



Review article

A mixed-methods systematic review of patients' experience of being invited to participate in surgical randomised controlled trials

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ABSTRACT

Rationale: Randomised controlled trials (RCTs) of surgical interventions are increasing. Such trials encounter challenges that are not present in RCTs of non-surgical interventions because of the nature of the intervention. Several studies have explored patients' experiences of surgical trials to improve recruitment or identify barriers and facilitators to research in this setting. Synthesizing these studies may reveal further insights or confirm whether saturation of relevant themes has been achieved.

Objective: This review aimed to understand the experiences of adults who are invited to participate in surgical RCTs.

Method: MEDLINE, Web of Science, and CINAHL were searched to identify articles meeting the inclusion criteria. Assessment of quality was conducted with studies given an overall quality rating of good, fair, or poor. A segregated approach was used to synthesize the data. This method included a thematic synthesis of the qualitative data and a narrative review of the quantitative data. The findings of both syntheses were then integrated. **Results:** Thirty-four articles reporting 28 trials were included. This review found that the decision to participate in a surgical trial is influenced by multiple factors including patients' individual circumstances and attitudes, and the characteristics of the trial itself. The study identified three themes which encompass both qualitative and quantitative findings. These themes reveal it was important for patients to i) make sense of the trial and trial processes, ii) weigh up the risks and benefits of their different treatment options and participation, and iii) trust the trial and staff.

Conclusions: A patient-centred approach to trial recruitment may help staff build trusting relationships with patients and address their individual concerns about the trial and the risks and benefits of participation.

1. Background

Recruitment to randomised controlled trials (RCTs) is often slower and more difficult than expected (McDonald et al., 2006). Between 1994 and 2002 less than a third of RCTs funded by the Medical Research Council and the National Institute for Health Research Health Technology Assessment achieved their original recruitment target (McDonald et al., 2006). Poor recruitment can lead to costly extensions to trials or results that are less precise. One common barrier to recruitment is patients' unwillingness to take part (McDonald et al., 2006). Qualitative studies have explored patients' reasons for accepting or declining trial participation. The perception of personal benefit may lead to a willingness to participate (McCann et al., 2010). Patients may also consent to trial participation if they accept equipoise (Mills et al., 2003), which is genuine uncertainty on the part of the clinical

investigator regarding the comparative therapeutic merits of each arm in the trial (Freedman, 1987). Conversely, perceiving potential harm from participation (Mangset et al., 2008) or having a treatment preference (Madsen et al., 2007) may lead to non-participation. Other research has suggested that the Theory of Planned Behaviour could be applied when examining people's choices to participate or not (Quinn et al., 2011). The Theory of Planned Behaviour proposes that behaviour and behavioural intentions are shaped by attitudes, subjective norms, and perceived behavioural control (Ajzen, 1991). Quinn et al. (2011) conclude that lung cancer patients' decisions to accept or decline clinical trial participation was shaped by their attitudes (fear and lack of hope for a good prognosis), subjective norms (the perception that their physician or family were supportive of participation or not), and perceived behavioural control (the sense of regaining control by choosing to participate or choosing a treatment). A meta-ethnographic synthesis

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of 12 qualitative studies, published between 2005 and 2010, highlighted the importance of an individual's personal circumstances to their decision (McCann et al., 2013). This synthesis explored people's reasons for accepting or declining trial participation. Only one study included in this synthesis reported patients' reasons for accepting or declining participation in a trial that included a surgical intervention.

Compared to RCTs of medical treatments, reports of RCTs of surgical interventions are sparse (Solomon and McLeod, 1998). Despite this research gap, in recent years there has been an increase in surgical trials and research to explore barriers, as well as facilitators to research in this setting (Ahmed Ali et al., 2013). Surgical RCTs can encounter challenges that are not present in RCTs of non-surgical interventions. Several reviews, including one systematic review of patient and clinician surveys, describe barriers to RCTs in surgery. These include the irreversibility of surgical treatments, difficulty in standardizing procedures due to varying surgeon expertise and ability, surgeon difficulties with equipoise, the influence of peri- and post-operative care on outcomes, strong patient treatment preferences, and a dislike of randomisation (Abraham et al., 2006; Lilford et al., 2004; McLeod, 1999). Although they provided a comprehensive list of barriers, these reviews did not seek to understand patients' experiences of recruitment in surgical trials.

Since these reviews, several qualitative studies exploring patients' experiences of surgical trials have been published, although little attempt has been made to synthesize the growing body of qualitative evidence specific to surgical trials. Synthesizing qualitative research allows qualitative findings to be combined to reveal new insights or identify whether saturation of themes has occurred (Campbell et al., 2011). In addition to qualitative evidence, several studies examining patients' experiences of recruitment and participation in surgical trials have collected quantitative data through questionnaires or structured interviews. This systematic review reports a synthesis of the evidence relating to patient experiences of surgical trials. Qualitative and quantitative data were included to allow a complete understanding of patients' experience to be achieved. A segregated approach was used, synthesizing the qualitative and quantitative evidence separately before integrating the findings of both syntheses.

This review aimed to answer the following question: 'What is the experience of patients (aged 18 and above) who are invited to participate in surgical RCTs?' The objectives of the review were to:

- (i) understand patients' experiences of recruitment and participation in surgical trials, and
- (ii) identify barriers and facilitators to participation in surgical trials.

2. Method

The Joanna Briggs Institute Reviewers' Manual was used to inform this review's methods (McArthur et al., 2017). This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Supplementary Table 4) and the Enhancing Transparency in Reporting the synthesis of Qualitative Research (ENTREQ) guidelines (Tong et al., 2012). This review was registered in PROSPERO in August 2017 (Phelps et al., 2017).

2.1. Inclusion and exclusion criteria

Studies of patients aged 18 years and over who were invited to participate in an RCT where at least one of the treatment arms was surgical were included. Studies that sought patients' views on hypothetical trials were excluded. Additionally, studies which report the experiences of patients participating in a range of trials were excluded if it was not clear which findings related to surgical trials. As this review was interested in understanding patients' experiences, evidence was restricted to interview, focus group, and questionnaire data. Conference abstracts and papers not reporting primary research findings were

excluded. Only papers published in English were included.

2.2. Search strategy

MEDLINE, Web of Science (Social science citation index and science citation index), and CINAHL were searched to identify published literature. An information specialist refined the search strategy (Supplementary Table 1). Searches used free text and MeSH terms relating to the following: i) sample, for example patients; ii) the phenomena of interest, for example RCT, surgery, and participation; iii) design, for example qualitative research and questionnaire; and iv) evaluation, for example experience and views. The reference lists of included studies were hand-searched to maximize the identification of relevant articles. Searches were conducted in March 2017 and repeated in November 2018 and February 2020.

2.3. Screening

The titles and abstracts of identified articles were assessed by one reviewer, with a second reviewer assessing 10% of the sample. Articles that clearly did not meet the criteria were rejected at this stage. Full text was retrieved for potentially relevant articles. These were read by two reviewers independently to determine whether they met the inclusion criteria. Disagreements between reviewers were discussed and resolved in discussion with a third reviewer.

2.4. Data extraction

Data extraction tools were designed for this review (Supplementary Tables 2 and 3), based on data extraction tools used in a previous review by one of the authors (Lucas et al., 2007) and on the guidance of the Centre for Reviews and Dissemination, University of York (NHS & Centre for Reviews and Dissemination, 2001). The tools were piloted to ensure that they captured all relevant data. The following information was extracted from all studies: i) setting; ii) sample size and characteristics; iii) aim; iv) methods of recruitment, data collection, and data analysis; and v) details of the RCT. For the qualitative studies, all text related to the review objectives within the 'results' and 'discussion' sections were extracted. All results relevant to our research objectives were extracted from the quantitative papers. Where studies collected data from multiple sources, for example from patients and staff, only data from the patients were extracted.

2.5. Risk of bias assessment

Qualitative studies and studies reporting qualitative and quantitative data were assessed using Harden et al.'s. (2004) seven quality criteria (Harden et al., 2004). These criteria, developed to appraise studies of people's views, were used to highlight possible flaws or biases within the qualitative studies. The criteria appraise the i) research aims, ii) description of study context, iii) sample and recruitment strategy, iv) data collection and analysis methods, v) attempts made to establish the reliability or validity of data analysis, vi) description of a theoretical framework or literature review, and vii) the inclusion of original data in the manuscript.

Quantitative studies were assessed using Petticrew et al.'s. (2006) framework for appraising survey research (Petticrew et al., 2006). This framework was selected as the quantitative studies in this review all used a questionnaire design and many reported descriptive statistics only. As comparisons between subgroups or variables were not relevant to our review objectives, the following three items were removed from the framework: i) is there evidence of multiple statistical testing or large numbers of post hoc analyses? ii) if the study compares different subgroups from the survey, were the data obtained using the same methods from these different groups? and iii) are the statistical analyses appropriate? The remaining 11 items appraised the appropriateness of

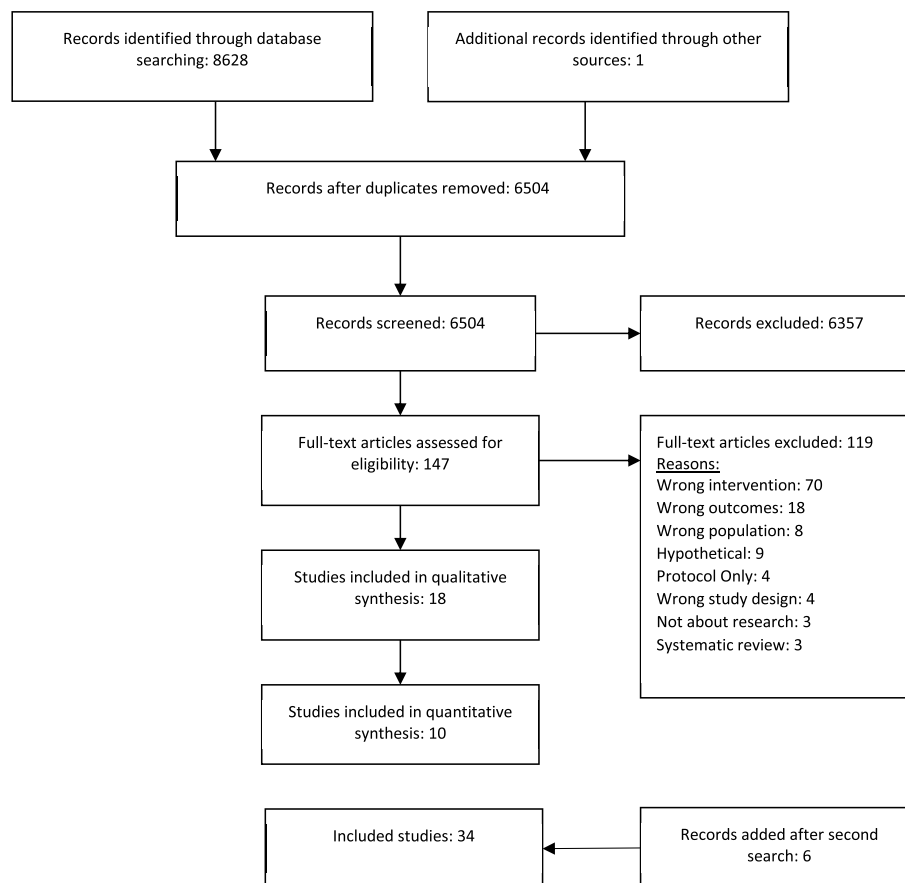


Fig. 1. Flow of studies into the review.

the survey, consideration of ethical issues, the description of the population and data, the sample, and evidence of bias.

Studies were given an overall quality rating of good, fair, or poor. One reviewer assessed the quality of all the articles, and a second reviewer assessed the quality of half the articles. Disagreements were resolved through discussion with a third reviewer. Studies were not excluded based on the quality of reporting, as this may lead to valuable insights being disregarded (Hannes, 2011).

2.6. Analysis

This review used a segregated approach, synthesizing the qualitative and quantitative evidence separately, before integrating the findings of both syntheses. This approach involved three stages. First, a thematic synthesis of the qualitative data was conducted.

Thematic synthesis is a widely used method of bringing together and integrating qualitative studies about peoples' experiences. It is based on thematic analysis, a method of analyzing data in primary qualitative studies (Thomas and Harden, 2008). Thematic synthesis was selected for this review as it can accommodate large numbers of studies and can be used to synthesize the findings of heterogeneous studies (Booth et al., 2016). In addition, this approach to synthesis fits with this review as it enables barriers and facilitators to be identified (Thomas and Harden, 2008).

The thematic synthesis was conducted by two experienced qualitative researchers, who drew upon qualitative research principles throughout the analysis. As described by Thomas and Harden (2008), a thematic analysis was conducted on extracted data. A reflexive approach to thematic analysis was used, which acknowledges the active role of the researcher in interrupting patterns of meaning within the data (Braun et al., 2019). This process involved coding the data from

the studies inductively line-by-line based on meaning. Semantic and latent coding were used to develop an in-depth understanding of participants' experiences. Coding was an iterative process, with new codes added and existing codes developed with the addition of each study. Codes were discussed and examined to check for consistency and whether additional codes were required. Categories were developed by comparing and organizing codes into groups. Themes were developed by exploring the categories in-depth and by comparing within and across studies. Categories and themes were revised and defined as our understanding of patients' experiences of participation evolved.

The following strategies were adopted to ensure trustworthiness in this analysis (Lincoln and Guba, 1985): Reviewers were immersed in the world of the participants through reading and rereading the data, data from the primary studies were included to illustrate the reviewers' interpretations, and detailed descriptions of the studies and review methods were provided. The team, with backgrounds in Psychology, Nursing, Public Health, and Surgery, met regularly throughout analysis to discuss the developing categories and themes.

Second, a narrative review of the quantitative data was conducted. A meta-analysis was not appropriate as the studies were too diverse in terms of setting, participants, and outcomes. The Joanna Briggs Institute Reviewer's Manual recommends, "where a systematic review seeks to address multiple questions, the results may be structured in such a way that particular outcomes are presented under specific questions" (McArthur et al., 2017: Online Chapter 4.3.4.6.3). As the quantitative data included in our review addressed multiple questions relating to patients' experiences of participating and being invited to participate in a surgical trial, findings were synthesized based on outcome. For example, all data relating to participants' recall and understanding were grouped together and summarized, as were all data relating to participants' reasons for participating.

Finally, the qualitative and quantitative findings were integrated by comparing the findings of both syntheses. Barriers and facilitators to participation in surgical trials were identified by the team through discussion of the syntheses.

3. Results

Of the 6504 records identified through our systematic searches, 6356 were removed at the title and abstract screening stage. Full text was retrieved for 147 articles. Of these, 28 met the inclusion criteria for this review. Reasons for exclusion are presented in Fig. 1. In November 2018, the searches were re-run to identify literature published since the previous searches, with 1652 records retrieved. Six of these met the inclusion criteria for this review and were added to the syntheses. The searches were re-run in February 2020 to identify any relevant literature published since the completion of the review, with 171 records retrieved. One qualitative study met the inclusion criteria for this review (Griffin et al., 2019). As it was published after the completion of the review, it was not added to the synthesis. This study does not reveal any new insights into patients' experience of participating in a surgical trial that are not reflected in this review.

During title and abstract screening, reviewers disagreed about the inclusion of three studies. Full text articles were retrieved for these studies. During full text screening reviewers disagreed about the inclusion of 12 studies. Most commonly, reviewers disagreed about whether certain interventions (e.g., coronary angioplasty) were surgical. Procedures, such as these, which are invasive or require anaesthetic, were included as the experience was considered to be similar to that of other surgical interventions.

3.1. Characteristics of included studies

Thirty-four articles (described in Table 1) about 28 surgical trials were included in this review. Eleven were quantitative and 21 were qualitative. Two articles report qualitative and quantitative findings. Twenty studies were conducted in the UK, five were from the US, five from other European countries, one from Australia, one from Japan, one from Canada, and one study was multi-country. These articles report the views of patients participating or invited to participate in trials for a variety of conditions as shown in Table 1. Eighteen articles included the views of participants and patients who declined to participate (hereafter referred to as 'decliners'), 13 only included study participants, and two only included study decliners. For one study, it was unclear who the participants were. Four studies included preference arms, where participants could participate in the trial and chose their treatment allocation. Throughout the results, studies are referenced by the number that appears in Table 1. Supplementary Table 5 summarizes the main results of the studies.

3.2. Risk of bias

Nineteen of the 23 studies assessed using Harden et al.'s. (2004) criteria were considered good quality and four were considered fair. The majority of the qualitative studies provided a clear description of the context and data collection and analysis methods, although the majority also provided insufficient detail of participant recruitment or participant characteristics. Five quantitative studies were considered good quality and six were considered fair using Petticrew et al.'s. (2006) framework. Most quantitative studies discussed ethical issues and used a survey that allowed the research question to be answered clearly. Supplementary Tables 6 and 7 summarize the risk of bias for each study.

3.3. Qualitative synthesis

The following three interrelated themes were developed from the

qualitative data: 1) making sense, 2) weighing up, and 3) trust. Patients sought to make sense of the trial processes and the treatment options available within and outside the trial and tried to weigh up the best option for themselves. Trust in the trial and clinician influenced patients' decisions. The three themes are presented in turn with illustrative quotes. Supplementary Table 8 shows the number of studies supporting each theme.

3.3.1. Making sense

Patients endeavored to make sense of the trial and consider what participation would mean for them. This process was often a struggle, which was not always resolved. Randomisation and equipoise were particularly difficult for patients to understand and accept, and the way in which the trial was communicated influenced whether patients could make sense of it.

3.3.2. Randomisation

In the majority of studies, the authors described a lack of recall or a degree of confusion relating to randomisation (In Table 1, studies 1–6,9–11,15,16,22,23). Three alternative accounts of randomisation were highlighted: 1) therapeutic misconception, 2) rationing, and 3) choosing treatments.

Confusion was often attributed to therapeutic misconception, which refers to confusion between the goals of research and clinical care (1,5,6,10,11,15,16,22,23). Some patients believed that they would receive the best treatment for them based upon their clinical needs. These patients believed that their treatment allocation was selected by the trial staff or a computer, which considered their clinical information. They trusted the trial and the computer to provide the right treatment for them.

"What does the computer decide on, age, how bad your cancer is? This is kind of a mystery to me. I wouldn't mind knowing why I was rejected".

Eng et al. (2005), p.2611

"Maybe, once they send the dye in, they would see which is the right treatment ... they will be doing the best thing for me ... I think it is a decision of the doctor who is doing the treatment."

Dickert et al. (2015), p.3

In two studies, participants believed random allocation was used to ration treatments due to limited resources or in order to reduce waiting lists (5,6):

Mr Bullock implied that the rationale for allocating him to a treatment was because a patient was needed to fill the quota for the laser treatment at the time he attended the clinic: "Well I think I was slightly cynical about it, I didn't really believe it. I thought that they, you know that ... I really thought that they were just going to divide people up. I thought it was a bit of a con".

Featherstone and Donovan (2002), p.714

Not all patients were aware of randomisation. Gammelgaard et al. (2004b) found some patients thought they were being asked to choose one of two treatments and believed the trial involved blood samples and examinations. Dickert et al. (2015) found patients believed they were being asked to make a decision to receive the study intervention:

The second group of patients did not understand that they had to decide whether or not they would like to participate in a trial. They believed that they were supposed to choose between two treatments; the primary angioplasty or the medical treatment.

Gammelgaard et al. (2004b), p.2317

In contrast, seven studies reported that participants typically understood or recalled randomisation (4,5,8,14,17,19,23).

Table 1
Characteristics of included studies.

Author, Year, Country	Sample	Participant characteristics	RCT details
1. Bidad et al. (2016), UK	27 (17 participants, 10 decliners)	- Women - Mean age 53.7 93% (n = 25) white British	Breast cancer - Quest A: extended autologous latissimus dorsi (LD) or implant-assisted (LD) breast reconstruction - Quest B: Immediate autologous LD or staged-delayed autologous LD procedures Early prostate cancer - Watchful waiting or radical prostatectomy
2. Bill-Axelsson et al. (2008), Sweden	9 (5 participants, 4 decliners)	- Men - Mean age of sample at the end of 2000 was 69.2	Prostate Cancer - Cryotherapy or external beam radiation therapy
3. Eng et al. (2005), Canada	11 (6 participants, 5 decliners)	Not reported	1. Acute or chronic urinary retention - Laser therapy or standard surgery 2. Lower urinary tract symptoms related to benign prostatic disease - Laser, surgery, and conservative management
4. Featherstone and Donovan (1998), UK	20 participants	Men	Common urinary symptoms - Laser therapy, standard surgery (transurethral resection of the prostate -TURP), or conservative management
5. Featherstone and Donovan (2002), UK	33 (22 participants, 11 decliners)	- Men - Aged 54-81	Acute Myocardial Infarction (MI) - Primary angioplasty or fibrinolysis Female stress urinary incontinence - Retropubic Tension free Vaginal Tape (TVT) or Solyx (and a new Single Incision Sling (SIS))
6. Gammelgaard et al., 2004b, Denmark	32 (23 participants, 9 decliners).	6 women - Aged 43-78	Invasive bladder cancer - Open or minimal access (laparoscopic or robotic) cystectomy
7. Gopinath et al. (2013), UK	23 decliners	- Median age 49 (34-75) 19 White British, 2 Asian, 2 Afro-Caribbean	Hip fracture - Dual mobility acetabular component or standard component
8. Harrop et al., 2016, UK)	10 decliners	8 male - Mean 63.5 (44-74)	Urinary incontinence and vaginal prolapse - Colposuspension/TVT or anterior repair
9. Huxley et al. (2016), UK	10 participants	9 female	Ankle fracture - Close contact casting (CCC) or Open Reduction, Internal Fixation (ORIF)
10. Jackson et al. (2010), UK	16 participants (2 randomised, 14 from the preference arm).	- Women, - Aged 38-81	Parkinson's disease (PD) - Three sham controlled intervention trials
11. Keene et al. (2016), UK	36 participants	- Mean age 67 (60-80). - White British. 27 female 98% white, 71% male, - Women 2 asylum seekers, 2 British Asians, 2 economic migrants from Africa and Europe and 2 white British women who had partners that were non white	Termination of pregnancy for pregnancies of less than 14 weeks' gestation - Medical termination of pregnancy or surgical termination of pregnancy
12. Kim et al., 2012b, US	90 participants.	9 female - Aged 18-35 - Various ethnicities	Unilateral vocal fold paralysis - Laryngeal reinnervation or thyroplasty
13. Lie et al. (2012), UK	30 participants (10 randomised, 20 from the preference arm)	- Aged between early 20s and early 30s 5 women	GORD - Minimal access surgery or continued optimised long-term medical management
14. Mat Baki et al. (2015), UK	11 interviewees (of the 17 patients eligible to participate in the trial – 10 agreed to participate, 4 were willing to be randomised)	<i>Participants</i> 11 male - Mean age 65 <i>Participants who declined their treatment allocation</i> - Mean age 74 1 male <i>Decliners</i> - Mean age 71 7 male	Muscle invasive T2/T3 transitional cell carcinoma of the bladder - A radical surgery (cystectomy) or selective bladder preservation
15. McCann et al. (2010), UK	13 (11 randomised, 2 from the preference arm, 2 decliners)	- Aged between early 20s and early 30s 5 women	
16. Moynihan et al., 2012, UK	24 (14 participants (2 declined their allocation), 10 decliners)	<i>Participants</i> 11 male - Mean age 65 <i>Participants who declined their treatment allocation</i> - Mean age 74 1 male <i>Decliners</i> - Mean age 71 7 male	
17. Paleri et al. (2018), UK	17 (6 decliners, 11 participants)	More men than women were interviewed	Head and Neck Cancer - Nasogastric tubes or gastrostomy
18. Robson et al. (2009) UK	30 (10 randomised, 20 from the preference arm)	- Women - Mean age 24.7 (16-38)	Termination of pregnancy for pregnancies of less than 14 weeks' gestation - Medical termination of pregnancy or surgical termination of pregnancy
19. Soomro et al. (2017), UK	8 (4 participants, 4 decliners)	Participants recruited to the trial were male, aged 55-79	Small renal mass (SRM) - Ablative treatment or active surveillance

(continued on next page)

Table 1 (continued)

Author, Year, Country	Sample	Participant characteristics	RCT details
20. Thornstenson et al. (2009) , Sweden	32 (participants)	• 10 female • Aged 20-38	• Complete rupture of the anterior cruciate ligament (ACL) • Arthroscopic surgical reconstruction plus training or training only
21. Whybrow et al. (2017) UK	19 (9 participant, 10 decliners)	• Men • Median age 36 (25–70)	• Recurrent bulbar urethral stricture • Urethrotomy or urethroplasty
22. Dickert et al. (2015) US	20 participants	• 15 men • Median age 56.5 (44–89) • 11 White/Caucasian	• Acute MI • A coronary ischemic post-conditioning procedure at the time of primary percutaneous coronary intervention (PCI) or PCI
23. Mills et al. (2003) , UK	21 (10 participants, 11 decliners)	• Men • Aged 50-69	• Localised prostate cancer • 1. Radical prostatectomy, radical radiotherapy or active monitoring • 2. Radical prostatectomy or radical radiotherapy
24. Cleret de Langavant et al. (2015) , France and Belgium	46 participants	• Mean age 44.3 (25–58)	• Early stage Huntington's disease • Early human fetal cell allografts or late human fetal cell allografts
25. Cannard et al. (2018) US	27 participants	• 27 of the 29 pilot study participants completed the questionnaire • Mean age of pilot study participants 61, (51–74) • 3 pilot study participants were female • Caucasian	• Early-stage Parkinson's Disease • Deep brain stimulation (DBS) plus optimal drug therapy (DBS + ODT) or ODT alone
26. Constantinou et al. (2012) , Australia	40 (20 participants, 20 decliners)	<i>Participants</i> • Mean age 72.2, • 12 male, <i>Decliners</i> • Mean age 73.1, • 11 male,	• Cataract surgery • Two Intraocular Lenses used in cataract surgery
27. Gammelgaard et al., 2004a , Denmark	181 (103 participants, 78 decliners)	<i>Participants</i> • Mean age 60, • 25% (n = 27) female <i>Decliners</i> • Mean age 61, • 30% (n = 23) female • Women, • Age ≥ 30 36% (n = 571),	• Acute MI • Primary angioplasty or fibrinolysis
28. Hannah et al., 2002 , International	1596 participants	• Mean age 61, • 30% (n = 23) female • Women, • Age ≥ 30 36% (n = 571),	• Breech presentation at term • Planned caesarean section or planned vaginal birth
29. Kim et al., 2012a , USA	71 (61 participants, 10 decliners)	<i>Participants</i> • Mean age 59.2 • 65.6% male (n = 40) • 96.7% white <i>Decliners</i> • Mean age 61.7 • 80% male (n = 8) • 90% white	• Parkinson's Disease • Sham controlled surgical trials
30. Mostafa et al. (2013) , UK	166 (135 participants, 31 decliners)	• Women • 62 aged 26–44, 85 aged 45–64 19 aged ≥ 64	• Female stress urinary incontinence • Single-incision mini slings (SIMS-Ajust) or standard midurethral sling (SMUS-TVT-O)
31. Salji et al. (2014) , UK	18 (4 participants, 14 decliners)	• Men	• Localised radiation-recurrent prostate cancer • Deferred androgen deprivation therapy (ADT) or upfront cryotherapy
32. Sato et al. (2010) , Japan	36 (6 participants, 30 decliners)	• Not reported	• Small hepatocellular carcinomas • Local ablation therapies (LAT) and surgery
33. Winters et al., 2015 UK	51 (23 participants, 28 decliners)	• Women	• Breast cancer • Quest A: extended autologous LD or implant-assisted LD breast reconstruction • Quest B: immediate autologous LD or staged-delayed autologous LD procedures
34. Zimmern et al. (2011) , US	520 participants	• Women	• Stress urinary incontinence • Burch Colposuspension and pubovaginal sling

“The computer would choose which option and it was because that's the fairest way to do the research so it's not sort of weighted by any other considerations”.

[Bidad et al. \(2016\)](#), p.5

Although some patients recalled that randomisation referred to the involvement of chance in their treatment allocation, some still held

alternative contradictory accounts of treatment allocation. These accounts suggest a degree of confusion (5,23).

“What he said it was either the knife or the radiotherapy or this wait and see business, which would be, if I would agree, by computer random choice and I said, “Well, yes” because I've got in back of my mind that whoever's programmed that computer has got to have some kind of medical knowledge because obviously someone whose

got a very large cancer, which could cause death straight away or within a few months, I can't imagine his name being down on a wait-and-see basis”.

Mills et al. (2003), p.277

3.3.3. Equipoise

Patients found clinical equipoise a difficult concept to accept. Some patients were determined to find the best treatment for them despite a lack of direction from their clinician. In contrast, for some patients equipoise enabled them to make sense of the trial.

In four studies, a minority of patients interpreted equipoise to mean that the treatments were equally successful as opposed to there being no evidence to conclude which was better (1,5,6,23). Others reported that equipoise was not explained to them (16).

“They told me they were doing the trial for mortality ... to see who lived longer ... but nobody used the word ‘equipoise’ or that they literally don't know which is better”.

Moynihan et al. (2012), p.5

Patients who understood equipoise did not all find it acceptable (8,10,14,16,23). Their beliefs about equipoise often shaped their feelings towards randomisation, with several studies concluding that the acceptability of randomisation was dependent upon patients believing that their clinician was genuinely uncertain as to which treatment would be better for them. Many patients felt that one treatment arm must be more suitable for them or that their clinician must have a preference and often referred to characteristics (such as age and past medication) that they felt should help clinicians determine which was right for them. Furthermore, Featherstone and Donovan (1998, 2002) found completing trial questionnaires reinforced this belief as patients thought the information collected could help clinicians determine which treatment was right for them:

Just over half of the participants (12) indicated that they had expected to receive treatment based on their diagnosis and an assessment of their specific needs by a clinician or practical issues, in the way that they perceived normal clinical practice to occur. Their experience of completing several questionnaires and various clinical tests and examinations within the trial helped to reinforce this belief

Featherstone and Donovan (2002), p.713

For some patients, lack of direction or input from their clinician was difficult (1,3,5,6,8,22). Some patients wanted a collaborative approach to decision-making (3), some believed that clinicians should make treatment decisions for patients (22), and others continued to ask their clinician which option they would choose for themselves or their family (2). Lack of direction resulted in these patients trying to decipher the best treatment for them through their own research (8), or by selecting the treatment with which they were familiar (8). These experiences reinforce the patients' difficulty accepting equipoise and their belief that there must be one treatment that is more appropriate for them.

This first patient described how a perceived lack of direction in his initial consultation led him to carry out his own research, which in turn seemed to pre-empt the discussions and decision-making, which took place in his subsequent appointments. He had entered these consultations with a clear idea of the treatment, which he wanted, and as a result could not recall hearing much about the trial at all: “I have done my own little research and in response to ‘well, what do you think?’ I said that I was interested in the neo-bladder operation, in particular the robotics ...”

Harrop et al. (2016), p.5

In contrast, Gammelgaard et al. (2004b) found the explanation of equipoise helped patients to make sense of the trial as it enabled them

to understand why their clinicians were unable to help them decide upon a treatment.

Many patients explained that they were told that the physicians did not know which of the two treatments was best. Some patients said that this piece of information explained why the trial made sense and why the physicians were unwilling to give them any advice.

Gammelgaard et al. (2004b), p.2316

3.3.4. Communication

Communication with research and clinical staff influenced how patients made sense of the trial and the treatment options. Three aspects of communication were raised: 1) trial jargon, 2) information sheets, and 3) inconsistencies between information they were given and equipoise.

In several studies, trial jargon caused confusion (4,16,20), with terms ‘random’ and ‘trial’ which have a specific meaning to researchers and a different meaning to patients. Featherstone and Donovan (1998) found patients considered the term ‘trial’ to mean a treatment was being ‘tried out’ while ‘random’ conveyed the idea of ‘without reason’. For some patients, the comparison of randomisation to a lottery led to concerns that this process resulted in winners and losers, which was considered an unacceptable way of allocating treatment.

“When you're desperate from pain and anxiety and worried what this is all about then a word like ‘lottery’ is not a word that you are really happy about, because it sounds like you'll die if you draw the wrong lot”.

Gammelgaard et al. (2004b), p.2320

Gammelgaard et al. (2004b) and Dickert et al. (2015) found that in an emergency context information sheets were difficult for patients. Some patients did not recall receiving an information sheet, some patients did not read it, and some patients who did read it could not make sense of it.

“They told me to read it and I said ‘alright’, but it made no sense to me at all because of the situation I was in—lying on an ambulance-stretcher not yet undergoing treatment, and then the first thing that happens is that they hand me this sheet”.

Gammelgaard et al. (2004b), p.2317

Patients noticed inconsistencies within the information provided to them (6,8,16). Harrop et al. (2016) reported that patients observed direct and indirect messages from the clinical team that undermined equipoise. For example, patients interpreted information about the benefits of robotic surgery, such as smaller cuts and quicker healing and being told that they were fit for robotic surgery during their pre-operative assessment, as confirmation that it was the better treatment. Awareness of their surgeon's reputation in delivering robotic surgery also led some patients to believe this would be their surgeon's preferred option. Gammelgaard et al. (2004b) found patients believed that the primary angioplasty was superior to medical treatment as the information sheet stated that in other countries studies have shown that acute balloon expansion provides a normal blood flow in 95% of patients compared to only 50% of patients treated with clot dissolving medicine. Furthermore, Moynihan et al. (2012) found staff initially told some patients that they only had one treatment option, only to be later told other options including trial participation were appropriate for them.

Only a small number of patients felt that their consultants conveyed equipoise or messages of uncertainty with regards to the different surgery options ... Others recalled the more general positive messages about keyhole and robotics which they received from their clinicians, which convinced them that this was the route to go down: “Well, he was saying about you know smaller cuts and that sort of

thing and that uh, less to heal and quicker, it'll heal quicker and all that sort of thing yes, everything in favour of it as I say ... the fact that that particular surgeon said 'well at least it's got a steadier hand than me'; I thought well that's something".

Harrop et al. (2016), p.6

3.3.5. Weighing up

Patients' decisions to participate were based upon weighing up several factors. Motivations for participation, namely altruism and personal benefit, were balanced against the strength of patients' treatment preferences and the potential risk of randomisation.

3.3.6. Conditional altruism

Seventeen papers (1–3,5–8,10,11,14–19,21,22) discussed altruistic motivations for participation, which both patients who declined trial participation as well as those who accepted it expressed. In some studies, altruism was described as conditional (1,10,15,17). Interest in participating stemmed from a desire to help future patients or contribute to science, although patients were unlikely to participate solely based on altruism. Participation tended to be dependent upon patients perceiving personal benefit or no/little harm or effort for themselves (1,10–12,17,19, 22). Common benefits of participation included: quicker access to treatment (14–16,20), more attention or monitoring (1,3,10,14,15,19), the ability to avoid making a decision about treatment (1,6,13,18), and the opportunity for a treatment that was otherwise unavailable (6,15,17).

Our main findings were (i) that willingness to help others and to contribute towards furthering medical knowledge featured strongly among the reasons people gave for being interested in participating in the trial, but (ii) decisions to take part were also presented as conditional on individuals additionally perceiving some benefit (and/or no significant disadvantage) for themselves.

McCann et al. (2010), p.4

3.3.7. Development of treatment preferences

Patients' preferences for one of the trial treatments ranged from no preference to strong preferences. Treatment preferences were based upon patients' perceptions of the pros and cons of each treatment, whether the treatment was new or standard, and the influence of others.

Patients developed preferences by weighing up the pros and cons of each treatment option. For some patients this was an active process that involved researching and thinking about their options. Other patients had instinctual feelings about the treatments. The factors that influenced patients' treatment preferences included invasiveness of surgical options (3,7,8,10,21), recovery times (3,8,10,21), and the desire for a curative or permanent solution (14, 20,21). Their individual circumstances also influenced how they perceived the pros and cons of each treatment, with recovery time important for those who work. Some patients' preference stemmed from wanting to avoid one of the treatments (1,11,14,16,18,19). Some patients did not have a preference, accepted equipoise, or found the pros and cons of the different treatment options were balanced for them (3,6,14,17,20,21,23) and for these patients randomisation was more acceptable.

"As soon as they said implant I baulked at implant because I didn't want an implant".

Bidad et al. (2016), p.5

"I wanted the best option and the least invasive option and that seemed to be the smallest cut and the better surgery seemed to be the robot".

Harrop et al. (2016), p.5

For some patients, whether the treatment was new or the standard treatment influenced their preference (3,7,11,22). Some patients favored standard treatments as these were tried and tested and they did not want to be 'guinea pigs' (3,7). On the other hand, some patients believed that the new treatment might be better as new technology could be more advanced (3,11,22). Some patients consented to participate as the new treatment was only available in the trial (3,11).

Success was associated with the availability of long-term data and that TVT was a commonly performed procedure. SIS being under research was associated with the negative rather than positive outlook about the success of the SIS. The guinea pig feeling was also described by some women.

Gopinath et al. (2013), p.971

There was a preference for CCC as participants had thought through this option as the 'new' intervention and were convinced of its value.

Keene et al. (2016), p.89

Patients drew upon a range of sources when weighing up their options (2,3,7,8,10,14,17–19,22). Sources included the experience of family or friends who had received these treatments, the experience of past patients, their own experiences of surgery, and the views of their GP or family and friends with medical backgrounds (2,3,7,8,10,14,17–19,22). Patients also carried out research on the internet or from books to learn about their options (3,7,8). Some patients considered cues from clinical staff which they believed suggested one treatment to be superior to the other, as discussed in the theme making sense (6,8). Others were told directly by their clinician which treatment they would advise (3,5–7,10,14) and in one study a clinician recommended a patient decline participation (3).

"I had a neighbour who was suffering terribly before he died, so for me it wasn't difficult to opt for surgery".

Bill-Axelson et al., 2008, p.360

3.3.8. Minimizing the risk of randomisation

The risk of not receiving the best treatment for them differed depending on the trial and patients' attitudes towards the treatments, randomisation, and equipoise.

In three studies some patients explained that they participated on the understanding that they could withdraw should they not get their preferred treatment (16,17,23). They wanted to participate but only if they would receive their preferred treatment. Conversely others explained that they would have accepted their least preferred treatment.

"... If I had been randomized to radiotherapy I would have dropped out ... I didn't tell anybody".

Moynihan et al. (2012), p.7

In four studies, there were preference arms allowing patients to select their preferred treatment and still participate (10,13–15,18). For these participants, the costs and benefits of participation differed to those who were allocated their treatment by randomisation. Those that did consent to randomisation in these studies did not express preferences or felt it was important to properly participate in the trial.

"Because I didn't know anything about operations and when he said that (...) I was a candidate for both. I thought, well if I'm going to do the study, you might as well do it properly because there's no point in half doing it".

Jackson et al. (2010), p.699

Patients' understanding of randomisation and acceptance of equipoise influenced how they weighed up the risks of participation. For patients who believed their clinician was genuinely uncertain as to which treatment was best for them or who did not have a treatment

preference, the risk of randomisation was, in a sense, minimized. Similarly, patients who demonstrated the therapeutic misconception avoided the decision to 'risk' not gaining the best treatment for them by participating, as they believed that they would be allocated the best treatment for them.

"I reckoned that if the two treatments were equally good, or if they did not know which one would be superior, then I might as well participate because after all they needed somebody to take part in this trial to find out about it".

Gammelgaard et al. (2004b), p.2319

3.3.9. Trust

Patients' trust in the trial and their clinicians shaped their decision to participate or not. While some patients demonstrated trust in the trial, others became distrustful. Trust in the skill of their surgeon was also important for some patients when deciding whether to participate.

3.3.10. Trust in the trial

Patients' trust in the trial was influenced by their trust in their clinician and their attitudes towards equipoise and randomisation.

Some patients described 'not knowing' the treatments (2,10,20). They did not have a preference or know which of the treatments were best for them. They were therefore reliant on the clinicians to take care of them and their decision to participate was dependent upon this trust.

"I didn't know anything ... you have to trust the doctor who's taking care of you".

Bill-Axelsson et al. (2008), p.360

For others, trusting that their clinician was genuinely uncertain about which treatment was best for them was important in their decision to accept randomisation and participate in the trial.

"I guess I'd like to think I could trust the surgeon to think, well, either way would be advantageous to me and (if) I was within that category that it didn't matter which operation, the outcome would be the same and so as long as I wouldn't have had any detrimental effects towards it, then I think I would have still gone ahead with it".

Jackson et al. (2010), p.701

"I don't care, since they don't know, but I trust the doctors".

Thornstesson et al. (2009), p.5

Patients demonstrating the therapeutic misconception, as discussed within the theme making sense, trusted the trial. They believed that they would receive the best treatment for them and trusted the trial to provide this for them.

"I've got in (the) back of my mind that whoever's programmed that computer has got to have some kind of medical knowledge because obviously someone who's got a very large cancer, which could cause death straight away or within a few months, I can't imagine his name being down on a wait-and-see basis. What I'm trying to say, there's got to be a level somewhere where they can say, "Yes, we'll wait," "No, we can't wait." I'm hoping, I'm putting my faith in it".

Mills et al. (2003), p.277

Trust also influenced how patients weighed up the risk of participation. Kim et al. (2012b) found that patients considered sham surgery acceptable despite its invasiveness since they trusted the researcher.

3.3.11. Distrust

Some patients expressed distrust in the trial. Distrust tended to stem from the difficulty accepting equipoise and randomisation or the way in which the trial was communicated.

Some patients struggled to accept that their clinicians did not know

which treatment would be more appropriate for them and this could lead to distrust and frustration.

Trust in the doctor-patient relationship is essential and has a crucial role in recruitment to randomized trials. Ultimately, it was around the issue of equipoise that the men's apparently contradictory views became reconciled (or not): Only if they could accept that the clinician was genuinely uncertain and the treatments were similarly effective could randomisation be seen as an acceptable method of deciding treatment.

Mills et al. (2003), p.279

Some patients questioned the aim of the trial. Some believed that the trial aimed to prove that one treatment was superior to the other (17) or that no treatment was the best option (23). Others believed the trial they were participating in aimed to prove a new treatment was only as good as the standard treatment (3).

However, a few patients did question whether the trial was driven from a position of clinical uncertainty or as a vehicle for proponents of one method to prove that their preferred approach was superior to colleagues.

Paleri et al. (2018), p.79

Some patients were sceptical of randomisation, believing it was used to ration treatments or reduce waiting lists as discussed in the theme making sense (5).

Communication with the trial or clinical staff could hinder patients' trust in the trial. Patients struggled with what they perceived to be inconsistencies within the information they were provided and between the information they received and their experiences, as described in the theme making sense. Featherstone and Donovan (1998) for example, found one patient felt misled as they did not pick the envelope containing their treatment allocation or see it being opened.

Information given to patients indicated that clinicians would open treatment allocation envelopes in front of patients. In practice, this was not possible. For some, not seeing the envelopes suggested that treatment could have been determined by clinicians. For Mr Symonds, it was the source of distrust about the study.

Featherstone and Donovan (1998), p.1179

3.3.12. Trust in their surgeon's skill

Trust in their surgeon's skill was discussed in two studies of patients who declined participation. As described within the theme weighing up, patients considered the expertise of the surgeon in performing the experimental treatment arm. Harrop et al. (2016) found that some patients considered the experimental arm to be tried and tested; they described confidence in their surgeon and were aware of their surgeon's strong reputation in delivering pioneering robotic surgery. For most patients this was their preferred treatment option and they trusted their surgeon to perform it.

"But he said 'oh but we're not sure yet' um 'what's the best' and I said 'well how long have you been doing (the robot) for?' And I think he said '2 years' but I could be wrong. And so I said 'I'll go for the robot' because you know it might be less invasive and easier to get better".

Harrop et al. (2016), p.7

In contrast, some patients expressed concern about the role of their individual surgeon in performing the new experimental procedure, due to a lack of local outcome data or lack of experience using the new procedure (7).

"(I) have looked online about Solyx and it has only been tested in a small group of patients. How many cases have you done here and how many cases has Dr. XX?".

Table 2
Summary of quantitative findings.

Category	Studies	Summary of findings
Recall and understanding	Dickert et al., 2015; Cleret de Langavant et al., 2015; Gammelgaard et al. (2004a); Mills et al. (2003)	• The majority of participants were able to recall information about the trials
Sources of information	Dickert et al. (2015); Gammelgaard et al. (2004a); Sato et al., 2010	• The majority of participants understood randomisation • In emergency contexts, not all participants read or recall reading the information sheet • Patients who declined participation reported referring to the information sheet as well as the opinion of their clinician, GP, family and other patients when making their decision
Satisfaction with information	Cannard et al. (2018); Cleret de Langavant et al., 2015; Gammelgaard et al., (2004a); Winters et al. (2015)	• Participants tended to agree that they were presented with sufficient information • More participants than decliners were satisfied with the information they received
Satisfaction with participation	Cannard et al. (2018); Gammelgaard et al. (2004a); Hannah et al. (2002); Zimmern et al., 2011	• The majority of participants would participate again • Travel time, completing forms, and the financial commitments (for example taking time off work) were reported to be the most burdensome aspects of participation
Reasons for decision	Cannard et al. (2018); Constantinou et al., 2012; Cleret de Langavant et al., 2015; Gammelgaard et al. (2004a); Kim et al. (2012a); Salji et al. (2014); Sato et al. (2010); Zimmern et al. (2011)	• Patients participated for personal benefits such as seeing an expert, gaining attention, and receiving an otherwise unavailable treatment • Patients also participated for altruistic reasons • Reasons for declining participation included patient treatment preferences, dislike of randomisation, and wanting clinicians to decide treatment
Ease of decision-making	Dickert et al., 2015; Gammelgaard et al. (2004a); Winters et al. (2015)	• Ease of decision-making differed between studies • Some patients made their decision within minutes or hours but for others it took days • Participants felt that they could have said no to participating in the study
Attitudes	Constantinou et al., 2012; Dickert et al. (2015); Gammelgaard et al. (2004a); Mills et al. (2003)	• The majority of participants and decliners reported moderate or a great deal of trust in the integrity of clinicians • The majority of participants reported a great deal of belief in future patients benefiting • More participants than decliners found it acceptable for clinicians to ask patients to make a decision about research after an acute MI • The majority of decliners did not accept equipoise

Gopinath et al. (2013), p.971

3.4. Quantitative synthesis

Data from quantitative studies were organized into seven categories: 1) recall and understanding, 2) sources of information, 3) satisfaction with information, 4) satisfaction with participation, 5) reasons for decision, 6) ease of decision-making, and 7) attitudes. Table 2 summarizes these categories.

3.4.1. Recall and understanding

Four studies report participants' recall or understanding of the trial (22–24,27). These studies showed the majority of participants understood randomisation and could recall information about the trial. Gammelgaard et al. (2004a) found participants were able to recall more information than decliners. Seventy-two percent ($n = 78$) of participants and 46% ($n = 36$) of decliners recalled being informed about the purpose of the study; 79% ($n = 85$) of participants and 46% ($n = 36$) of decliners understood that treatment would be allocated by drawing lots; and 89% ($n = 96$) of participants and 82% ($n = 64$) of decliners understood that participation was voluntary. Despite such rates of recall, less than half of participants (40%, $n = 43$) and decliners (20%, $n = 15$) recalled the potential benefits (40%, $n = 43$) and fewer participants (29%, $n = 31$) and decliners (17%, $n = 13$) recalled the risks of participation. Mills et al. (2003) found that participants' and decliners' recall were similar. Nine of 10 participants clearly recalled 'chance' and eight of nine decliners clearly or possibly recalled 'chance'. All participants and decliners clearly or possibly recalled 'treatment comparison', although all decliners clearly or possibly recalled 'equipoise' compared to only seven of 10 participants. Cleret de Langavant et al. (2015) found that the majority of participants understood the

consequences of randomisation (69%, $n = 32$) and recognized the research purpose of the trial (80.4%, $n = 37$). The mean number of risks recalled by participants was 5.5 out of 9. Dickert et al. (2015) found 11 of 20 participants recalled being asked to participate in a research study while they were in hospital.

3.4.2. Sources of information

Three studies reported participants' and decliners' interactions with the information sheet. In an emergency context, Gammelgaard et al. (2004a) found 80% ($n = 62$) of decliners and 25% ($n = 27$) of participants did not read the information sheet and Dickert et al. (2015) found 76% ($n = 13$) of participants did not read or could not recall whether they read the forms they were given. Sato et al. (2010) found that the majority of decliners (76.6%, $n = 23$) referred to the information sheet when making their decision along with the opinion of a clinician ($n = 36$), family ($n = 4$), and other patients ($n = 2$).

3.4.3. Satisfaction with information

Four studies reported participants' and decliners' satisfaction with the information they received (24,25,27,33). Cannard et al. (2018) found 96% ($n = 26$) of participants agreed they were presented with sufficient information about the study and 100% ($n = 27$) agreed they were presented with sufficient information about participation. All participants agreed that they were provided with accurate representations, that the principle investigator was able to answer their questions, and that the research team communicated effectively. Winters et al. (2015) and Gammelgaard et al. (2004a) found that more participants than decliners were satisfied with the information they received about the trial. Seven percent of decliners from both Winters et al. (2015) ($n = 2$) and Gammelgaard et al. (2004a) ($n = 5$) studies reported receiving too much information while 29% ($n = 23$) of decliners from Gammelgaard et al. (2004a) study reported receiving too little

information. Furthermore, Winters et al. (2015) found the majority of participants and decliners (70.6%, $n = 36$) reported that the DVD about the study was useful. In Cleret de Langavant et al. (2015) study, the mean score for satisfaction with the information was 16.9 out of 23.

3.4.4. Satisfaction with participation

Four studies reported participants' and decliners' satisfaction with participation (25,27,28,34). Hannah et al. (2002) and Gammelgaard et al. (2004a) found the majority of participants would participate again. Gammelgaard et al. (2004a) found 81% ($n = 87$) of participants would make the same decision again compared to 48% ($n = 37$) of decliners. Similarly, Hannah et al. (2002) found 87.1% ($n = 1375$) of participants would definitely or probably participate again. Hannah et al. (2002) found 61% ($n = 988$) of women liked being in a trial as they felt reassured about their infant's health, while 5.8% ($n = 93$) disliked participation as they did not like the intervention they received. During their final follow-up visit in the Zimmern et al. (2011) study, around a quarter (24%, $n = 125$) of participants reported travel time to be the most bothersome factor of participating. This factor was followed by completing forms, which 21% ($n = 109$) of participants reported as most bothersome. Cannard et al. (2018) found 100% ($n = 27$) of participants agreed that their experience in the trial was positive and would recommended participating in a trial to family/friends but only 81% would participate in another trial. Aspects of participation that were reported as burdensome included the financial commitment (e.g., taking time off work), neuropsychological testing, and washout periods. These were reported by 30% ($n = 8$), 26% ($n = 7$), and 25% ($n = 7$) of participants respectively. Thirty-seven percent ($n = 10$) reported no part of the study to be burdensome.

3.4.5. Reasons for decision

Eight studies report participants' motivations for participation (24–27, 30–32,34). Participants were often motivated by multiple factors. The most common reasons tended to be for personal benefit (24,25,26,27,30,31,34) or altruistic reasons (24,25,27,30–32,34). Personal benefits included being examined by an expert (Gammelgaard et al., 2004a), learning more about their condition (25,26,34), gaining attention (26,34), the chance of receiving an otherwise unavailable treatment (25), and to feel cared for or receive the best care (24,34). Additionally, not knowing which treatment was best and being happy with the idea of randomisation were also reported as reasons for participation (31).

Five studies (27, 30–33) raised reasons for declining participation. These reasons included treatment preferences (31–33), dislike of randomisation (27, 30–33), wanting the clinician to choose their treatment (31,33), and believing that surgeons already had a good idea of which intervention they thought was best (33). Additionally, Sato et al. (2010) found 48% ($n = 14$) of decliners made their decision about treatment before they were invited to participate in the study.

Kim et al. (2012a) and Constantinou et al. (2012) compared the expectations of participants and decliners, and found that participants expected more personal and societal benefits from participation than decliners did. Furthermore, Kim et al. (2012a) and Constantinou et al. (2012) found that decliners perceived greater risk from participation than participants did. For example, in the Constantinou et al. (2012) study 90% ($n = 18$) of decliners expected a moderate or great deal of risk from undergoing trial treatments compared to 45% ($n = 9$) of participants.

3.4.6. Ease of decision-making

Three studies reported ease of decision-making. Gammelgaard et al. (2004a) found 31% ($n = 33$) of participants and 59% ($n = 46$) decliners found decision-making difficult or relatively difficult. Winters et al. (2015) on the other hand, found in one of two studies reported in their paper that 87.5% ($n = 28$) found the decision easy to make and 75% ($n = 24$) made the decision in minutes or hours. In the other study,

63.2% ($n = 12$) found the decision easy to make and for 52.6% ($n = 10$) the decision took days. Meanwhile, Dickert et al. (2015) found that 13 of 16 participants felt that they were able to make the decision and 62% ($n = 8$) reported having enough time to make the decision. Furthermore Dickert et al. (2015) found that all participants ($n = 13$) felt they could have said no to participation.

3.4.7. Attitudes

Constantinou et al. (2012) asked participants and decliners about their general attitudes towards research. Sixty percent ($n = 12$) of participants and 15% ($n = 3$) of decliners reported their attitude towards medical experiments as very satisfied or satisfied. Ninety percent ($n = 18$) of participants and 70% ($n = 14$) of decliners reported a moderate or great deal of trust in the integrity of clinicians. Most (85%, $n = 17$) participants and 35% ($n = 7$) of decliners reported a moderate or great deal of belief in future patients benefiting. All participants and 70% ($n = 14$) of decliners reported a moderate or great deal of trust in the hospital. Nearly three quarters (70%, $n = 14$) of participants and 50% ($n = 10$) of decliners reported their attitude towards being recruited by the trial clinician as very satisfied or satisfied. A quarter (25%, $n = 5$) of participants and 20% ($n = 4$) of decliners expected the trial clinicians to dislike it when participation was refused.

Gammelgaard et al. (2004a) asked patients, who had suffered an acute MI, whether they found it acceptable that patients in their situation had to decide whether to participate in a scientific study. Fifty percent ($n = 54$) of participants and 34% ($n = 33$) of decliners gave an affirmative answer while 26% ($n = 28$) of participants and 51% ($n = 40$) of decliners gave a negative answer. Dickert et al. (2015) found three of 17 participants thought doctors should have made this decision instead of asking them.

Mills et al. (2003) found that one of 11 decliners showed clear evidence of accepting equipoise while six of 11 showed clear evidence that they did not find equipoise acceptable. In contrast, five out of 10 participants showed clear evidence of accepting equipoise while three showed clear evidence that they did not find equipoise acceptable.

3.5. Mixed-methods synthesis of findings

The qualitative and quantitative syntheses revealed that the decision to participate in a surgical trial is complex, with multiple factors involved in the decision. These factors are encompassed within the three qualitative themes: making sense, weighing up, and trust. Fig. 2 demonstrates the relationship between the qualitative and quantitative findings, depicting how the quantitative categories fit within the qualitative themes. Four quantitative studies reported findings relating to satisfaction with participation. This category does not fit within the qualitative themes.

Qualitative studies highlighted the difficulty patients may experience when making sense of trial concepts such as randomisation and equipoise. Some patients struggled to understand randomisation, some misunderstood randomisation, and for others randomisation was understood but not considered acceptable. Four quantitative studies assessed participants' understanding and recall of the trial. These studies showed that the majority of participants had good understanding or recall of the trial in which they were participating and the concept of randomisation. Gammelgaard et al. (2004a) found decliners tended to be less informed about the study and fewer decliners understood randomisation. Despite this finding Mills et al. (2003) found using both qualitative and quantitative methods that although participants appeared to understand and recall the study information, their accounts of the study often demonstrated confusion and contradictions. Similarly, several qualitative studies demonstrated that being able to recall and understand features of the study did not mean they necessarily made sense to participants. Both qualitative and quantitative studies highlighted that randomisation is not an acceptable method of allocating treatment for all patients. In addition, not all patients accepted

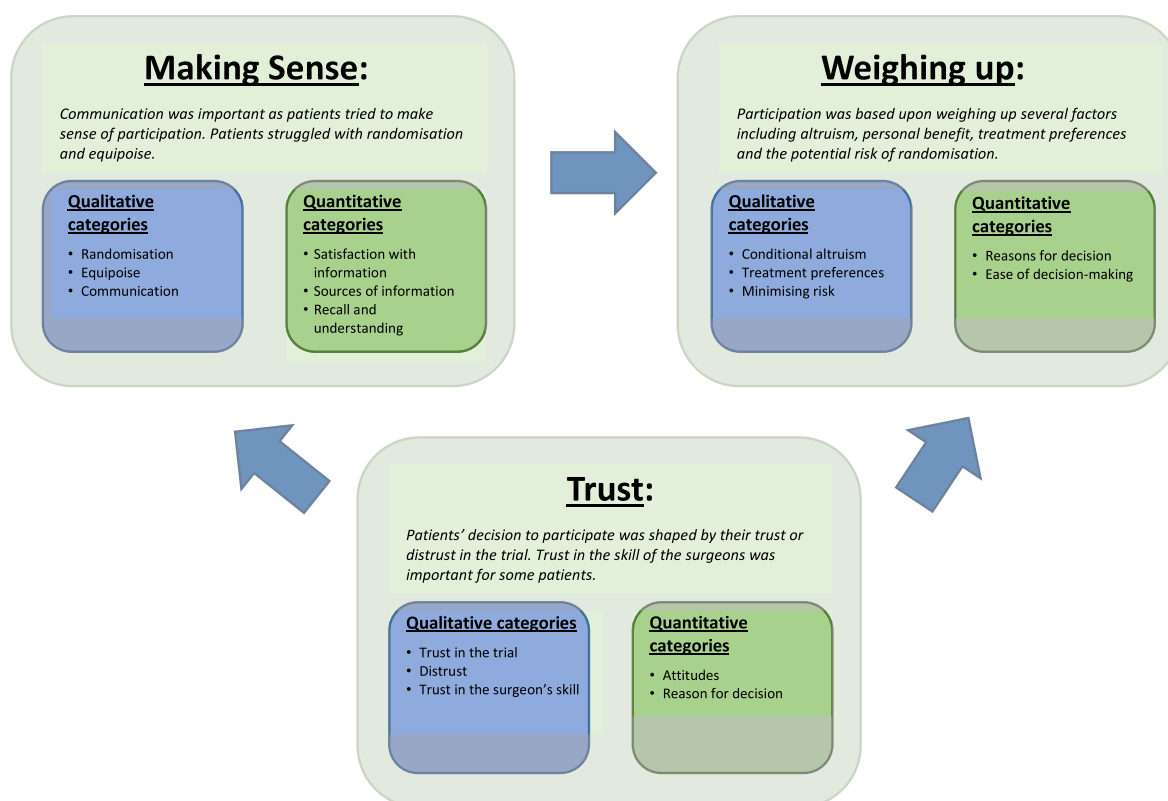


Fig. 2. A thematic map demonstrating the relationship between the three qualitative themes. The ways in which patients made sense of the trial shaped how they weighed up their decision. Trust influenced both how patients made sense of a trial and how they weighed up their decision to participate. Qualitative and quantitative categories are included to show the integration of the quantitative categories within the qualitative themes.

<u>Barriers</u> • Patients struggle to make sense of trials and trial concepts such as randomisation and equipoise (1-5,8-11,14-16,20,22,27) • For some patients, randomisation and equipoise are unacceptable (often because they believed one treatment must be more appropriate for them) (6,8,10,15,16,30-33) • Use of trial jargon such as 'lottery' or 'random' may have negative connotations for patients (3,20,16) • Indirect messages or biased information suggesting one treatment is better than the other can undermine patients' trust in equipoise (5,6,8,16) • Distrust in the purpose of the trial (3,5,17,23) • Patient treatment preferences (1,3,7,8,10,11,14,16,18,19,21,22,31-33) • Risk or harm/ effort to self (1,7,10,12,14,15,17,19,22,26,27,30,31,32) <u>Facilitators</u> • Careful communication to avoid trial jargon and to ensure information is presented in a balanced way (4-7,16,20) • Trust that their clinician is genuinely uncertain as to which treatment would be best for them or that the treatments would have equal benefit (1,5,6,10,20,23,31-33) • Inclusion of preference arm (10,13,15,18) • Potential for personal or altruistic benefit (1,2,3,5-8,10,11,13-21,24-26,34)

Fig. 3. Barriers and facilitators to trial recruitment identified from this review (numbers in parentheses refer to study numbers, see Table 1 for the key).

equipoise as they believed their clinician already had a good idea as to which intervention was best.

Both syntheses highlight the potential for personal benefit as patients' primary motivation for participation, while a desire to help others or further science tends to be secondary. Participants from qualitative and quantitative studies reported treatment preference or dislike of randomisation as reasons for non-participation. Qualitative data demonstrate that patients' decisions to participate or not was based upon weighing up the benefits of participation and their desire to help others or further science with the risks of participation and the strength of their personal treatment preference. These findings support the notion of conditional altruism, with patients motivation to participate in research dependent on the potential to benefit or the unlikelyhood of being disadvantaged or harmed.

In the qualitative studies, trust and distrust featured throughout patients' and decliners' accounts of their experiences. Patients' trust that their clinician did not know which treatment was best for them was particularly important to their decision. Similarly, in three quantitative studies, some patients' reasons for declining participation indicated that they did not accept equipoise or believe that both treatments were likely to be equally beneficial to them. For example, [Winters et al. \(2015\)](#) found that 93% ($n = 26$) of decliners agreed with the statement "I think surgeons already have a good idea of which type of surgery they think best to use", suggesting distrust. In contrast, in two quantitative studies some participants indicated that they believed the treatments would have equal benefit to them.

Including qualitative and quantitative data in this review allowed a more complete understanding of patients' experiences to be achieved. The findings of both syntheses supported one another, increasing confidence in the findings and reducing the potential for bias that either synthesis method may introduce. Furthermore, the qualitative findings provided further insight into the quantitative results.

This review aimed to identify potential barriers and facilitators to participation in surgical trials and identified seven barriers and four facilitators. [Fig. 3](#) presents these barriers and facilitators with references to indicate from which studies each are based.

4. Discussion

This review synthesized studies of patients' experiences of being invited to participate in a surgical trial. Three interrelated themes, encompassing qualitative and quantitative findings, were evident. These relate to: 1) the way in which patients make sense of trials and trial concepts, 2) the way in which patients weigh up participation and the different options available to them, and 3) the influence of trust on how patients make sense of and weigh up participation. First, these three themes will be discussed and then they will be considered in relation to the Theory of Planned Behaviour. Finally, the implications of these findings for clinical practice and the strengths and limitations of this review will be highlighted.

4.1. Discussion of themes

As depicted in the thematic map ([Fig. 2](#)), patients' understanding of the trial and their trust in the trial and staff influenced how they weighed up the risks and benefits of participation. Studies have highlighted trust, altruism, treatment preferences, communication, and understanding as factors that contribute to trial decision-making ([Harrop et al., 2016](#); [Lie et al., 2012](#); [Mat Baki et al., 2015](#); [McCann et al., 2010](#); [Mills et al., 2003](#)). Synthesizing the findings of these studies demonstrates the inter-related nature of these factors. Furthermore, this framework proposes that trust plays a central role in influencing how patients make sense of the trial and how they weigh up their options.

This review found that patients often struggled to make sense of randomisation and equipoise. Where patients recalled these concepts,

confusion was still evident at times. Patients' interpretation of the information they received was shaped by the way in which the information was conveyed. Patients' expectations and attitudes towards healthcare providers and systems also influenced their interpretation of this information. This finding highlights the ethical challenge of achieving informed consent, which relies on patients making a voluntary decision after being fully informed of and considering all aspects of what participation means for them. Checking patients understanding of trial information during the informed consent process has been recommended ([Jefford and Moore, 2008](#)). The findings of this review suggest that tailoring informed consent discussions to the individual might help staff to check and evaluate patients' interpretations of the information they have received and what it means for them.

Patients' understanding of equipoise and randomisation were considered when weighing up their decision about treatments and participation. The consequences of randomisation differed for patients who accepted equipoise compared to those who were determined to receive the best treatment for them. Patients' attitudes towards the different treatment options such as the desire to avoid a certain treatment also influenced their decision to participate. For some, this was described as instinctual while others actively researched their options.

The studies in this review differed in context. Some studies were trials of two standard treatments, some included one surgical arm and one non-surgical arm, some offered patients the chance to receive an intervention that was otherwise unavailable to them, and some included a preference arm allowing patients to choose their treatment while contributing to research. Therefore, the implications of participating differed between trials and these differences were reflected in how patients weighed up their options. This may be an important consideration for surgical trials as the risks and benefits of the treatment arms can differ greatly.

The findings emphasise the importance of trust for patients considering trial participation. Trust in healthcare professionals is believed to relate to competence and best interest ([de Melo-Martín and Ho, 2008](#)). These components are also important to patients' trust in a surgical trial. Some patients considered their surgeons' skill or competence, particularly for new treatments when weighing up whether to participate or not. This process is of importance to surgical trials as they are skill dependant. Some participants considered randomisation acceptable as they believed that their clinician was acting in their best interest. Distrust in the trial tended to stem from a belief that their clinician was not acting in their best interest.

4.2. The Theory of Planned Behaviour

The Theory of Planned Behaviour ([Ajzen, 1991](#)) has been used to understand patients' decision-making about clinical trial participation ([Quinn et al., 2011](#)). The core concepts from the Theory of Planned Behaviour, attitudes, subjective norms, and perceived behavioural control, are evident within the three themes. As described above, when weighing up the decision to participate or not, patients were influenced by their attitudes towards clinical trials and the treatments available to them. They also drew upon a range of sources when considering their treatment and participation, echoing the influence of subjective norms on behaviour. Patients' decisions were influenced by their family and friends, their trust in the healthcare professionals involved in the trial, and a desire to help future patients, which is likely to be perceived as socially desirable behaviour. Patients' perceived behavioural control over their decision and ability to overcome barriers to participation were also reflected within these themes. Qualitative and quantitative studies highlighted potential barriers or burdens of participation such as the time and effort involved, which patients needed to overcome to participate. The studies also demonstrated perceived behavioural control over decision-making, with some patients explaining that they would withdraw should they not receive their preferred treatment or others agreeing to participate as this provided them with an

opportunity to receive an otherwise unavailable treatment.

The application of health behaviour models such as the Theory of Planned Behaviour to trial participation could be valuable. Research into health behaviour shows that changing attitudes, the influence of others, and perceived control over behaviour play a more important role in achieving behaviour change than providing information (Ajzen, 1991). The findings of this review suggest that this may also be the case for trial participation. As these factors will vary between patients, a tailored approach to recruitment is needed to allow patients' attitudes towards trials and treatments to be understood and addressed.

4.3. Implications for practice

Three implications for practice are evident from this synthesis. First, these findings support the use of a patient-centred approach to trial recruitment, which takes into account patients' individual circumstances, attitudes, and expectations. Talking through studies with patients allows staff to pick up cues about patients' concerns and enables staff to acknowledge and potentially address these concerns and tailor information where appropriate. Furthermore, tailoring information to the needs of the individual could help patients to understand what participation means for them, as required to achieve informed consent. Shared decision-making could also be incorporated in a patient-centred approach to trial recruitment. This is where clinicians provide patients with information about all the options that are appropriate for them, enabling patients and clinicians to reach a decision together (Coulter et al., 2008). This synthesis revealed that some patients wished for greater direction from their clinician when deciding which treatment to have or whether to participate or not.

Second, these findings highlight the need for researchers to be aware of the importance of trust, which influenced how patients made sense of trials and how they perceived the costs and benefits of participation. A patient-centred approach to recruitment where staff discuss patients' individual circumstances, concerns, and expectations may enhance the rapport between patients and research staff and foster trust in the trial.

Third, this review showed that the nature of the trial and interventions can influence how patients perceive the risks and benefits of participation. Considering the unique features of the trial as well as patients' individual circumstances and concerns when providing trial information to patients may support their decision-making.

4.4. Strengths and limitations

There are several methodological limitations to this review. Only studies published in English were included and the search did not include grey literature. These limitations may have led to relevant studies being missed. Due to resource constraints, not everything was duplicated so it is possible some errors were made. The quality of the studies included in this review was generally fairly good. No studies were deemed to be of poor quality and no evidence of biases that may influence the trustworthiness of the studies or the interpretation of data were identified. The context in which the studies were set were well described, particularly the details of the trials, although some of the studies included in this review contained small or poorly described samples, which may hinder the transferability of findings. This review included studies from a range of countries and clinical settings. Despite the variation in contexts, this review highlights themes that were common across these studies. Although this review was interested in surgical trials, the findings may have relevance in other clinical settings.

Synthesizing qualitative findings can reveal new insights or identify whether saturation has been reached (Campbell et al., 2011). Despite such advantages, there are limitations to synthesizing qualitative data. Only data that the authors included in their manuscripts was available for inclusion in this review, which might not represent all available data

(Luckett et al., 2013). The authors' interpretation of their data set therefore shaped the data available for this review and consequently the interpretation of the data.

Since completing this review, one study meeting the inclusion criteria has been published (Griffin et al., 2019). The findings of this study support the framework identified within the review. The themes making sense, weighing up, and trust from this review are evident within Griffin et al. (2019) findings. This qualitative study explored frail older patients' experiences of being asked to participate in a surgical trial of two different methods of fixing distal femoral fractures. Griffin et al. (2019) found: i) patients were rarely able to describe the trial in their own words but could recall the trial involved either a 'nail' or a 'plate' to fix their fracture, ii) patients participated as they wanted to help future patients, and iii) patients trusted their surgeon to fix them.

4.5. Future research

The findings of this review emphasise the importance of trust and patients' individual circumstances and attitudes when making a decision about participation. Future research to develop strategies that support staff in tailoring information to patients' individual needs could be considered. This type of research may allow staff to acknowledge and address patients' concerns about a trial and may enhance the rapport between staff and patients. These may in turn influence patients' ability to make an informed decision. Understanding how to foster trust in trials and trial staff could also be beneficial to recruitment.

5. Conclusions

Recruitment to surgical RCTs is challenging. The decision to participate or not is influenced by multiple interrelated factors. These include patients' perceptions of the risks and benefits of participation, their treatment preferences, and the features of the trial. Patients' difficulty understanding and accepting randomisation and equipoise as well as their trust in the trial and trial staff also influence their decision.

The Theory of Planned Behaviour can be used to understand patients' decisions about trial participation. Strategies to improve recruitment to trials often focus on the information about the trial and the way in which it is conveyed. While providing information is important, research into health behaviour using the Theory of Planned Behaviour has shown that changing attitudes, the influence of others, and perceived control over behaviour play a more important role in achieving behaviour change. This finding should be taken into consideration when talking to patients about trials.

The findings of this review suggest that staff should adopt a patient-centred approach to trial recruitment which includes tailoring information to the individual patient and acknowledging and addressing their concerns and attitudes towards the trial. This process may: i) ensure patients are fully informed about the trial, ii) help recruiters build a trusting relationship with patients, and iii) support patients to make their decision about whether to participate.

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Appendix A. Supplementary data

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