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A systematic review to identify and collate factors influencing patient journeys through clinical trials

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Abstract

Patient-centred trial design and delivery; improves recruitment and retention; increases participant satisfaction; encourages participation by a more representative cohort; and allows researchers to better meet participants' needs. Research in this area mostly focusses on narrow facets of trial participation. We aimed to systematically identify the breadth of patient-centred factors influencing participation and engagement in trials, and collate them into a framework. Through this we hoped to assist researchers to identify factors that could improve patient-centred trial design and delivery. Robust qualitative and mixed methods systematic reviews are becoming increasingly common in health research. The protocol for this review was prospectively registered on PROSPERO, CRD42020184886. We used the SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research Type) framework as a standardised systematic search strategy tool. 3 databases were searched as well as references checking, and thematic synthesis was conducted. Screening agreement was performed and code and theme checking were conducted by 2 independent researchers. Data were drawn from 285 peer-reviewed articles. 300 discrete factors were identified, and sorted into 13 themes and subthemes. The full catalogue of factors is included in the Supplementary Material. A summary framework is included in the body of the article. This paper focusses on outlining common ground that themes share, highlighting critical features, and exploring interesting points from the data. Through this, we hope researchers from multiple specialities may be better able to meet patients' needs, protect patients' psychosocial wellbeing, and optimise trial recruitment and retention, with direct positive impact on research time and cost efficiency.

Keywords

Clinical trials (epidemiology)<Epidemiology<NON-CLINICAL, effectiveness of care<Evidence based practice<CLINICAL

Introduction

In February 2023, clinicaltrials.gov had more than 350,000 interventional trials registered across 220 countries.[1] It is hard to estimate the premature discontinuation rates of clinical trials, as most do not report their closure to ethics committees.[2] However, some studies estimate that up to 80% of registered clinical trials will not be completed.[3] The most common reasons for premature trial discontinuation are inadequate recruitment[2–4] and poor retention.[2–4]

Patient-centred trial design improves participant satisfaction[5]; better meets patients' biopsychosocial needs[6–8]; minimises negative downstream consequences of participation[6,8]; and ensures recruitment from a more diverse, thus more representative, cohort.[9,10] It has been shown to increase recruitment speed, ensure trials meet their recruitment targets,[11,12] and improve retention,[4,13] with a positive impact on improved time and cost efficiency[4,14] and lower trial failure rates.[3,4]

To achieve patient-centred design, it is necessary to seek key stakeholders' views and experiences of trial participation and engagement.[15–18] Research in this area is increasing, however mostly focuses on narrow aspects of participation, such as patients' views of their experiences of the consent process. As such, understanding patient journeys through trials and trying to identify areas to improve patient-centredness can be fragmented.

We aimed to capture the breadth and diversity of patient-centred factors influencing participation and engagement in trials across the whole trial journey. Following this, we planned to present them in a coherent framework to assist researchers in identifying factors that could improve patient-centred trial design and delivery. Participation and engagement in countries with high quality healthcare and a strong trials portfolio are likely to be intrinsically and systematically different from low resource countries with poor access to healthcare, therefore at this stage the work is limited to high resource settings.

Methods

Qualitative and mixed methods systematic reviews are becoming more common in healthcare research and should be subjected to the same academic rigour

as qualitative reviews. The protocol was registered on the Prospective Register of Systematic Reviews (PROSPERO):CRD42020184886 and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research Type) framework was used as a standardised systematic search strategy tool (Table 1).

Search strategy

Medical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medica Database (EMBASE), and Psychological Information Database (PsychINFO) were searched. The MEDLINE search strategy is in the Supplementary Material. References of all papers meeting the eligibility criteria were searched for additional material. Last database searches were performed on 1st May 2020. Full eligibility criteria are shown in Table 2.

Paper screening and eligibility assessment

All papers were screened by title and abstract by the lead reviewer (RD). A second reviewer (JM) screened a random 10% of the sample. Both reviewers assessed the full text of all papers that passed screening. A third reviewer was prospectively identified to provide tiebreaker input. Exclusion of papers based on quality assessment of individual qualitative studies risks losing data richness, therefore, no formal assessment was made.[19] The eligibility criteria specified that only peer reviewed work would be included to afford additional quality control.

Coding and thematic analysis

There is no pre-existing framework to map patient journeys through clinical trials. Therefore, an inductive approach based on the structure laid out in Braun and Clarke's seminal paper, 'Using Thematic Analysis in

Table 1. SPIDER framework for the systematic review.

S- Sample	Adult/paediatric patients potentially eligible to take part and/or have taken part in an interventional trial in a high resource setting. Research relating exclusively to healthy volunteers or public perception was excluded. Animal research was excluded.
PI- Phenomenon of Interest	Patient journeys through interventional trials.
D- Design	Qualitative research including case studies, interviews, observational field work, and focus groups. Quantitative and mixed-method research including structured surveys and questionnaires, preference selection experiments, audit and database analysis. Peer reviewed research only.
E- Evaluation	Data relating to patient-centred factors that invested stakeholders (patients, parents, carers, healthcare professionals) think influence patient journeys through an interventional clinical trial.
R- Research Type	Qualitative, quantitative and mixed-method research.

Table 2. Eligibility criteria.

Inclusion	Exclusion
1a) The study identified invested stakeholders' opinions on patient-centred factors that may influence the patient journey through interventional clinical trials OR 1b) The study explored participant demographic or baseline characteristic data influencing engagement and experiences of interventional clinical trials 2) Adult or paediatric interventional trials 3) All peer reviewed primary research including surveys, interview-based studies, preference selection experiments, observation and field work, audit and chart review, focus groups or case reports and case series 4) Studies conducted in countries with a top rank Human Development Index according to the United Nations Development Programme 5) Studies published between 1st January 1999 and 31st December 2019	1) No English language full text available 2) The paper did not address interventional trials (e.g. limited only to observational trials, monitoring trials with no planned intervention or biobank trials) 3) Studies designed exclusively to develop or evaluate patient led core outcome sets for a given disease 4) Trials in animals 5) Research that had not been subjected to peer review 6) Studies where the primary focus was public perception of research or research in healthy volunteers 7) Studies where the primary focus was on designing or evaluating a specific intervention within the trials space 8) Studies which examined patient perception of clinical care delivery only 9) Studies conducted in low resource settings

Psychology', was used.[20] This is the most common method of thematic analysis. Analysis was completed in ATLAS.ti. A random 10% sample of papers were reviewed by a second researcher to ensure the codes generated by the primary coder corresponded with the original sources and to check that no potential coding units had been overlooked. Once the framework had been refined, it was presented using the sorted and labelled themes and subthemes alongside their coded extracts.

Results

Through the methods used in the primary research, data from more than 800,000 stakeholders were incorporated into the final synthesis. Studies were from 25 countries. Oncology: 49%, mixed disease groups: 11% and neurology: 11%. The remaining papers came from 20 specialities (Figures 1 and 2).

Thematic saturation was reached after four cycles of coding. More than 300 systematically extracted factors were identified and sorted into groups that share similar properties or features. The primary output is the catalogued factors sorted into an organising framework. The framework aims to provide a comprehensive guide to the factors which may impact on patients' experiences of research. It can be found in the Supplementary Material. An outline framework is shown in Table 3.

Figure 1. PRISMA flowchart of records included in the systematic review. *Screening agreement on the 10% sample was excellent (Cohen's kappa coefficient 0.97). **No tie breaker input was required.

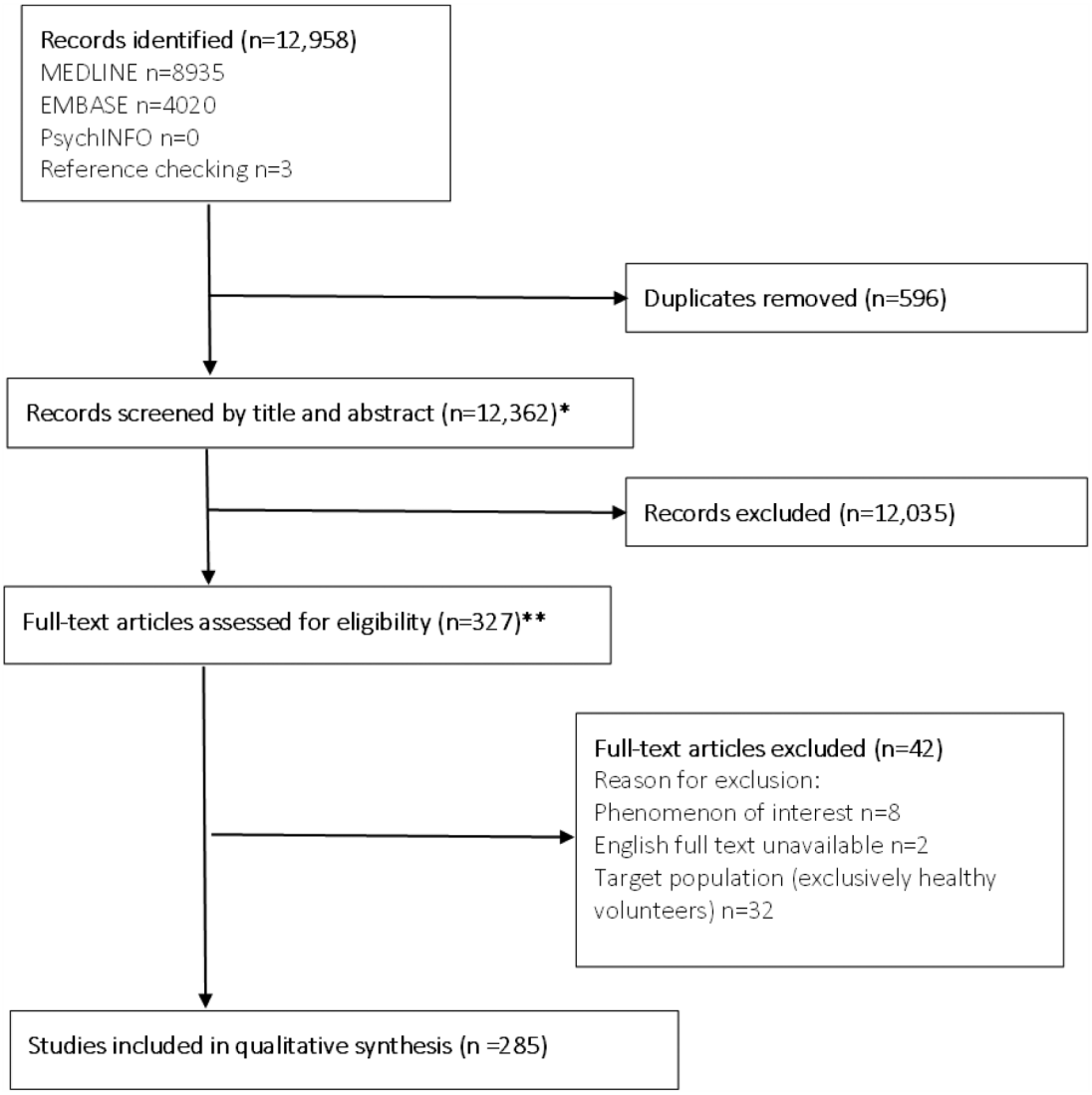

Figure 2. Pie chart showing paper breakdown by disease area.

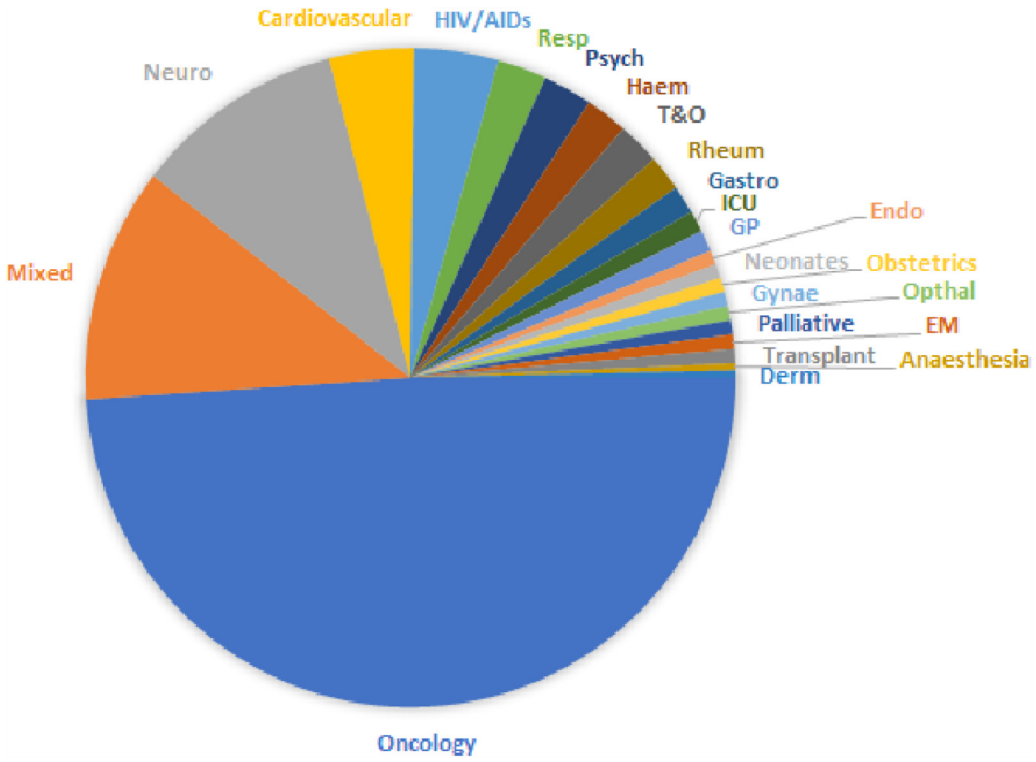

Table 3. Thematic mapping outline framework – quick view guide.

Theme	Subtheme
Prior to clinical trial participation	Patient population perceptions of research
	How patients learn about trials
	Recruitment methods
Motivation to take part in trials	Altruistic and societal motivations
	Individualistic motivations
	Individualistic and altruistic interaction
Barriers to participation	Practical barriers
	Attitudinal barriers
	Protocol design barriers
	Investigational product factors
	Conflict of interest concerns
	Barriers created by study timelines
Facilitators to participation	Increasing trial flexibility

(continued)

Table 3. (continued)

Theme	Subtheme
	Financial compensation
	Overcoming cultural and language barriers
	Assisting patients to understand the trial
	Improving trial design factors
Demographic factors influencing the decision to enrol in trials	General considerations and interaction potential
	Knowledge and trust
	Age
	Gender
	Sexuality
	Race and ethnicity
	Socioeconomic status (SES)
	Education level
	Language, religious and cultural considerations
	Functional status
	Family structure
	Employment status
Impact of care structure and care experience on trial enrolment	Location and structure of clinical care
	Previous trials experiences
	Previous healthcare experience
Two-way interaction between health status and trials	Interaction between health status and trial enrolment
	Interaction between trial participation with health and other Healthcare Professionals (HCPs)
Psychological impact of participation	Factors modifying impact on psychological wellbeing
	Positive psychological consequences
	Negative psychological consequences
Validity of consent	General considerations
	Paediatric specific consent/assent
	Consent in difficult circumstances (e.g. intrapartum trials)
	Consent of incapacitated adults
Impacts of participation on day-to-day life	Aspects of trial participation with significant negative impact on life
	Factors improving trial participant experience

(continued)

Table 3. (continued)

Theme	Subtheme
Special considerations	Reproductive health
	End of life trials
Leaving a trial before protocol completion	Choosing to withdraw from a trial
	Intervention related reasons leading to withdrawal
	Trial design or implementation related reasons leading to withdrawal
	Major life events resulting in withdrawal
	Early closure or patient ineligibility
Experiences of trials ending	Anxiety about the end of trials
	Post-trial follow-up arrangements

Discussion

We systematically drew data from 285 peer reviewed primary sources and identified >300 factors influencing patient journeys through trials from start to finish. Due to the breadth of this review, each discrete factor and its implications for practice in individual disease models cannot be fully explored within the confines of this paper. Instead, we focus on outlining common ground that themes share, highlighting critical features, and exploring points of interest from the data. Some of the factors will be relevant to research in all disease areas, and others may have specific implications depending on associated factors such as the predominant population demographics, disease symptoms or available treatments. Those conducting research should interpret the findings within the parameters and nuances of their own speciality.

Prior to research participation

'Patient population perceptions of research', *'How patients learn about trials'* and *'Recruitment methods'*.

In general, patients believe trials are important and are keen to participate. Despite this, a significant proportion do not fully understand the purpose of trials, or the principles involved in their conduct.

More than 20 ways of learning about trials were identified, broadly split into active and passive. Leaving patients to identify trials for themselves introduces biased recruitment of a more engaged group. The media's role is complicated, with negative attention reducing trust and positive attention increasing interest, although patients recognise that certain information sources may be inaccurate. In general, patients want to hear about trials, even if they are ineligible to participate. They report insufficient material about trials and want centralised resources to aid identification.

Patients favour personal recruitment methods for example, phone calls, and preferably recruitment by their own physician. Where this is not possible, compensatory mechanisms include recruitment by a doctor, the recruiter taking longer to explain the study, or a perception that the recruiter is enthusiastic or trustworthy.

Motivation to take part in trials

'Individualistic motivations', *'Altruistic or societal motivations'* and *'Individualistic and altruistic interaction'*.

Patients have multiple motivations for trial participation. Several studies suggest patients feel guilty participating for predominantly individualistic reasons. Conditional altruism seems to play an important role, 'I am taking part to improve my health, if it also benefits others, that's great'. Motivations when parents enrol a child, or proxies for a dependent, appear different from the decision to enrol oneself, with lower weighting towards societal motivations for parents and proxies.

The weight placed on individual motivators seem to interact with other factors like prognosis. For example, patients with diseases with mild symptoms may be less likely to participate to improve their symptom burden but may seek social aspects of participation. However, across all diseases, patients may include many of the factors listed in the Supplementary Material in their personal profile of motivation to participate.

Barriers to participation

'*Practical barriers'*, '*Attitudinal barriers*', '*Protocol design barriers*', '*Investigational product related barriers*', '*Conflict of interest related barriers'* and '*Barriers created by study timelines'*. More than 50 barriers were identified and are listed in the Supplementary Material.

Some barriers have a paired 'facilitator'. Others are difficult to address for example, '*Fear of the risks'*. Clear explanation about how risks are managed may reduce these fears, but ultimately some concerns are rational. Additionally, there are some intangible factors that are likely to be even harder to address, for example, '*Mistrust of the pharmaceutical industry*'. Being aware of specific barriers may assist researchers in understanding the extent of the challenge and catalyse important conversations.

Most barriers translate across specialities but affect different proportions of patient populations. To illustrate, '*Complex social circumstances for example, homelessness or entanglement with the law'* could impact patients with any diagnosis. However, it is likely to affect more of the recruitment pool in substance abuse trials than cancer trials. Similarly, factors like '*Missing out on activities (school, work)'* have a greater impact with a predominantly young patient demographic for example, asthma, when compared to conditions affecting older patients for example, Alzheimer's disease, where '*Frailty'* and '*Cognitive impairment'* are more prevalent.

Facilitators to participation

'*Increasing trial flexibility'*, '*Financial compensation'*, '*Overcoming cultural and language barriers'*, '*Assisting patients to understand the trial'* and '*Trial design factors'*.

No individual facilitator seems likely to improve trial appeal, but appropriate combinations may substantially improve patient-centredness. A critical 'facilitator' is, 'reduce study demands'. This includes reducing the visit frequency or the number of uncomfortable procedures. Thus, 'reducing study demands' could overcome barriers such as '*Lack of time'*, '*Missing out on activities (school, work)'* and '*Difficulties finding childcare'*. The quintessence of trials is to capture sufficient data to assess an intervention's safety and efficacy parameters. Therefore, 'reducing study demands' is not a simple strategy. However, when designing trials, researchers should scrutinise every visit and procedure and ensure the gain from additional data collection is worth the loss in terms of reduced patient-centredness and the knock-on effects on recruitment and retention. Telemedicine should be explored to reduce study demands.

Demographic factors influencing the decision to enrol in trials

'*General considerations and interaction potential'*, '*Knowledge and trust'*, '*Age'*, '*Gender'*, '*Sexuality'*, '*Race and ethnicity'*, '*SES'*, '*Employment status'*, '*Family structure'*, '*Functional status'*, '*Language'*, '*Education level'* and '*Cultural and religious background'*.

Demographic features associated with lower engagement in clinical care seem amplified in trials.[21,22] Older patients, those from ethnic minority backgrounds, or accessing trials in an additional language, with lower functional status, and of lower SES were less likely to participate and more likely to drop out of trials. Physician-initiated trial discussions can have complex interactions with demographic features. 'Cherry picking' patients for trials may increase the unrepresentativeness of recruited subjects[23,24]

Patients in trials appear to have better outcomes than those not on trials,[25,26] therefore, recognising this and engaging a more diverse cohort may reduce health inequality. The challenges presented by most of the demographic factors are deep rooted and unlikely to be amenable to simple interventions. A few considerations could overcome less pervasive factors for example, taxi provision could reduce the effects of frailty, or interpreter services could overcome language barriers. Researchers should consider the impact of their decisions on marginalised groups. For example, not providing a stipend is likely to have a greater impact on those of lower SES. Clearly, however, a huge amount of work is required to address these inequalities.

Impact of care structure and experience on trial enrolment

'*Location and structure of clinical care'*, '*Previous trial experiences'* and '*Previous healthcare experiences'*.

Patients who receive clinical care at a hospital with a strong research culture are more likely to be offered opportunities to participate in trials. Patients from backgrounds traditionally harder to engage in healthcare may be less able, or willing, to travel for appointments thus may be more likely to receive treatment in local rather than tertiary centres.[27,28] Networked trial delivery may go some way to alleviate this, however the referral process can still disadvantage some groups of patients.

Patients had more positive attitudes about trial participation on trial completion than at enrolment.[29,30] Most were keen to participate again. Positive experiences of healthcare similarly encourage enrolment and correlate with many of the demographic features discussed in the previous theme. This theme provides further examples of how demographic disparity can be driven throughout the trials journey.

Two-way interaction between health status and trials

'*Interaction between health status and trial enrolment'* and '*Interaction between trial participation with health and other HCPs'*.

Many sources suggest that patients have different motivations for participating in research depending on the nature of their underlying diagnosis. Additionally, it was suggested that patient groups create a community identity which influences decisions to enrol in trials. Patients with higher levels of symptom or treatment burden were more likely to accept the inherent risks of participation, and the availability of standard treatment options also influenced decisions to participate.

Conversely, trial participation appears to impact on patients' health experiences. For example, patients may have altered behaviour patterns when taking part in trials if they start to feel better on the trialled medicine. There are a few confounders to consider within this subtheme because people who enrol in trials seem to be different from those who do not. However, patients seem to become more adherent after enrolment in trials than they were prior to enrolment, for, as they believe their clinical care improves, they have fewer therapeutic misconceptions and find it easier to engage with clinical teams.

Psychological impact of participation

'*General considerations on psychological wellbeing'*, *'Positive psychological consequences'* and '*Negative psychological consequences'*.

Generally, participants felt positive aspects outweighed potential negative consequences of participation. Trial participation can provide hope, pride, optimism, and a sense of control. Thus, it can empower and improve confidence. The 'hype vs. hope' effect was described, where realistic expectations provide positive psychological benefit, but unrealistic expectations result in significant disappointment or anxiety when the anticipated benefits are not obtained. Ensuring realistic expectations at enrolment is critical to ensure valid consent and vital to protect participants' psychological wellbeing.

Minimising negative psychological experiences of participation may reduce trial attrition, and could increase intention to enrol in subsequent trials, important in rare disease research. Participants need to live with their disease alongside, and after, trials. Thus, it is important to prevent negative sequelae on health perceptions or relationships with clinical teams. Identified factors that can impact negatively on psychological well-being included '*Allowing an illness to play a greater role in patients' lives*', and '*Regularly seeing objective measures of health – especially deteriorating measures*'. Trials' teams should empower patients to raise their concerns. Patients may experience frustration that trial protocols do not provide the same collaborative flexibility that they expect through their routine clinical care. If the lines between trial and clinical care are blurred, this frustration can become directed at the clinical team. Ensuring trial and clinical care are well demarcated will reduce transferred frustration at lack of protocol flexibility. These psychological impacts are likely to be generalisable across most diseases, though to different extents depending on the disease characteristics and the population demographics.

Validity of consent

'*General Considerations'*, *'Paediatric assent/consent'*, *'Consent in difficult circumstances'* and '*Consent of incapacitated adults'*.

Despite reporting high satisfaction with the consent process, many participants appear to have poor understanding of trials, including risks, aims, or concepts like randomisation. In extreme scenarios, participants have not realised they were enrolled in trials. Consent forms are frequently described as too complex. HCPs report that the onus seems to rest on accurate form completion, rather than appropriate knowledge sharing. Compensatory factors include proficiency of the person obtaining consent and allowing more time to be devoted to the process.

Encouragingly, most articles reported that patients do not perceive external pressure to participate, even if asked by their regular physician. Generally, patients seemed to recognise that refusal will not impact care, though some have a sense of moral obligation to participate. Several sources suggest that patients of Asian ethnicity perceive greater pressure to participate, illustrating how cultural background can influence engagement in trials.

Consent can be more complex in certain circumstances, for example, in perinatal and emergency trials. Proposed facilitators include taking oral consent at enrolment and completing paperwork later. Interestingly, most HCPs surveyed did not feel comfortable with this, even in clearly demarcated circumstances, reflecting the fact that the burden of responsibility attends to the accurate completion of forms. Co-design of consent/assent forms and adequate training in consent procedures may contribute to improving consent validity. HCPs should keep patients' health literacy level in mind and the use of interpreters and translated material could aid the consent process for some. Preferred consent procedures for incapacitated adults are outlined within the framework.

Children and teenagers seem keen to be involved in the consent/assent process but described feeling pressure from their parents, or that their dissent is not respected. If appropriately facilitated, most children can express views on participation, but are seldom empowered to contribute meaningfully.

Impacts of trial participation on day-to-day life

'*Positive impact on day-to-day life'* and '*Negative impact on day-to-day life'*.

With psychological impacts in a separate theme, the negative impacts predominantly relate to the demands of participation, and further support to ensure every protocol-mandated event is proportionate to assessing the trial's outcomes. Side-effects or toxicity also impact negatively on participation. If the side-effects or toxicity are worse than the disease symptoms or other available treatments, it seems unlikely that the intervention will be of clinical utility.

Many of the factors that could improve the trial experience seem simple to implement such as Wi-Fi provision, refreshments, and study newsletters. Patients value building a rapport with the trial team, a factor motivating participation for many. Good communication and adequate time with patients appear critical to improving participant experience. Patients who have realistic expectations of the trial at the outset have a more positive experience of participation, again underscoring the importance of grounding expectations through the consent process.

Special considerations

'*End-of-life trials'* and '*Reproductive considerations'*.

Sadly, patients in end-of-life trials seem to have lower quality of life and higher levels of psychological distress than those receiving end-of-life care clinically. Plausibly this correlates with the suggestion that patients on end-of-life trials seem to have fewer conversations with their clinical teams about life-expectancy and less acceptance of prognosis. Recognition of this phenomenon will be essential to support patients through end-of-life trials.

Patients generally recognise the importance of contraception in trials. It is highlighted that contraceptive requirements in trials inevitably disadvantage women more than men and should be proportionate. Reproductive considerations are especially relevant in chronic diseases affecting young populations. This review found evidence that behavioural change may occur where patients feel better on the intervention, including anticipation of pregnancy or parenthood. Recommendations for novel drug use in pregnancy remain controversial even outside the context of a trial.

Leaving a trial before protocol completion

'*Trial design or implementation related reasons leading to withdrawal', 'Intervention related reasons for trial withdrawal', 'Major life events resulting in trial withdrawal'* and *'Early closure or patient ineligibility'*.

Patients who withdraw from trials often have similar levels of satisfaction as those who do not. Patients mostly know they have the right to withdraw, but not all know how to raise the discussion. The decision comes with uncertainty and even guilt. Teams need support patients accordingly.

Although drug side-effects were a reason to leave a trial, they were not the most frequently cited. Unrealistic expectations at enrolment and being allocated a different arm to the one expected were both important factors leading to higher drop-out rates. This biased attrition is a fundamental flaw of open-label trials and provides further evidence to ensure patients understand the trial from the outset.

Trial withdrawal has complex associations with numerous factors, including demographic characteristics, study demands, and reasonableness of expectations from participation. The already proposed interventions to improve patient-centredness of trial participation for marginalised groups, reducing study demands, and assisting patients to understand the trial from the outset may also be important targets to reduce drop out. Additionally, it seems that relatively simple interventions could aid retention such as ensuring that staff make patients feel appreciated and respecting their time.

Potential scenarios for leaving a trial before protocol completion include non-voluntary circumstances for example, the trial closes early or the patient becomes ineligible, perhaps because of unanticipated biomarker changes. Sources emphasised that *choosing* to leave was different from *having* to leave a trial. Some patients reported feeling confused, anxious or angry if their trial closed earlier than expected.

Experiences of end of trials

'*Anxiety about trial completion'* and '*Post trial follow-up'*.

Trial completion marks an important transition and is accompanied by anxiety in the lead up to the end and beyond. Patients may be concerned about stopping the intervention if it has been beneficial or worry about separating from the trials team, who often become a source of emotional and practical support. Patients may need to continue to engage with the trial team during a transition phase and such arrangements should be made clear. Many patients believed that they should have access to the trialled drugs on trial completion and this is potentially achievable in phase III trials for example, via Managed Access Programmes, but harder in early phase trials.

Patients want to hear study updates, trial results and their randomisation allocation; a substantial proportion had not. Patients would prefer to be updated by the trials team, regarding it as a mark of appreciation for their participation and were more inclined to participate in future trials if this appreciation is shown. Patients

think it is important to publish study results, even negative results, although report disappointment if trials did not meet the endpoints.

Strengths and limitations

Strengths of this review include the systematic extraction of data from a large pool of methodologically diverse resources. Data came from 22 specialities across 25 countries. Screen checking demonstrated high inter-reviewer agreement, and collaboration with a second researcher reduces bias in coding and thematic analysis. A pre-registered protocol was followed.

Only studies conducted in regions with a very high human development index were included. Participation and engagement in countries with high quality healthcare and a strong trials portfolio may be different from low resource countries. Those looking to conduct trials in low resource settings are likely to find limitations from this framework. Furthermore, it is acknowledged that the inclusion of studies from predominantly English-speaking nations introduces bias and may limit transferability of the data.

Conclusions

The aims of this review were to systematically identify patient-centred factors influencing journeys through clinical trials and collate them into a coherent framework. To our knowledge, this review is the first to systematically collate data from all disease models and for all stages of patient journeys through trials. The review was not intended to provide a unifying theory as to what influences participation and engagement, but to provide a structure for use when designing patient-centred trials. Through this, we hope researchers may be better able to meet patients' needs, protect patients' psychosocial wellbeing, and optimise recruitment and retention to trials with direct positive impact on research time and cost efficiency.

Author contribution: RD, GM, JM, SM, MB and FK have no conflicts to declare. JCD has performed clinical trial leadership roles, educational and/ or advisory activities for the following: Abbvie, Algipharma AS, Bayer AG, Boehringer Ingelheim Pharma GmbH & Co. KG, Eloxx, Enterprise, Galapagos NV, Genentech, ImevaX GmbH, Ionis, LifeArc, Nivalis Therapeutics, Inc., Krystal Biotech, Novartis, PARI Medical Holding GmbH, ProQR Therapeutics III B.V., Proteostasis Therapeutics INC., Pulmocide, Raptor Pharmaceuticals Inc, Recode, Vertex Pharmaceuticals. JSE has provided consultancy and advice for Vertex, Celtaxsys, Corbus, Ionis in clinical trial design and delivery. He also holds an EU Innovative medicines Initiative grant with Novartis, Polyphor and Alaxia. No external funding was used for the review. No ethical approval was required for this work that did not directly involve human subjects. RD cowrote the protocol and search strategies, conducted the searches, screened the papers, was the primary analyser and led on manuscript preparation. GW assisted with analysis and manuscript. JM screened 10% of papers and assisted with analysis. MB and FK advised on the protocol and guided the manuscript write up. JCD and SM cowrote the protocol and guided search strategies, oversaw the analysis and provided input into the write up. SM contributed to all of the above activities as well as providing overarching oversight for the project.

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