)

Theme	Quotations	Sources
Social gains and belonging to the community		
Altruism and reciprocity	"I knew that I wanted to be a part of it and it was a good thing…Someday, even if not in my lifetime, there being a cure and just helping somebody else. That's the main thing – helping somebody else, you know, it really is. I mean it's not about you. It's about somebody else" [35].	[32,33,35,36,38,40–42,44,46,48–53,55–58,60–62,96,99,100,101,105,106,109–113,115–117,119,122,125]
	"And it's also my way of giving something back, because I've, like, I've met some beautiful people through this journey in the last two and a half years and, yeah, it's just being part of the bigger picture I guess" [111].	
Connectedness, sense of belonging and peer encouragement	By participating in a clinical trial, people experienced a better understanding of their disease and they experienced a sense of personal enrichment. They learned a lot about themselves and gained more confidence [109].	[32–34,43–47,49,50,52,56,57,62,96,99,104,109,117,120,122]
	Participants valued meeting other people who were taking part in the same clinical trial. They found it helpful to debrief about common side effects and felt encouraged when they heard of someone else having positive results during trial participation [122].	

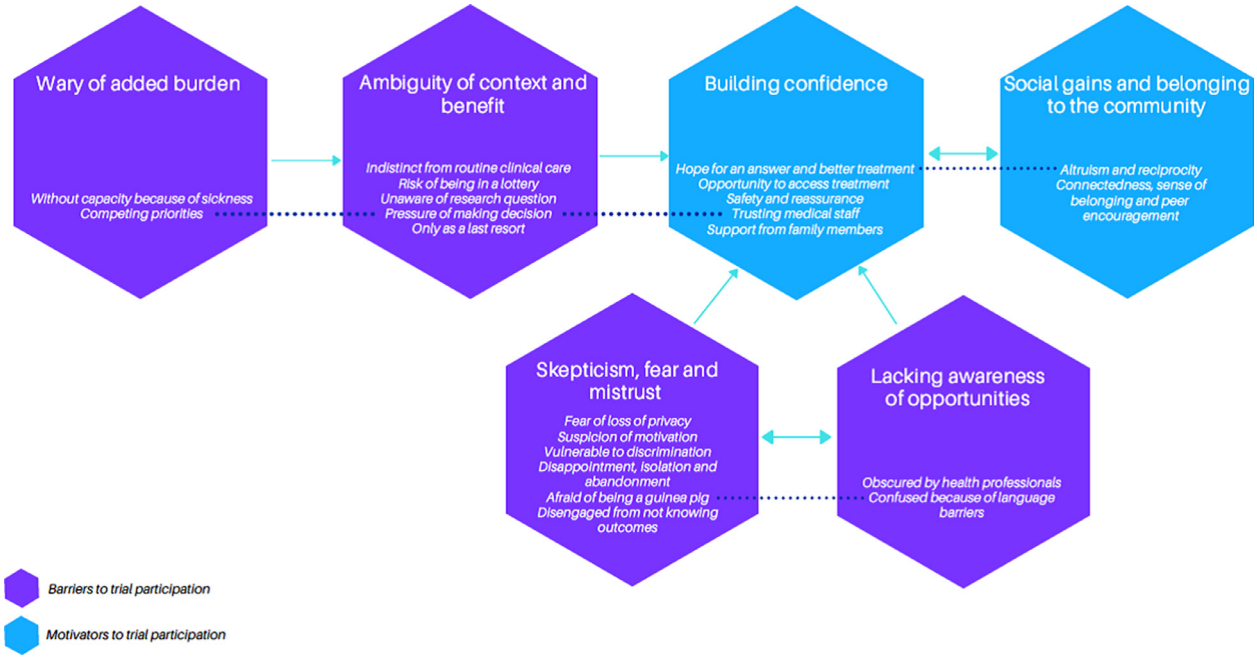

Fig. 2. Thematic schema.

5. Lacking awareness of opportunities

5.1. Obscured by health professionals

Some patients "had never heard of [trials] before" [36] or reported that their physicians warned them "to be wary of a trial" [47] because "[patients] mustn't let science get in the way of the best treatment for [them]" [48]. Some patients believed that general practitioners were resistant to engaging patients in trials due to their limited knowledge or interest in research.

5.2. Confused because of language barriers

Patients were dissuaded from participation in trials by lengthy and complex written information, particularly if it was not written in their native language. Some relied on interpreters, patients navigators or family members to comprehend the complex language, because they "understood bits of [information provided]" [44,49] but worried about misunderstanding the aims and risks. Patients were not able "to interpret clinical hieroglyphics" [50] in the

information and consent forms. Participants remarked that "a person without a medical background would probably not understand what [medical lingo] means" [51] and this discouraged trial participation.

6. Wary of added burden

6.1. Competing priorities

Patients considered the "investment of emotional and physical energy" [52] of their family and work responsibilities before participating in clinical trials. Some mentioned that time, financial and logistic barriers prevented their ability to attend follow-up visits, and thus decided to drop out of the trial. Some patients had "lost enough of their life" [50] and were reluctant to attend additional appointments at the hospital.

6.2. Without capacity because of sickness

Some patients with cancer felt too unwell and overwhelmed by their disease to comprehend and process information about the trial – "If my health is not good, I will not join" [53]. Some participants reported that health professionals approached them whilst they were ill and without capacity to comprehend the information and make decisions about participating in the trial – "They've got to have some sort of knowledge of when they hit you up for it. Not when you're at your worst" [50].

7. Skepticism, fear and mistrust

7.1. Fear of loss of privacy

Some were concerned about potential breach of confidentiality and access to their personal data. They were hesitant about giving consent because they were uncertain about who would access their personal information and how their data were be used.

7.2. Suspicion of motivation

Some patients, particularly in the United States, questioned their physicians' motivations for recommending participation in clinical trials and suspected the reasons could relate to potential "financial constraints in the health service" [54] or to gain "prestige" and recognition [55]. Some patients believed the information and consent process was designed to protect physicians from litigation.

7.3. Afraid of being a guinea pig

Patients were scared to be treated like a "guinea pig" for drugs that had unknown effects and were not approved for market – "It seemed too much like an experiment" [55]. Taking new medications was considered "risky" [56] because of the unpredictable adverse events. Patients were scared of unfamiliar procedures (eg, injection) that caused pain, discomfort or anxiety.

7.4. Vulnerable to discrimination

Some hesitated to participate in trials because they suspected that health professionals may take advantage of them. Patients from ethnic minority groups were skeptical about clinical trials because of the history of unethical medical experimentation in their population, and believed that the findings would not benefit their community given entrenched inequities of access to effective treatment and quality care. Particularly for African American patients in the United States, some felt "treated as aliens" [44,49] in the healthcare system and thus refused to participate in trials.

7.5. Disappointment, isolation and abandonment

Patients felt disappointed, "lonely" [37] and "helpless" [56] if their expectations for improved health were not met, for example if they had to drop out the trial for medical reasons. Patients feared they could be abandoned once the trial was completed because during the study "[the doctor] made me feel like I wasn't alone" [34]. They were anxious about "no longer having easy access to healthcare professionals" [57] after the trial and were longing to take part in other studies to liaise with medical staff.

7.6. Disengaged from not knowing outcomes

Some felt disengaged and that their time and commitment were not respected, and were reluctant to suggest participation in trials to their peers or lost motivation to participate in future trials. As such, some patients felt "used" [48] because after the trial "there [was a] breakdown of communication" [48] whereby they did not receive any feedback or trial results.

8. Building confidence

8.1. Hope for an answer and better treatment

Patients hoped to gain personal benefit in participating in trials, particularly if they had no other treatment options. Patients with cancer considered trials as "the light at the end of the tunnel" [52], and while they did not set high expectations, they wanted to try something new that could help them. Some felt they "had nothing to lose" [58] and were willing "to participate in anything since there is care" [40] provided to them.

8.2. Opportunity to access treatment

Patients believed that being enrolled in a trial was a "privilege" [34] because they received extra attention, better care and faster access to procedures and screening tests

that were otherwise unavailable. One patient with cancer mentioned: "I was told I need a computer tomography scan but the scanner was very busy and I can expect it to happen in a week's time. And then I was seen by a consultant and his team and I gave my consent…and miraculously the computer tomography scan was done within a couple of hours" [48]. Patients believed they could be the "first to be cured" [40] with the newest treatment options, saving their own money and timing. Particularly for patients in the United States, participation in a trial meant that they could access treatments they could not otherwise afford.

8.3. Safety and reassurance

Closer and regular monitoring visits during the trial provided reassurance to patients that their health would be constantly under control. Being in trial meant they had "extra support between appointments" [59], and any costs incurred because of complications during the study period would be covered by insurance. They felt comforted in knowing that could withdraw from the trial in case of unexpected effects. Some were grateful for ongoing opportunities to participate in because they could be still in contact and supported by medical staff.

8.4. Support from family members

Patients "would listen to [their] significant other" [60] before making a decision about clinical trials. If a family member supported the decision, patients felt more confident because they "were often unable to capture and retain all information" [59]. Patients also considered the benefits, risks and the impact that participation in trials might have on their ability to work and care for their family.

8.5. Trusting medical staff

Some patients had "infinite faith in the doctors" [60] and participated in trials if it was suggested by their trusted physician – "…at the end of the day, whatever the doctors have done, they've done for my benefit" [61]. They emphasized that the opportunity to participate in the trials had to be communicated in a friendly and accessible manner – "It wasn't like going to see a doctor and a nurse, it was almost like going to see two friends and I think that was exceptional, because that actually makes [the process of participating in a trial] so much easier" [57].

9. Social gains and belonging to the community

9.1. Altruism and reciprocity

Patients with chronic conditions wanted to participate in trials to help future generations or their relatives who could develop their same conditions. Patients were motivated to contribute for "the common good" [62], "If nobody takes a step, then how will medicine advance?" [53]. Patients felt doctors/institutions had done a lot for them and participation in trials was an opportunity to give back. They reflected that successful treatments were possible because other patients had participated in trials – "I have been the beneficiary of drugs which have previously been trialed by other people, and if I'm in a position to do the same for the next generation then there's no reason at all that I shouldn't do so" [58].

9.2. Connectedness, sense of belonging and peer encouragement

Being part of a trial had enriched patients' personal lives because felt they had become part of a community with similar conditions. Participation in trials had given them the opportunity to meet and interact with other people, sharing knowledge and learning how manage their disease from experiences of their peers to improve their retention in clinical trials. Patients believed they could inform other patients about opportunities to participate in research, provide "patient-written for patients" [50] documents and recommend clinical trials to other possible participants. They appreciated to learn about the experiences of other patients on clinical trials allowed them to understand the "reality of trial participation" [45], including the potential adverse events.

10. Discussion

Patient perspectives on recruitment and retention in clinical trials were related to trust/mistrust in health professional, patients and family, and institutions. For some patients, a lack of clarity about the context and potential benefit of the trial, feeling pressured in making immediate decisions, being overwhelmed by the disease and treatment burden, having little knowledge of opportunities were barriers to participating in trials. Some were concerned about being randomized to the control arm and not gaining benefits from participating in the trial. Patients were also concerned about loss of privacy, discrimination, and the notion of being experimented on with interventions that had unknown effects. Some patients who had participated in trials felt disillusioned when expectations for improved health were not met or lost motivation because the trial results were not communicated back to them and were discouraged from participating in future trials or recommending others to participate. The burden of trial participation, particularly to attend follow-up visits, included the time, effort, costs required amidst other competing priorities. However, other patients were motivated to participate in trials in the hope that they and other patients would be able to access better care and treatment, close medical follow-up and opportunity to access treatments otherwise unavailable. At the same time, some felt anxious about being isolated and

abandoned after completion of the trial. Patients had confidence about participating in trials if they trusted health professionals, had support from their families or were encouraged by other patients who had participated in trials.

While the themes were generally similar across populations and settings, we noted some differences based upon healthcare setting, ethnic minority status and illness severity. For patients in countries such as the United States, which is without a universal healthcare system, participating in trials was a means of accessing free healthcare and some were concerned about being able to continue treatment and medical follow-up due after the trial. The lack of awareness and communication with clinicians about trials was particularly apparent in the United States owing to barriers in accessing healthcare practitioners. Participants from disadvantaged and minority groups, particularly African American patients in the United States, were wary of discrimination in healthcare and were reluctant to participant in trials in fear that they would be taken advantage of by clinicians and researchers. They also speculated that their communities would not benefit from the results of the trial because of the pervasive inequities in access to healthcare. For those with less severe stages of cancer or curable conditions, some felt it unnecessary to participate in trials because they believed trials were a last resort for those with life threatening conditions. These reasons explain, to some extent, the lower rates of trial recruitment in specific populations. There were no differences noted between patients who accepted or declined to participate in clinical trials.

In this systematic review, we conducted a comprehensive search and developed a new framework of themes on patient perspectives on trial participation and retention. However, there were some potential limitations. We deliberately chose not to include patient perspectives derived from studies that were focused on specific trials. Studies where perspectives were elicited on why patients decided to participate or not in a specific trial were excluded, and only studies where perspectives about participation in trials in general were collected and deemed eligible. The decision on this inclusion criterion was undertaken due to the large amount of data we anticipated to find, which made it unlikely that further concepts could emerge from the excluded studies related to specific trials. Compared with previous studies [17,63], our review showed that the saturation of themes was achieved. We did not include non-English studies, and the majority of studies were conducted in high-income countries, which may limit the transferability of our findings. There were insufficient data to distinguish between trial-naïve patients and patients that had participated clinical trials. We also acknowledge that more than half of the studies included patients with cancer.

Our findings reinforce prior systematic reviews [16,17,63,64] and previously identified concepts including conditional altruism, hope for positive clinical affect, best treatment option, and peer encouragement [18,65]. However, we have identified a cross-cutting concept of trust that relates to the patient-doctor relationship, communication, sensitivity to the patients' needs and commitments, ensuring transparency about aims and findings of the research, which may help to better engage patients in clinical trials. This review has potential to inform strategies to improve recruitment and retention in clinical trials that address in the areas of raising awareness and understanding, supporting decision-making and consent, minimizing the burden of participation and demonstrating respect for patients. Suggestions for each of these areas are provided in Table 4. Current strategies to improve recruitment include expanding selection criteria, using and opt-out consent approach, optimizing trial information and resources, engaging trusted clinicians, and sending reminders after the initial invitation [9,16,66–68]. Offering financial incentives and implementing risk-based monitoring are strategies to increase retention in clinical trials [68,69]. Patients have suggested that media coverage of trials, advertising and training medical staff to communicate opportunities to participate in trials may support recruitment [70,71]. Involving caregivers in the decisions to participate in trials, promoting flexibility of appointments and providing reassurance of protecting confidentiality have also been suggested [72,73]. Our findings suggest the need to be sensitive to the patient's journey by ensuring that the timing of decision-making is sensitive to their psychological and cognitive state, and ensure the dissemination of results back to patients.

Some patients believed they would gain personal benefit from participation in clinical trials, meaning that they may not have understood or may potentially mislead information reported in the consent form. According to the Declaration of Helsinki [74], each participant must be adequately informed on the foreseeable benefits, potential harms and discomfort related to the trial and that there is no guarantee that any individual will receive personal benefit from trial participation [75].

However, there are some "indirect" benefits as identified by patients including gaining a sense of purpose in life, connection to community, knowledge, and being able to share experiences with their patients. We also suggest that patient information sheets should be explicitly state that participant may not gain direct benefits from taking part in a trial to increase transparency in the recruitment process.

The majority of themes were related to recruitment rather than retention in clinical trials. Dropping out of the trial due to either medical reasons, financial or personal commitments were the only barriers to trial retention as identified by patients. This review highlights important barriers to trial participating in marginalized populations, including ethnic minority groups and non-English speaking patients. Efforts to engage with trusted community leaders, involvement of family and caregivers, providing training to staff that addresses cultural respect and how to respond to fears and anxieties about discrimination appear warranted.

Table 4. Suggestions for improving participant recruitment and retention in clinical trials

Domain	Considerations and suggestions
Raising awareness and understanding	**Make trial opportunities visible:** make research information more visible and provide information about trials (eg, newsletters, brochures, posters, website) **Facilitate peer promotion of trials:** connect patients with other study participants to encourage participation, focusing on benefits that are relevant to the patients and the impact of adverse events
Harness trust	**Partner with clinicians:** involve trusted and reliable health professionals (general practitioners, nephrologists, nurses) in providing information about the value of trials and discuss potential burden, risks and side-effects of treatment **Promote effective and clear information:** consent form should explicitly state that participant may not gain personal benefits from participation
Supporting decision-making and consent	**Clarify the aims and outcomes:** explain purposes, potential benefits, adverts events, time commitment and outcomes **Provide information in a comprehensive and consistent manner:** use plain language, visual aids **Provide succinct information:** reduce the amount of paperwork providing unmistakable and relevant information in the consent form **Ensure comprehension:** check if participants understand information about the trial (eg, using a verbal test and asking participants about the aims and potential benefits and risks) **Give time for taking decision:** allow time for participants to review and consider the information and to involve family members in the decision-making process **Give opportunity for discussion:** provide a point-of-contact for questions about the trials, promote proactive counseling **Be sensitive to the patient's circumstances and context:** consider the timing in recruiting participants and consider events that may limit capacities to consider participation (eg, during acute or severe episodes of illness, complications) **Involve communities:** educate community leaders in research to promote clinical trials **Translate information:** translate study materials in the primary language of the participant **Provision of bilingual medical staff:** involve bilingual health professionals or from same cultural background to avoid racial and social discriminations, facilitate gender matching between patients and staff **Address concerns about discrimination:** discuss potential fears and concerns about ethics and discrimination **Promote altruism and social gains:** support the impact that new treatments could have on the next generations and increase belonging to the community
Minimize burden of participation	**Minimize effort of commitment:** link appointments with patient clinical visits to reduce disruption to other commitments (eg, work, study, family) **Offer flexibility in preferred days and times:** offer convenient modalities of follow-up and promote remote participation to reduce the impact on lifestyle **Provide financial reimbursement:** reimburse patients for out-of-pocked costs incurred with participating in the trial (eg, parking, transportation) **Send reminders:** help participants to remind next appointment date or other information related to the trial (eg, exams/scans needed, drugs administrations, reinforce aims and outcomes)
Demonstrate respect and value	**Provide trial results to participants:** discuss trial results during and at the completion of the trial **Seek feedback:** give opportunity to ask questions and provide feedback on the process and results

In addition to ensuring that trial information and consent are translated, we suggest that approaches to ensure that patients have comprehended the information may be required, for example by asking patients to relay back information about the trial [8,76–83].

While patient involvement across all stages of research is widely advocated to enhance recruitment and achieve high retention rates [84,85], they are infrequently involved in designing and implementing recruitment strategies [82]. Most of this has been limited to providing feedback on information and consent forms [86–89]. Further work is needed to facilitate and evaluate patient involvement in other aspects of supporting trial recruitment, for example, in disseminating trials results. Of note, the World Medical Association has urged that the communication of research results back to participants is an ethical imperative and a way of demonstrating respect for patients effort and commitment in participating in the trial [74,90–92]. Informing patients about trial findings can motivate participation in research [92–94]. We also suggest that further research could be conducted to explore patient perspectives on participation in novel trials for example, registry-based studies, pragmatic trials and adaptive trial designs, which are increasingly being used [95]. For patients, participating in trials requires trust. Challenges in participation in trials remain because of limited awareness of opportunities and knowledge about the trials, pressure and decisional conflict, uncertainty about randomization and harms, language barriers, lack of capacity in the context of the disease and treatment burden, personal costs in terms of time, energy and finance, social discriminations and being demoralized when trials do not meet expectations. Strategies are needed

to improve the visibility of trials, support informed decision making, minimize the burden of extra clinical appointments, and ensure motivation, confidence and involvement in participating in trials.

Author contributions

Patrizia Natale: data curation, formal analysis, investigation, software, validation, visualization, roles/writing - original draft, writing - review & editing; Valeria Saglimbene: data curation, formal analysis, validation, visualization, roles/writing - original draft, writing - review & editing; Marinella Ruospo: data curation, formal analysis, validation, visualization, roles/writing - original draft, writing - review & editing; Andrea Matus Gonzalez: data curation, formal analysis, validation, visualization, roles/writing - original draft, writing - review & editing; Giovanni FM Strippoli: conceptualization, investigation, methodology, project administration, supervision, validation, visualization, roles/writing - original draft, writing - review & editing; Nicole Scholes-Robertson: data curation, validation, visualization, roles/writing - original draft, writing - review & editing; Chandana Guha: data curation, validation, visualization, roles/writing - original draft, writing - review & editing; Jonathan C Craig: conceptualization, investigation, methodology, project administration, resources, supervision, validation, visualization, roles/writing - original draft, writing - review & editing; Armando Teixeira-Pinto: supervision, validation, visualization, roles/writing - original draft, writing - review & editing; Tom Snelling: validation, visualization, roles/writing - original draft, writing - review & editing; Allison Tong: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, roles/writing - original draft, writing - review & editing.

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Supplementary materials

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