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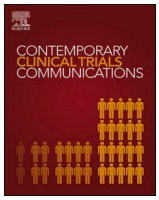

Influences on clinical trial participation: Enhancing recruitment through a gender lens - A scoping review

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ABSTRACT

Background: Suboptimal clinical trial recruitment contributes to research waste. Evidence suggests there may be gender-based differences in willingness to participate in clinical research. Identifying gender-based differences impacting the willingness of trial participation may assist trial recruitment.
Objectives: To examine factors that influence the willingness of men and women to participate in clinical trials and to identify modifiable factors that may be targeted to optimise trial participation.
Material and methods: Electronic databases were searched with key words relating to 'gender', 'willingness to participate' and 'trial'. Included studies were English language and reported gender-based differences in willingness to participate in clinical trials, or factors that influence a single gender to participate in clinical trials. Studies were excluded if they described the demographic factors of trial participants or if the majority of participants were pregnant. Extracted data were coded, categorized, analysed thematically and interpreted using Arksey and O'Malley's framework.
Results: Sixty-three studies were included. Two main themes were identified: trial characteristics and participant characteristics. A number of gender-based differences moderating willingness to participate were observed although only one, 'concern for self' was found to influence actual trial participation rates between genders.
Conclusion: The relationship between factors influencing willingness to participate in clinical trials is complex. The influence of gender on willingness to participate, while important, may be moderated by other factors including socioeconomic status, ethnicity and health condition. Exploring factors that influence willingness to participate specific to a study cohort likely offers the most promise to optimise trial recruitment of that cohort.

1. Introduction

Clinical trials are the gold-standard for evaluating the effectiveness of interventions [1]. However, conducting a successful clinical trial can be challenging [2]. A key contributor to clinical trial failure is low participant recruitment rates [3,4]; up to 35% of clinical trials are discontinued because of difficulties recruiting participants [5] and only 17% of randomised clinical trials in surgery reach target sample sizes within the planned timeframe [4]. Additionally, one third of completed clinical trials are at risk of being underpowered as pre-specified recruitment targets are not attained, jeopardising the trustworthiness of trial findings [4,6].

Strategies to overcome low recruitment rates can include extending trial timelines and incorporating additional recruitment sites [4,6]. However, these strategies often incur a rise in trial costs. In some instances, the cost of overestimating trial recruitment rates can exceed the planned budget by 260% [3]. Moreover, suboptimal clinical trial recruitment and the associated delay or discontinuation raises ethical concerns. Discontinued, delayed or underpowered trials may not meaningfully answer the research question [7], unnecessarily exposing

Abbreviations: WTP, willingness to participate.

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participants to trial interventions without a worthwhile contribution to knowledge. This compromises the implicit ethical contract between researchers and participants [3,6]. Consequently, strategies optimising participant recruitment may reduce clinical trial waste and improve adherence to ethical standards [3].

Many factors influence an individual's willingness to participate (WTP) in a clinical trial, with previous reviews investigating factors among diverse cultures and ethnicities [8–13], and health conditions [13–19]. Despite the breadth of factors investigated in previous reviews, the influence of gender on WTP in clinical trials has not been explicitly explored. Further, while strategies to enhance recruitment to clinical trials have been explored, there is a notable gap in addressing the potential influence of gender on WTP [20]. Men and women do not participate in randomised clinical medical trials at the same rate [21], with a recent systematic review of 300 randomised controlled trials reporting the overall mean enrolment rate of women was 41% of the total number of participants enrolled [22]. Further, men and women differ with regard to health information; women more actively seek health-related information, are more attentive to the health effects of their purchases and receive more informal health-related information from their family members [23]. It follows that men and women may approach the decision to participate in clinical research differently or be influenced by different trial features. However, little is known about the factors influencing the WTP from the perspective of gender. Determining the factors influencing the WTP of both men and women in clinical trials may inform strategies to increase the WTP of both genders, potentially boosting trial recruitment rates. Therefore, the aim of this scoping review was to identify gender-specific differences relating to WTP in clinical trials. With the goal of reducing research waste, a further objective was to summarize any pertinent findings and present them in an accessible format that could function as 'a checklist' for researchers. This format is designed to address the main drivers of willingness to participate for both genders. In this scoping review, 'gender' refers to personal identification while 'sex' refers to biological sex.

2. Material and methods

2.1. Methodological framework

A methodological framework for scoping reviews developed by Arksey and O'Malley [24] was used to guide this review and present a narrative account of the existing literature. The PRISMA-ScR reporting criteria were adhered to Ref. [25].

2.2. Search strategy

A search strategy relating to the terms 'gender', 'willingness to participate' and 'trial' was developed and tested on six electronic medical databases. The search strategy was then refined by one researcher (LH) in consultation with a senior librarian and researchers SB and PO (Appendix 1).

Electronic databases Medline, EMBASE and PsychINFO were searched in July 2022 and uploaded to the bibliographic management software Endnote X7. All primary research was included. Preliminary trials of the search strategy conducted on the CINAHL, PUBMed and Cochrane databases determined these databases did not yield further articles. References of key articles and Google Scholar were also reviewed. Search results were imported into the web-based software platform Covidence [26]. Duplicate references were removed.

2.3. Selecting studies and charting the data

Included studies were English language, peer-reviewed, primary research, qualitative, quantitative or mixed methods studies involving adults that reported gender-based differences in WTP in clinical trials, or factors that influence a single gender to participate in medical clinical trials. Medical clinical trials encompassed studies conducted in healthcare settings, evaluating specific interventions such as medical products, medical devices, lifestyle modifications, or surgeries. These trials compared the effectiveness of the intervention against a comparator, which could be a placebo, no intervention (i.e., standard practice), or another form of intervention [19,20]. Studies exploring WTP in both actual and hypothetical trials were included. Quantitative studies using surveys and questionnaires were included to identify factors influencing WTP in clinical trials and qualitative studies were included to further explore the context of these factors. The review examined responses reported directly by trial participants. Studies were excluded if a majority of participants were pregnant or if the study only described the demographics of those who did or did not participate.

Four researchers (SB,EN, PO [women]; LH [man]) independently assessed study titles and abstracts against inclusion and exclusion criteria in two teams of two, ensuring double checking was adhered to. Full-text articles were retrieved for studies meeting the inclusion criteria and for those requiring further examination to determine eligibility. A final decision on study eligibility was made by consensus.

Data were synthesised using a framework analysis approach adapted for the context of a scoping review. This approach is designed to sift, chart and organise data in accordance with key issues or themes [27]. This method involved familiarization and data extraction, developing a thematic framework, and synthesis and interpretation [27]. Three researchers read the full texts (LH, EN, PO) and extracted relevant content using a standardised data extraction pro rata spreadsheet. Two researchers (LH, EN) used open coding [28] to identify key concepts relating to WTP in a clinical trial, in all papers. Codes were grouped into categories from which a thematic framework was developed. Manuscripts were re-read by two researchers (LH, EN) to refine categories and ensure the thematic framework captured all key concepts outlined in included studies. Themes and domains that emerged from the key concepts and categories were presented to all researchers with final consensus reached by discussion. For single-gender studies, themes were developed separately and then compared and contrasted between the genders. Two researchers (LH, EN) summarised the main facilitators and barriers of WTP for both genders into a table. All authors then reviewed the table, provided comments, and the table was subsequently updated through consensus.

3. Results

Sixty-three studies were included (Fig. 1), comprising a total of 20,414 participants (10,710 women; 9704 men) across 62 (98%) studies. Notably, one study did not report the number of participants included [29]. Study characteristics are summarised in Table 1 and themes are presented in a narrative form below. Appendix 2 provides a summary of the two main themes influencing WTP: trial factors and participant factors. The breakdown covers the 12 identified domains, further categorized into three gender groups: mixed-genders, men, and women.

Two main themes influencing gender-based WTP in clinical trials were identified: factors relating to the trial (trial characteristics) and factors relating to the individual (participant characteristics). A further twelve domains relating to the two main themes were identified (Appendix 3). Themes and domains are described narratively. Illustrative quotes from qualitative studies are included for context (Table 2). In the discussion, domains were further summarised and presented as strategies that may enhance WTP in a clinical trial for both genders.

4. Theme 1 trial characteristics

4.1. Logistics of participation

The perceived burden of trial involvement encompassing factors such as effort, commitment and disruption (e.g. attending appointments,

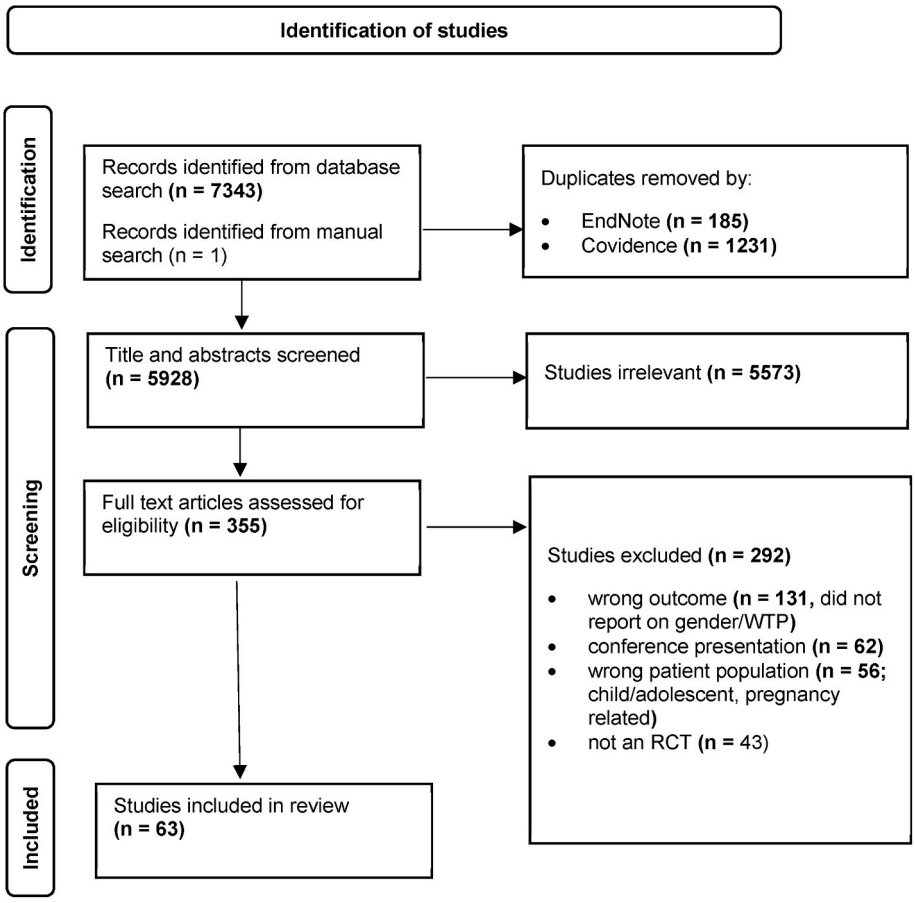

Fig. 1. PRISMA flow chart of study identification.

access to transportation, travel difficulty), emerged as a primary factor contributing to a decreased WTP across all studies. Notably, this was more pronounced in women [30–65] and was consistently observed across different ethnicities, geographical locations and health conditions.

In both mixed and single-gender studies, women reported that interruption to child-care, caring and family responsibilities were barriers, although the percentage of women reporting trial logistics as a barrier was moderated by other factors like age. For example, in a study investigating WTP in a diabetes prevention trial among women with a history of gestational diabetes mellitus, younger women were more concerned with travel associated with trial involvement [40]. Additionally, a study of Indian female sex workers reported that those who were more willing to be apart from their family had increased WTP [46]. In contrast, inconvenience as a barrier to trial participation was reported to concern 9% of men in one men-only trial [66].

Trials that offered flexibility (e.g. in appointment times) were reported to increase WTP by a number of women-only studies [44,47]. Further, access to car parking, public transport options or transport provided by the trial facility positively influenced women's WTP [35,36,67]. Long travel distances to trial sites reduced WTP for both genders [68,69]. Additionally, some women-only studies reported WTP increased when the burden of participation was reduced, e.g. the intervention arm had fewer medical appointments than standard treatment [33] or follow-up took place over the phone [37].

The concept of cost neutral trial participation was considered important [39,65,70] and substantially increased WTP for both genders. In a study involving healthy fertile women, it was found 77% of participants would have declined trial participation if 'reasonable expenses' had not been provided [54]. Financial incentives were viewed as appropriate to cover the costs of participation (e.g. childcare, transportation, parking) [32,39] and acknowledgement of participant's time [61].

While remuneration increased the WTP of both genders, the underlying reason why sometimes differed. Men considered remuneration important to ensure their family would be 'taken care of' should trial participation expose them to harm. In both mixed and women-only studies, compensation for the time required to participate and the gesture it represented towards valuing their effort was considered more important by women [61,71].

4.2. Trial design

The domain of trial design encompassed the acceptance of entrenched research concepts and the impact of trial structure on WTP. The inclusion of the research concepts of randomisation, placebo, and equipoise reduced WTP in both men and women [37,48,66,72–74]. A study involving men with prostate cancer reported the concept that a computer 'decides' who receives the intervention was deemed unacceptable by participants [72]. In a study examining the barriers and drivers affecting recruitment to breast cancer trials among women, it was found 39% of non-participants expressed concerned about the process of randomisation [75].

Similarly, the concept of 'placebo' was often misunderstood by both genders and reduced WTP. In one mixed-gender exploring WTP among urban minority HIV patients, women expressed concern about being in a placebo group, where they would not receive HIV medicine, fearing potential instability in their health condition [76]. In contrast, men were more likely to conflate the concept of placebo with a distrust of the medical system [76]. In another men-only study investigating WTP in a

Table 1
Characteristics of the included studies.

Author and year	Country	Study cohort	Age	Actual or Hypothetical Trial*	Data Collection
Mixed gender studies					
Al Subeh & Alzoubi 2020 [91]	Jordan	University students in Jordan (n = 1265; 256 M, 1,009W)	<18 yrs = 4 (0.3%); 18–25 = 1246 (98.5%); >25 yrs = 15 (1.2%)	Hypothetical	Survey
Bass et al., 2015 [76]	USA	HIV positive patients with urban minority ethnic backgrounds (n = 50; 22 M, 28W)	47 (28–63)	Hypothetical	Survey
BeLue et al., 2006 [71]	USA	African Americans from diverse educational and socioeconomic backgrounds (n = 67; 32 M; 35W)	Men: mean age 32.3, range 19–60; Women: mean age 42.7, range 19–65	Hypothetical	Focus group
Ding et al., 2007 [89]	USA	People attending internal medicine and cardiology clinics (n = 783; 383 M, 400W)	Men: mean age 55.2 (SD15.6); Women: 52.8 (SD15.6)	Hypothetical	Survey
Fox et al., 2021 [90]	UK	Adults with cancer (n = 93; 56 M, 37W)	Median age category was 60–69 years	Hypothetical	Survey
Lobato et al., 2014 [83]	Brazil	Adults residing in an area of Brazil endemic for intestinal helminth infections (n = 143; 48 M, 95W)	Mean age 34 years	Actual	Questionnaire
Stone et al., 1997 [67]	USA	People receiving primary care for HIV (n = 202; Gender demographics are for the entire study (n = 260; 186 M, 74W))	Age distribution: age 21–34 35.4% age 35–49 57.7% 50 and above 6.9% Age demographic are for entire study (n = 260) while reasons for nonparticipation were collected from n = 202	Actual	Survey
Sullivan et al., 2007 [69]	USA	Adults with HIV or AIDS (n = 6892; 5010 M, 1882W) *Only people who had not participated in a clinical trial were asked about reasons for non-participation (83% M, 85%W)	Age distribution: Both genders: 18-29: 11% 30-39: 36% ≥40: 53%	Actual	Interview
Woodsong et al., 2006 [29]	India, Malawi, South Africa, Tanzania, USA, Zambia, Zimbabwe	Standard of Care Study (Study 1): Mostly female research participants who were past or potential research participants, selected among those who had participated in previous HIV prevention studies and/or were non-study consumers of HIV prevention and treatment services (n = not reported; approximately 10 individual interviews or 2 focus groups were conducted with potential participants at each of the 9 research sites) Measures of Condom Use (Study 2): Women and men who had recently completed participation in a condom promotion study (n = 80)	Study 1 and Study 2: ≥18 yrs	Hypothetical	Interview and focus group
Woodsong et al., 2012 [88]	Malawi, Zimbabwe	Women who participated in a previous RCT of two candidate microbicide gels and their male partners (n = 106; 40 M, 66W)	Not reported	Actual	Interview
Men only studies					
Bruce et al., 2016 [70]	USA	Injured urban black men admitted to trauma centre (n = 83)	Mean age 38.2 (16.2)	Actual	Interview
Chakrapani et al., 2012 [81]	India	Men who have sex with men in Chennai and Mumbai, India (n = 68)	Mean age 28, age range 20–46	Hypothetical	Focus group
Connochie et al., 2019 [86]	USA	Young men who have sex with men at high risk of HIV infection (n = 137)	Mean age 21.7 (1.83)	Hypothetical	Survey
Hays & Kegeles 1999 [66]	USA	Young gay and bisexual men (n = 390)	Age range 18–29	Hypothetical	Survey
Koblin et al., 1997 [82]	USA	Gay and bisexual men who were HIV-1 antibody negative enrolled in an HIV-1 vaccine preparedness study (n = 698)	Mean age 31.5 years	Hypothetical	Questionnaire
Mendenhall et al., 2021 [74]	USA	Men aged ≥50 years (n = 1046)	Age distribution: <60 years 386 (37%); 60+ years 628 (60%); Missing 32 (3%)	Hypothetical	Survey
Mills et al., 2003 [72]	UK	Men with localized prostate cancer (n = 21)	Age range: 50–69 years	Actual	Interview
Newman et al., 2014 [68]	India	Men who have sex with men in Chennai and Mumbai, India (n = 400)	Median age 25 years; Age distribution: ≤25 years 51.75%; >25 years 48.28%	Hypothetical	Survey

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Table 1 (*continued*)

Author and year	Country	Study cohort	Age	Actual or Hypothetical Trial*	Data Collection
Perisse et al., 2000 [78]	Brazil	HIV seronegative homosexual and bisexual men in Rio de Janeiro, Brazil (n = 815)	Age range 18–50 years	Hypothetical	Questionnaire
Turriff et al., 2019 [73]	USA	Men with X-linked retinoschisis (n = 13)	Median age = 47 (range 23–72)	Actual	Interview
Women only studies					
Abhyankar et al., 2016 [85]	UK	Women receiving cancer treatments (n = 21)	57, 29–81 yrs	Actual	Interview
Anderson et al., 2020 [30]	USA	Adolescents and young women with cancer (n = 1264)	Age at diagnosis 15–39 years. Age at survey not reported.	Actual	Survey
Andrasik et al., 2014 [31]	USA	Transgender women (n = 42)	18–24 yrs 16.7%, 25–29 yrs 19.0%, 30–39 yrs 28.6%, 40–49 yrs 21.4%, >50 yrs 14.3%	Hypothetical	Focus group
Bakali et al., 2011 [79]	UK & USA	Women attending urogynecology clinics (n = 363)	Not reported	Hypothetical	Questionnaire
Blödt et al., 2016 [32]	Germany	Women participating in a trial evaluating app-administered self-care acupressure for menstrual pain (n = 25)	Incentive group: mean age 26.4, range 24–33; Nonincentive group: mean 22.7, range 21–25	Actual	Interview
Brewer et al. (2014) [84]	USA	African American women attending The Links, Incorporated 2012 National Assembly (n = 381)	Mean age 58 ± 10, range 20–87	Hypothetical	Survey
Burks et al., 2020 [33]	USA	Women enrolled in a phase 2 clinical trial using IORT for early stage breast cancer (n = 20)	Mean age 67.8 (6.99), range 51–79	Actual	Interview
Canidate et al., 2020 [34]	USA	Women with HIV and hazardous drinking (n = 20)	Mean 49.3	Actual	Interview
Cheung et al., 2008 [35]	Canada	Postmenopausal women who had been contacted for potential participation in the RUTH trial (n = 270)	Mean 68.6 (8.0)	Actual	Survey
Courvoisier et al., 2022 [36]	Switzerland	Women living with HIV (n = 20)	Mean 48	Hypothetical	Interview
Gopinath et al., 2013 [37]	UK	Women who had declined participation in a surgical RCT (n = 23)	Mean 49, range 34–75	Actual	Interview
Hepworth et al., 2002 [38]	Australia	Post-menopausal women (n = 21)	Mean 57, range 50–69	Hypothetical	Focus group
Hohmann et al., 2009 [39]	USA	Women presenting for screening appointments for either barrier or hormonal contraceptive efficacy trials (n = 108)	Age range 18–40; Barrier subjects: 28 (18–40); Hormonal subjects: 23.5 (18–36)	Actual	Survey
Infanti et al., 2014 [40]	Ireland	Women with a recent history of GDM who declined participation in a RCT (n = 156)	Not reported	Actual	Narrative statement
Jenkins & Fallowfield 2015 [75]	UK	Women with breast cancer (n = 152)	Age range 29–87 years; the majority of women were in the age group 51–69 years (65%)	Actual	Questionnaire
Jennings et al., 2014 [41]	USA	Women who survived rectal or anal cancer (n = 94)	Consenting women (56 years (11.2)) younger than those who declined (69 years (12.7))	Actual	Interview
Juraskova et al., 2015 [77]	Australia & New Zealand	Initial pilot: members of Breast Cancer Network Australia (n = 25); Main pilot: women identified as eligible for the SNAC-2 trial (breast cancer surgical trial) (n = 20)	Initial Pilot: mean age 52.8 years, (SD 10.32); Main Pilot: mean age 52.7 years, (SD 12.78)	Initial pilot: Hypothetical; Main pilot: Actual	Questionnaire and interview
Katz et al., 2019 [42]	South Africa, Uganda, Zimbabwe	Women who were former VOICE trial participants (n = 171 of which n = 106 also completed questionnaire)	Mean age 28.9 years, Age range 20–41	Actual	Interview and/or focus group; questionnaire
Kemeny et al., 2003 [80]	USA	Women with breast cancer eligible for open treatment trial (n = 154; 77 matched pairs of younger (<65 years old) and older (≥65 years old) women)	Mean age: Younger group 48 years; Older group: 74 years	Actual	Questionnaire (narrative data)
Liamputtong et al., 2015 [43]	Thailand	Thai women living with HIV/AIDS (n = 26)	Age ranges 20–30: 15.5% 31-40: 65.5% >40: 19%	Actual	Interview
Martin et al., 2013 [44]	USA	Black and Latina postpartum women who declined participation in a RCT to assess the impact of a behavioural educational intervention aimed at preventing postpartum depression (n = 128)	Mean age 29 (SD 6)	Actual	Interview
Mayanja et al., 2020 [45]	Uganda	HIV negative sex workers in Uganda (n = 311; 219 cases, 92 controls)	Median age 27 years (IQR: 23–32)	Hypothetical	Questionnaire
Mensch et al., 2013 [46]	India	Female sex workers in southern India (n = 730 surveyed for hypothetical WTP; of these who were eligible, n = 267 enrolled in actual trial, n = 99 eligible but did not enrol in trial)	Mean age 30.8 years; approximately 18% aged under age 25; 13% 40 aged years old or over (those surveyed for WTP)	Hypothetical and Actual	Survey

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Table 1 (*continued*)

Author and year	Country	Study cohort	Age	Actual or Hypothetical Trial*	Data Collection
Moody et al., 1995 [47]	USA	Post-menopausal African American women approached for participation in a trial for osteoporosis (n = 8)	Not reported for WTP sample. Mean age of 66.9 years (SD 10.95) for sample recruited to substudy (N = 21).	Actual	Not specified, likely interview
Mostafa et al., 2013 [48]	UK	Women with stress urinary incontinence eligible for a surgical trial (n = 166)	Age distribution: 26–44 years: 34.1% accepted, 51.6% refused; 45–64 years: 54.1% accepted, 38.7% refused; ≥65 years: 11.8% accepted, 9.7% refused	Actual	Questionnaire
Mouton et al., 1997 [49]	USA	Nonrespondent women initially invited to participate in the Women's Health Initiative (n = 80)	Mean age 62 years (range 37–86)	Actual	Survey
Muir et al., 2005 [50]	Australia	Australian women at high risk of breast cancer (n = 35)	Mean age 37.7 years; age range: 30-45	Hypothetical	Interview
Neill & Chessa 1998 [51]	USA	Women in nontherapeutic drug clinical trials (n = 13)	Mean age 26.75 years; age range 21–46	Actual	Focus group
Nguyen et al., 2005 [52]	USA	Asian-American women with cancer (n = 19)	Age range 33–71 years	Hypothetical	Interview
Paskett et al., 1996 [53]	USA	Women with breast cancer (n = 82)	Age distribution: <65 years 55%; ≥65 years 45%	Actual and hypothetical	Interview
Pickersgill et al., 1998 [54]	UK	Women who had volunteered to participate in contraceptive pill trials (n = 126)	Mean age 30.5 years; Age range 18–40	Actual	Questionnaire
Schaefer et al., 2001 [87]	USA	Women who considered participating in the breast cancer prevention trial (BCPT) (n = 26)	Mean age 53 years; Age range 44–67	Actual	Interview
Sharp et al., 2006 [55]	UK	Women with abnormal cervical screening results who enrolled in or declined participation in the TOMBOLA trial (n = 629; n = 492 agreed to participate; n = 137 declined to participate)	Age range 20–59 years	Actual	Questionnaire
Sikorskii et al., 2011 [56]	USA	Women with breast cancer (n = 123)	Age for people who declined participation and provided reasons for unwillingness to participate was not recorded. Mean age for participants who dropped out early: 58.12 (SD 12.66) Mean age for participants who completed baseline interview: 57.34 (SD 11.36)	Actual	Interview
Smith et al., 2007 [57]	USA	African American woman (n = 31)	Age range 30–60	Hypothetical	Focus group
Sutherland et al., 1993 [58]	Canada	Healthy women enrolled in randomised controlled trials of cancer prevention (n = 66)	Mean age not reported; at least 30 years	Actual	Questionnaire
Tharawan et al., 2001 [59]	Thailand	Thai women from an area of higher HIV infection rate (n = 370)	Mean age = 26.9 years (SD 6.7)	Hypothetical	Questionnaire
Unson et al., 2001 [60]	USA	Older African American women invited to participate in a clinical trial on osteoporosis (n = 16)	Mean age = 75; age range 67–86	Actual	Focus group
Veit 2004 [61]	USA	Post-menopausal women (n = 180)	Age distribution: <70 years 70–80 years	Hypothetical	Questionnaire
Verghese et al., 2021 [62]	UK	Postmenopausal women with symptomatic Pelvic Organ Prolapse eligible to participate in the LOTUS study (n = 32)	Age distribution: <65 68% ≥65 14% Age range 52–76 years	Actual	Interview and focus group
Voytek et al., 2011 [63]	USA	African-American women at high risk of HIV infection (n = 17)	Mean age = 36.4 years	Actual	Interview
Williams et al., 1997 [64]	USA	HIV positive women (n = 116)	Age range 23–55 years	Actual	Survey
Yao et al., 2015 [65]	China	Female sex workers in China (n = 404)	Median age 24 (IQR 20–30)	Hypothetical	Interview

Abbreviation Definitions: LOTUS: Local Oestrogen Treatment in Postmenopausal Women Undergoing Pelvic Organ Prolapse Surgery; IORT: Intraoperative Radiation Therapy; RUTH: Raloxifene Use for the Heart; RCT: Randomised controlled trial; GDM: Gestational diabetes mellitus; SNAC-2: Sentinel Node Biopsy versus Axillary Clearance 2; VOICE: Vaginal and Oral Interventions to Control the Epidemic trial (MTN-003); IQR: Interquartile range.

preventive HIV vaccine trial, participants reported the concept of placebo as unethical and associated it with receiving an ineffective intervention [66]. One women-only study exploring the motivation and experiences of Thai women living with HIV/AIDS participating in clinical trials involving HIV drugs, found WTP was reduced in studies that compared a placebo with a proven intervention. However, WTP increased when the placebo option was removed, and the trial involved the comparison of two established interventions [43].

Both men and women were concerned by the concept of equipoise. They expressed scepticism researchers genuinely felt the options being investigated were equal in terms of patient outcomes [37,66,72]. In a study involving men with prostate cancer, it was reported that 91% of

Table 2
Illustrative quotes.

Logistics of participation	(I am) so busy and have many family and social issues, so cannot commit to any further follow-up (Woman; [48]) I think that women are busy with children and have no time to do that (be in a study) (Woman; [36]). When I went there … I was thinking about the tokens, money in my pocket to eat with … (Woman; [63])
Trial design	I realise blind studies are necessary to compare and contrast the effects of new drugs, but it would really piss me off if I discovered I was in the placebo group (Man; [66]) … I think, well, one of the three (study groups) is going to be better than the other two for me (Man; [72])
Trial information and materials	I thought the screening was really good because you actually had a doctor there and you could ask any question under the sun about what was going to happen with the drugs and the interactions that might occur and any side effects that might happen (Woman; [51])
Altruism: research and knowledge	I would feel privileged to know that, if my participation helped lead to a vaccine, I had played some small roll in its creation (Man; [66])
Altruism: societal	If you tell me that researching this will help save millions of lives then I'm more apt to do it than if it's some rare thing and it might one day help somebody. So if you can make a closer link to how my participating can actually help, I'll be more likely to want to get involved (Gender not specified; [71]) If more attention were being paid to the African American community, and dealing with diseases in the African American community, dealing with the health issues, I would be willing to offer my time or whatever I needed to help out research in those particular situations (Gender not specified; [71]) I am brave and ready to volunteer for the study in order to prevent people like me from infection. I take this stance like I am deputing myself to the military (Man; [81]) I would like to improve the level of provided healthcare for future patients (Woman; [48]) I am happy to take part in any trial that may benefit not only me, but others who may need to have treatment for cancer (Woman; [75]) 44 I feel that it is my duty as a gay man to undergo a little inconvenience in order to put an end to the AIDS epidemic (Man; [66])
Benefit to self	Honestly, I hope that there's benefit to myself personally (Man; [73]) I am very pleased to be asked to take part in these trials as I think they will be beneficial to myself e.g. having extra scans, blood tests etc. and to help other people with my illness on the outcome of the trials (Woman; [75]) My main intention was to receive ya tan (antiretroviral drugs). It was free then and the doctor said that it was free because they wanted patients to look and feel better (Woman; [43]) I decided to go into a trial because if I did not, I might die quickly like my husband. When I started to take part in a trial, too many people I knew were dying (Woman; [43])
Concern for self:safety	If for some reason I felt I was risking my own health by participating, I would not do it (Man; [66]) I don't want to be anyone's guinea pig (Man; [66]) My understanding was they were going to shoot me with AIDS or HIV and see if your body can counteract it like a mouse to a scientist (Transwoman; [31]) If you go in for a vaccine trial and want to be a part of it you are admitting to be at high risk … you are admitting to be one of the marginalised populations (Man; [81]) I have a whole lot of (trans) girlfriends that want to know about the vaccine … but they too scared to go into certain places to learn about it because they don't want no one to think that they have it [HIV], which they don't have it (Transwoman; [31])
Concern for self: autonomy	When you get my age, you should make your own decisions anyhow, you know, because you know it is your body, and you know what you want to do with it." (Woman; [60])
Relationships: professional	I contacted the research team and spoke to the trial team when I went home, I felt this was a brilliant service (Woman; [62]) Oh, I felt [the physician] and the people that work with her were very good at explaining the trial to come and what the procedure entailed, and they it, and I just felt very well informed and secure in their talents (Woman; [33]) A lot of it is the attitude of the person conducting the research … if they have a negative attitude that makes me feel uncomfortable (Woman; [71]) (I participated) because you helped me so much the first time. It was very thoughtful (Man; [70]) 45 If they had a representative from our community that was hired to work for them and advocate to us on their behalf, then we could actually have some kind of relationship (Transwoman; [31]) That is why I will never do something without asking my doctor (Woman; [36])
Relationships:personal	When you sit in a clinic environment you definitely feel on the spot and though there were a number a questions going through my mind, in clinic I did not feel I could make a decision. But when I went home spoke to my husband and then contacted the trial team I felt more confident (Woman; [62]) [We are] … affected by our peers … I talked with [my friend] and.., immediately the fears go away (Woman; [51]) Because the gel will prevent her from contracting HIV as well as pregnancy. When I considered all these, I decided to encourage her to continue using the gel (Man; [88])
Trust	I'm saying it's a guise to suggest that all clinical research is for the purpose of making sure that people survive. Some clinical research is for the purpose of making sure people can make money. We should call it that (Man; [71]) I trust the doctors here, and I trust the results they've gotten from A to Z (Man; [73])

non-participants found the concept of equipoise unacceptable [72].

Studies of both genders hypothesised that a clear explanation of placebo, randomisation and equipoise, detailing why these concepts are included in clinical trials and how these concepts impact an individual's participation, was important to alleviate concern and increase WTP [48,52,66,72,73,75–78]. In a HIV vaccine efficacy trial conducted among HIV negative female sex workers in Uganda, it was reported actual WTP increased when research concepts were understood [45].

Further, trial structure was noted to moderate the WTP for both genders, but was reported more often in women-only trials. For example, in a study assessing the willingness of postmenopausal women to participate in a long-term hormone replacement therapy clinical trial, participants indicated that a five-year study timeframe was more

acceptable than a ten-year commitment [38].

Additionally, trial structure relating to the type of comparator arms used moderated WTP for both genders. In a study evaluating decision making regarding prostate cancer treatment and research participation, WTP increased 21% when trial interventions were perceived to produce similar outcomes, compared to trials where the outcomes of the two interventions were perceived to differ significantly [74]. Further, one women-only study reported WTP was higher for trial designs evaluating an existing surgical procedure with a new procedure than when trials evaluated two new surgical procedures [79]. Additionally, WTP reduced when a trial intervention design was perceived to be burdensome for example, when trial participation required diary keeping [58] or regular blood tests [63,65].

4.3. Trial information and materials

The domain of trial information and materials included whether trial information was presented to potential participants, as well as the clarity of the information. Providing adequate trial information was equally important to both men and women. One mixed gender study reported 75% of men and 75% of women who declined participation indicated lack of information was critical to their decision [69]. Further, a number of mixed and male and female single-gender studies indicated the main reason for non-participation in clinical research was lack of information about the trial or not being offered enrolment [30,31,67,69,80].

Trial materials (e.g. handouts or advertisements) that were easy to understand, free from medical jargon and included clearly stated goals [32,36,38,53,55,62,78,81] increased WTP. One women-only study found individuals who had a good understanding of research where four times more likely to participate [53]. Both genders valued honest information describing the risks and benefits of clinical trial participation [36,76,82]. Trial information available from multiple sources (e.g. written format and face-to-face sessions with researchers) and the availability of staff to answer questions about the trial in a timely manner were noted by a number of women-only trials as increasing WTP [51,77].

5. Theme 2 participant factors

5.1. Altruism

Altruistic motivations emerged as an important enabler in WTP in clinical trials for both genders [71,83]. Two types of altruism were noted: Altruism relating to 'research and knowledge' described a willingness to be part of a process that specifically advanced knowledge or solved a problem; societal altruism described a WTP motivated by a desire to improve the well-being of others. One mixed-gender study noted both research and societal altruism were equally important to both genders [71] while another mixed-gender study noted that, altruism significantly influenced women [83]. Additionally, research and societal altruism were noted as important moderators of WTP in both men and women-only studies, although there were exceptions. While two women-only studies, including women with pelvic organ prolapse and Thai women at risk of HIV, noted societal altruism was the most important factor influencing WTP [59,62], two other women-only studies (women with breast cancer and women on hormone replacement therapy) noted altruism had minimal impact on WTP [38,75]. Societal altruism in particular appeared important to both men and women from minority communities, including ethnic or sexual orientation, when there was a perception that trial outcomes would specifically benefit that minority [84], particularly immediate family members, or future generations of that minority [35,57,60,70,71].

Improving the health outcome of people with the same health condition also influenced WTP and was observed in both men and women. This was particularly evident in health conditions with outcomes perceived as life-threatening, including cancer and HIV/AIDS [43,53,59,63,64,66,68,75,76,80,81,85–88]. Conversely, when a minority perceived they would not benefit from research, WTP among that minority diminished. One study noted the prevailing consensus was transwomen would be last to benefit from HIV vaccine research. Consequently, transwomen perceived minimal benefit to their community, which reduced their WTP in research [31].

5.2. Benefit to self

The concept of 'benefit to self' included access to perceived new or superior health management (e.g. new medication or procedure), improved or more timely access to medical services (e.g. bypassing the waitlist), increased exposure (e.g. more consultations) to people perceived as having greater expertise in managing a particular health condition, accessing health services, medication or health equipment at a reduced cost, and an opportunity to better understand their health condition.

Benefit to self (when an individual perceived trial participation would improve their health outcomes) was described by many studies as a powerful factor influencing WTP among both genders [32–38,42,46,49,50,55,64,65,71,74,75,85,88]. In particular, both men and women were motivated by the hope that trial participation would improve their health. For example, all but one participant in a study of men with X-linked retinoschisis participated in a trial in the hope of therapeutic benefit [73].

Benefit to self in the form of improved access to health services appeared to be a particularly strong motivator for trials involving both men and women from lower socioeconomic areas and developing countries where access to basic health services was perceived as limited [42,43,59,64,68,83,88].

Improving health outcomes was also a strong motivator for men and women facing life-threatening outcomes i.e. HIV and cancer, with participation perceived as a means to prolong life [33,54,85]. One study of women with cancer noted that engaging with research was perceived as an active pursuit of treatment and the only option available [85].

5.3. Concern for self

Concern for self was the most reported concept influencing WTP. Three different types of concern for self were noted: safety, autonomy and appropriateness.

Safety concerns that trial participation may be detrimental to health outcomes, in particular, cause undesirable side-effects, pain or a worsening of their health condition, reduced the WTP of both genders. However, it was in this domain that the only quantifiable gender-based difference in WTP was reported. One mixed study of cardiovascular patients determined women were 15% less willing to participate in hypothetical cardiovascular trials than men [89]. This result was attributed to gender-based differences in the perception of benefits and harms, with women perceiving more harm. Another study conducted during the COVID-19 pandemic observed that, while women had higher levels of anxiety and concern than men, no significant difference in trial participation rates was observed between the genders [90]. Willingness to participate was observed to increase when strategies to mitigate concerns were apparent, for example, a women-only study noted WTP increased when an anti-dote for potential side-effects was included [60].

The fear of being 'experimented on' was another major barrier to participation and was related to the idea that researchers viewed participants as human guinea pigs [67]. This was observed in both men and women. Further, one women-only gynaecology study noted WTP reduced when there was a concern the intervention under investigation (a new surgical procedure) may not be delivered proficiently [37].

Safety concerns also included potential psychological and societal harm when trial participation was perceived to threaten a person's reputation or position in society. This was observed in two male-only

trials in developing countries [68,81], one trial of transwomen [31] and a trial of female sex-workers in China [65]. Closeted gay men in India expressed concern they would be exposed to stigma, discrimination and loss of social status should their participation in a HIV/AIDS vaccine prevention trial reveal their hidden sexuality to their immediate community [68,81]. Similarly, transwomen perceived their participation in a preventative HIV vaccine trial would exacerbate their already marginalised reality as they were concerned others would erroneously think they were HIV positive [31].

Concern about autonomy was observed only in women and involved the perception trial participation may result in relinquishing control over their health management to others, often strangers [36,60,76]. One mixed-gender study of people with HIV reported some women feared trial participation may compromise the stability their current medication regime provided [76].

Concern about one's own appropriateness to participate in research influenced WTP [87]. People who perceived their health condition was too far progressed, or that other health comorbidities were too substantial, demonstrated reduced WTP [35,38,67]. Similarly, people who perceived their health was too good (i.e. they had a mild form of the health condition being investigated) also had reduced WTP. This concept was observed mainly in women [35,37,40,41,47,62] but was also observed in men in two mixed-gender trials [67,90].

5.4. Relationships

The relationships with significant others both professional (e.g. members of the research team, medical professionals) and personal (e.g. family, friends) influenced WTP, although mixed findings were observed. Two mixed-gender studies reported the concept of relationships influenced the WTP of women more than men [71,83]. However, another mixed-gender study observed the influence of relationships on WTP was equal among women and men [76], and was also observed in two men-only studies [81,82].

The intentional fostering of personal relationships by the research team was reported more frequently as highly valued by women [38,62,71]. This included when researchers were perceived to take a genuine interest in the individual, were responsive to the individual's needs and concerns, listened to participants, answered questions, were respectful of privacy, and were understanding of the difficulties encountered when participating in research [31,38,49,62,63]. Positive interactions with the research team increased women's confidence to participate [62,87].

A substantial proportion of women from minority communities were observed to be more willing to participate when a member of the community was represented in the research team [5,31,57,84]. Transwomen indicated that having representation on the research team would increase researcher's understanding of that minority, which would lead to relationship building and ultimately increase transwomen's WTP in research [31].

The approval or recommendation of a trusted doctor or health professional substantially increased WTP of both men and women [30,31,33,37,51,76,81] although this was particularly noted among women from minority communities. One women-only study of Asian American women reported increased rates of research participation among women with Asian oncologists, possibly due to a language and cultural congruence [52]. Similarly, having a personal doctor or health professional involved in the study, or the perception the facility had expertise in the area, increased WTP of both genders. This was related to a decreased risk of harm associated with prestigious organisations [33,51,71,81].

The opinion of family and friends substantially affected the WTP of both genders. Both men and women were noted to consult extensively with family and friends prior to committing to participate in clinical trials [33,34,42,46,52,54,76,81,83]. Researchers that encouraged and acknowledged input from significant family members or friends were perceived to provide an opportunity to emphasize the safety of trial involvement [45]. Conversely, WTP reduced when it was perceived family members were not supportive of trial participation [46,47,53,75].

The influence of personal relationships on WTP was observed to be particularly powerful in some cultures and geographical locations. For example, in Jordan and parts of Africa, a large proportion of both men and women valued and expected a significant family member, usually male (e.g. male spouse, father or brother), to endorse a woman's participation in a clinical trial [29,88,91]. Women from India were observed to consult their extended family more broadly for approval to participate [29,46] compared to women from Jordan and Africa. In contrast, both men and women in the USA held the belief that women should make a decision regarding trial participation independent of men [29].

5.5. Trust

The concept of trust was observed to moderate the WTP in men more than women and was reported in a higher percentage of mixed and men-only studies. Two mixed studies reported men were more likely to be suspicious of, or to hold conspiratorial views about, research [71,76].

Higher levels of research mistrust were also observed in women from minorities [49,52,57]. For example, one study of African American women found there was a general perception that research was biased to benefit white people [57]. Transwomen were also observed to have high levels of research distrust [31].

5.6. Research disinterest

Several studies, encompassing mixed-gender, men-only, and women-only cohorts, concluded that pre-established negative attitudes toward research was a major factor influencing WTP. Notably, certain studies reported over 40% of eligible people were not interested in participating in clinical research [41,56,74]. In contrast, research disinterest was as low as 3% in other studies [40]. The concept of research disinterest was predominately reported in women-only studies.

6. Discussion

A scoping review of 63 studies explored gender-based differences influencing WTP in clinical trials. Two themes emerged that influenced the WTP in clinical trials of both genders: trial characteristics and participant factors. Consistent with these themes, strategies to enhance the WTP for both men and women were developed.

Differences between the genders moderating WTP in clinical trials were identified: social impact of participation, risk perception and mistrust. The social impact of trial participation appeared to influence women more than men. While the WTP of both genders was moderated by the perceived burden of participation, women more commonly related this to social impact. In particular, the impact of trial participation on women's ability to care for their family or dependents was important. Consequently, factors that eased burden of trial participation or increased the efficiency of trial participation (e.g. access to transport and parking, telephone follow-up) increased WTP in women. This review included articles from different socioeconomic, ethnic and geographical backgrounds, including some studies from more 'traditional' cultures, which may explain this finding. Additionally, women placed a higher value on the personal connection with the research team. Women's WTP in trials was observed to increase when it was perceived the researchers were intentional about building rapport and demonstrated empathy and understanding. Women valued an environment where they were able to tell their story, and felt heard, respected and valued. Being treated as a 'number' substantially reduced women's WTP.

Women were more concerned about potential health risks from trial participation than men. While both genders were observed to

overestimate the health risks associated with trial involvement, one hypothetical mixed-gender study reported this concern reduced women's WTP by 15% [89]. The authors speculated that these results may be explained by sociocultural norms promoting coping styles in women that are less effective at reducing anxieties provoked by external threats [92]. However, another explanation may be the higher risk-taking behaviour observed in men. Men take health promotion messages less seriously and are more likely to refrain from consulting medical professionals [93,94]. There is speculation these behaviours are related to the societal pressure to act 'masculine' [95,96]. Paradoxically however, while men's risk-taking behaviours may be detrimental at the level of the individual, men's tendency to accept risk may mean men have fewer concerns regarding clinical trial participation.

On the other hand, men were also observed to be more suspicious, distrustful and conspiratorial of the research process than women, [71,76,89]. Why men demonstrate higher levels of conspiratorial thinking is not well understood [89,90,97], however, similar findings were observed in relation to COVID-19, with more men subscribing to conspiratorial views about the pandemic [97]. Although higher levels of research distrust were observed in men, one hypothetical study of people with cardiovascular disease [89] found this did not translate into an observable decrease in WTP in clinical trials. Trials embracing transparency of research goals, conflicts of interest and research proficiency may further increase the WTP of men in clinical trials.

Although gender-based differences in WTP in clinical trials were observed, substantial areas of similarity between the genders were noted, including in the areas of remuneration; non-acceptance of the research concepts of placebo, randomisation and equipoise; the importance of trial information; altruism; recommendations of trusted health professionals and the consulting with trusted individuals. However, the reasons *why* a concept was important sometimes differed between the genders. For example, remuneration for trial participation was observed to increase the WTP of both genders. For women, remuneration was viewed as an acknowledgement of their participation. In contrast, men viewed remuneration as providing financial stability in the event trial participation resulted in an adverse health outcome. Trials offering remuneration will likely increase the WTP of both genders although the reasons underpinning *why* remuneration is a moderator of willingness differs between genders. Consequently, how remuneration (cash incentive) is presented in the trial design when recruiting for clinical trials may be important in increasing the WTP of men compared to women. For instance, for women, acknowledgement of their participation holds greater significance as a form of remuneration, whereas for men, remuneration is perceived as a more transactional process.

What underpins the decision to participate in a clinical research trial is complex. Gender appears to be an important factor that moderates the decision making process, however the influence of gender is also moderated significantly by other factors including socioeconomic status, geographical location, ethnic and cultural background, and the health condition being investigated. This dynamic is observed to be fluid; changes in one factor change the weight of impact of another factor [61]. For example, when the perceived risk of an intervention increased, the amount of remuneration required to maintain WTP also increased, however, the amount of remuneration increase required to maintain WTP was contingent on the individual's age and ethnicity [61]. The more barriers reduce WTP, proportionally greater incentives are required to maintain WTP. It therefore stands to reason that, to increase overall WTP, trial designs mitigate as many barriers to participation as possible while amplifying as many factors that increase WTP as possible.

Consequently, based on these review findings, strategies that may enhance WTP among both men and women are summarised and presented in Appendix 4. While it is acknowledged that some drivers may hold more significance for one gender over the other, a comprehensive checklist covering all aspects of WTP for both genders is deemed more effective in reducing overall research waste. In some instances, factors other than gender, such as cultural background, the type of health condition being studies, or whether participants are from a minority, may play a more crucial role in WTP. Therefore, a checklist that encompasses both genders is deemed more appropriate in these situations. Addressing these strategies in trial design and execution may offer opportunities to increase the WTP in clinical trials of both genders. However, given the complexity of interactions influencing WTP in clinical trials, exploring WTP specific to a particular study cohort is recommended to optimise recruitment.

6.1. Design considerations and limitations

This review included studies from different geographical locations, cultures, ethnicities, minorities, marginalised groups, health conditions and interventions. Consequently, emergent strategies to influence WTP in clinical trials may be translational across contexts. However, this scoping review has a number of limitations. Only ten mixed-gender studies explicitly compared differences in WTP between genders. A larger number of mixed-gender studies may be required for gender-differences to be fully explored. Additionally, this review may have been constrained by the design of included studies; a number of studies used questionnaires or surveys where participants chose between predetermined options set by the researcher to indicate reasons for WTP. This method is known to suffer from several drawbacks relating to validity and biases, where this inflexible design may not capture the depth of participant responses [98,99]. Also, studies exploring hypothetical WTP were included. Care must be taken when interpreting these study findings as behavioural intention does not always translate to actual behaviour [6]. Further, in line with scoping review protocols [24], risk of bias and quality of included studies was not assessed, potentially reducing the accuracy of our findings. However, the aim of this scoping review was to understand the landscape of the influence of gender on WTP in clinical trials, therefore studies were not excluded based on quality, and a robust search strategy appropriate for scoping reviews was adhered to Ref. [24]. Further, this review reported the recurring themes from a large number of studies and generated pragmatic strategies to increase the WTP of both genders.

7. Conclusions

A number of important gender-differences moderating WTP in clinical trials were observed in the areas of social impact of trial participation, risk perception and distrust. However, the reasons that fully determine WTP is complex. Exploring factors that influence WTP specific to a study cohort likely offers the most promise to optimise trial recruitment of that cohort.

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Institutional review board or ethics committee approval

This review was based on published literature and did not involve the participation of study subjects. Therefore, no IRB or ethics committee approval was required.

CRediT authorship contribution statement

Lyndon J. Hawke: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Elizabeth Nelson:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing

– original draft, Writing – review & editing. **Penny O'Brien:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Kay M. Crossley:** Writing – review & editing. **Peter F. Choong:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. **Samantha Bunzli:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Michelle M. Dowsey:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 1. Search strategy example (Medline)

1	Searches sex factors/
2	(women* or men* or female* or male*).ti,kf.
3	(women* or men* or female* or male*).ab.
4	female/or male/
5	gender.mp. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	(gender difference* or gender preference* or gender participat* or gender role*).mp. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	1 or 2 or 3 or 4 or 5 or 6
8	Patient Selection/
9	(recruitment or patient selection or sign up or recruiting or involvement or involved).ab.
10	(recruitment or patient selection or sign up or recruiting or involvement or involved).ti,kf,ab.
11	(recruit or recruitment or participat* or willing* or involv* or consent or difference* or different or barrier* or incentive* or enrol* or accru*).mp. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	9 or 10 or 11
13	clinical studies as topic/or exp clinical trials as topic/or observational studies as topic/or qualitative studies as topic/or survey as topic/
14	(clinical trial or clinical trials or controlled trial or controlled trials or medical research or clinical research or clinical study or clinical studies).ti,kf.
15	(clinical trial or clinical trials or controlled trial or controlled trials or medical research or clinical research or clinical study or clinical studies).ab.
16	13 or 14 or 15
17	7 and 12 and 16
18	((women* or men* or female* or male* or gender*) adj6 (recruit or recruitment or participat* or willing* or involv* or consent or difference* or different or barrier* or incentive* or enrol* or accru*)).ab,kf,ti.
19	17 and 18
20	(women* or men* or female* or male* or gender*).ti.
21	19 and 20
22	(recruit or recruitment or participat* or willing* or involv* or consent or difference* or different or barrier* or incentive* or enrol* or accru*).ti.
23	21 and 22

Appendix 2. Summary of themes and domains relating to willingness to participate for each study

	Theme												
	Trial factors			Participant factors									
	Domains												
	Logistics of participation	Trial design	Trial materials	Altruism: Research and knowledge	Altruism : Societal	Benefit to self	Concern for self: Autonomy	Concern for self: Safety	Concern for self: Well being	Relationships: Personal	Relationships: Professional	Research: No intention to participate	Trust
Articles: Mixed Genders (n = 10)													
Al Subeh et al. (2020)		✓ M, W								✓ M, W	✓M, W		
Bass et al. (2016)	✓Both	✓M, W	✓M, W				✓W	✓M, W	✓Both	✓M	✓M, W		✓M(I), W(I)
BeLue et al. (2006)	✓M, W		✓M		✓Both			✓M, W			✓M, W		✓M(I)
Ding et al. (2007)	✓W	✓Both				✓W		✓W			✓Both		✓M(I)
Fox et al. (2013)	✓Both							✓Both	✓W				
Lobato et al. (2014)				✓Both	✓W	✓Both				✓W	✓Both, W		
Stone et al. (1997)	✓Both	✓Both						✓Both	✓Both			✓Both	
Sullivan et al. (2007)		✓M, W	✓Both					✓M, W					✓M(I), W(I)
Woodsong et al. (2012)					✓Both	✓Both				✓M			
Woodsong et al. (2006)										✓Both			
Articles: Men (n = 10)													
Bruce et al. (2016)	✓	✓			✓	✓					✓		
Chakrapani et al. (2012)	✓	✓	✓		✓			✓		✓			✓
Connochie et al. (2019)					✓								
Hays & Kegeles (1999)	✓	✓		✓	✓	✓		✓	✓			✓	✓
Koblin et al. (1997)	✓	✓	✓	✓	✓	✓		✓		✓	✓		✓
Mendenhall et al. (2021)	✓	✓	✓									✓	
Mills et al. (2003)		✓	✓				✓						✓
Newman et al. (2014)	✓		✓			✓		✓		✓			
Perisse et al. (2000)	✓	✓	✓	✓	✓			✓					✓
Turriff A et al. (2019)				✓	✓	✓		✓			✓		✓
Articles: Women (n = 43)													
Abhyankar et al. (2016)		✓	✓	✓	✓	✓		✓		✓	✓		✓
Anderson et al. (2020)	✓	✓	✓					✓	✓		✓		
Andrasik et al. (2014)	✓		✓	✓				✓			✓	✓	✓
Bakali et al. (2011)		✓											
Blödt et al. (2016)	✓	✓	✓	✓	✓	✓		✓					
Brewer et al. (2014)		✓			✓	✓		✓				✓	✓
Burks et al. (2020)	✓	✓	✓			✓		✓		✓	✓		✓
Canidate et al. (2020)	✓	✓				✓		✓		✓	✓		
Cheung et al. (2008)	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓
Courvoisier et al. (2022)	✓	✓	✓	✓		✓		✓	✓		✓	✓	✓

Gopinath et al. (2013)	✓	✓		✓				✓		✓	✓		✓
Hepworth et al. (2002)	✓	✓	✓			✓		✓	✓	✓	✓		✓
Hohmann et al. (2009)	✓			✓	✓	✓				✓			
Infanti et al. (2014)	✓							✓	✓			✓	
Jenkins & Fallowfield (2015)		✓	✓		✓	✓	✓			✓		✓	✓
Jennings et al. (2014)	✓								✓		✓	✓	
Juraskova et al. (2015)		✓	✓			✓					✓		
Katz et al. (2019)	✓			✓	✓	✓				✓			
Kemeny et al. (2003)		✓		✓		✓	✓	✓				✓	
Liamputtong et al. (2015)	✓			✓	✓	✓					✓		
Martin et al. (2013)	✓	✓							✓	✓		✓	
Mayanja et al. (2020)	✓	✓		✓	✓	✓		✓	✓	✓			
Mensch et al. (2013)	✓		✓	✓		✓		✓		✓			✓
Moody et al. (1995)	✓		✓					✓	✓	✓	✓		
Mostafa et al. (2013)	✓	✓	✓	✓	✓	✓	✓					✓	
Mouton et al. (1997)	✓			✓	✓	✓		✓			✓	✓	✓
Muir et al. (2005)	✓	✓		✓	✓	✓		✓	✓				
Neill & Chessa et al. (1998)	✓		✓	✓	✓	✓		✓		✓	✓		
Nguyen et al. (2005)	✓		✓					✓		✓	✓		✓
Paskett et al. (1996)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Pickersgill et al. (1998)	✓		✓	✓		✓				✓	✓		
Schaefer et al. (2001)			✓		✓	✓	✓	✓	✓	✓	✓		✓
Sharp et al. (2006)	✓		✓	✓	✓	✓		✓			✓		
Sikorskii et al. (2009)	✓								✓			✓	
Smith et al. (2007)	✓		✓		✓	✓		✓			✓		✓
Sutherland et al. (1993)	✓			✓	✓	✓		✓		✓	✓		
Tharawan et al. (2001)	✓	✓			✓	✓		✓		✓			✓
Unson et al. (2001)	✓			✓	✓	✓		✓		✓	✓		
Veit (2004)	✓		✓			✓		✓			✓		
Verghese et al. (2021)	✓	✓	✓		✓		✓	✓			✓		
Voytek et al. (2011)	✓				✓	✓		✓		✓			✓
Williams et al. (1997)	✓				✓	✓		✓		✓			
Yao et al. (2015)	✓			✓	✓	✓		✓		✓			

. (*continued*).

Appendix 3. Themes and domains for the main factors affecting willingness to participate for both genders

Theme	Domains	Description
Trial characteristics	Logistics of participation	• Time, effort and commitment to participate e.g. transportation •Remuneration and compensation •Social responsibilities
	Trial design	•Trial design concepts e.g. equipoise, placebo, randomisation are or are not acceptable to participant •Type of intervention being investigated
	Trial materials	•Adequate provision of trial information e.g. trial protocol provided, risks vs benefits of trial participation clearly defined and articulated •Participant's ability to comprehend trial information e.g. information is presented clearly without medical jargon
Participant factors	Altruism: Research and knowledge	•Advance understanding of a health condition to help solve a health problem •Positive attitude toward research participation
	Altruism: Societal	•Improve well-being of others e.g. people with the same condition, future generations or minority group with which participant identifies
	Benefit to self	•Improve health and well-being of self •Acquire access to health system and services
	Concern for self: Autonomy	•Loss of autonomy over health decisions
	Concern for self: Safety	•Trial participation viewed as detrimental to own health and well-being including: •Being experimented on •Intervention will fail

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Theme	Domains	Description
		•Side-effects
		•Stigma and discrimination resulting from trial participation
	Concern for self: Appropriateness	•Feel either too unwell or too well to participate
	Relationships: Personal	•Family members and friends do or do not support trial participation
	Relationships: Professional	•Relationship with researchers
		•Participant's doctor or clinician directly involved with trial or recommends participation
		•Reputation of facility conducting trial
	Trust	•Trust or mistrust of the concept of research, researchers or those endorsing, funding or potentially benefiting from research e.g. government, health services
	Research: Disinterest	•No intention to participate in research

Appendix 4. Identified strategies to enhance willingness to participate in a clinical trial for both genders

Domain	Sub-theme	Strategy to increase willingness to participate
Logistics of participation	Accessibility	•Minimise travel distance
		•Consider availability and ease of parking e.g. provide parking close to research facility
		•Consider providing transport e.g. provide taxi vouchers or volunteer drivers
		•Consider availability of public transport
		•Consider participants functional mobility e.g. cater for participants who are unwell or who have mobility aids
		•Consider traveling to the participant
		•Consider conducting the trial, or parts of it, remotely e.g. utilise telehealth, verbal or electronic consent
		•Conduct follow-up sessions via telephone
	Minimise disruption	•Be flexible with appointment times; be willing to work around participant's life e.g. child care, carer responsibilities
		•Minimise number of appointments e.g. combine investigations like scans or blood tests with intervention appointments
		•Minimise frequency of appointments
		•Keep appointments brief e.g. minimise time spent waiting to see researcher
		•Minimise timeframe of trial involvement; shorter timeframes increased willingness to participate
		•Participant completes parts of trial in own time e.g. electronic surveys
	Reduce financial burden	•Attempt to make participation cost neutral e.g. waive parking costs
		•Consider remuneration for trial involvement; the gesture may be more important than the amount
		•Compensation or reimbursement for expenses incurred e.g. travel expenses, lost income, child care
Trial design	What is research?	•Explain the concept and importance of research
	Address key research components	•Clearly explain the concepts of ***randomisation, placebo*** and ***equipoise***; why they are important to the research project
		•Be transparent about expected outcomes of control and intervention groups and how they may differ
		•Address issues of confidentiality, especially when confidentiality breaches could threaten the perceived safety of participants
	Relevance	•Explain how the research is relevant to the individual
Trial materials	Keep it simple	•Trial information worded at level of participants' comprehension; take into account health literacy levels of participant
		•Avoid research and medical jargon
		•Trial information is presented in an appealing and interesting format; does not provoke anxiety
		•Avoid conflicting and contradictory information
	Transparency	•Trial information is honest and transparent
		•Clearly explain why trial is being conducted e.g. trial goals and expected outcomes
		•Clearly explain the ***benefits vs risks*** of participation
	Distribute information to ***everyone***	•Distribute trial information to all eligible participants; consider gender, age, minorities
		•Use unique locations frequented by study cohort to distribute trial information e.g. recruitment of African-Americans more successful when trial information distributed through churches
		•Embrace emerging technology to distribute trial information e.g. social media
		•Trial information available in diverse culturally and linguistically formats e.g. multiple languages
		•Trial information presented in culturally sensitive format
Altruism: Research and knowledge	Gaining knowledge	•Highlight how clinical trial will advance knowledge of the health condition
		•Highlight why research topic is ***interesting***
		•Highlight how clinical trial will solve a health problem; use practical real-world examples
Altruism: Societal	Helping others	•Highlight how trial will help people with same condition
		•Highlight how specific groups e.g. minorities, ethnicities may specifically benefit from research
		•Highlight how research will help future generations
		•Highlight how research may benefit large numbers of people; demonstrates the research has impact and reach
Benefit to self	Helping myself	•Highlight any opportunities that clinical trial participation may benefit an individual's health outcomes e.g. increased regularity of health checks, reduced waiting time, reduced medical costs, access to medical expertise
		•Highlight any potential for participation to reduce pain and improve function e.g. long-term monitoring of health condition
Concern for Self: Autonomy	Maintaining control	•Emphasize participant's ability to make health decisions is not diminished by trial involvement
Concern for self: Safety	Participating in research is unsafe	•Clearly describe how known risks/side-effects of participation will be mitigated
		•Alleviate fear of being experimented on e.g. how the trial is adhering to rigorous moral and ethical guidelines
		•Emphasize trial safety protocols

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Domain	Sub-theme	Strategy to increase willingness to participate
		•Acknowledge specific safety protocols for at risk groups e.g. minorities or people with certain health conditions like HIV
Concern for self: Appropriateness	Too unwell or not sick enough	•Clearly define eligibility and exclusion criteria in terms of symptom severity or how the individual is feeling or functioning
Relationships: Personal	What other people think matters	•Provide opportunity for buy-in from significant others e.g. partner attends consultations
		•Address concerns from significant others; acknowledge the views of people who are not participants •Encourage input from significant others •Be aware of cultural values e.g. some cultures value and expect a significant male to be involved in decision making processes
Relationships: Professional	Rapport is everything	•Be accessible, friendly, open and honest •Invest time to develop rapport; a personal connection with the research team is highly valued by participants •Be willing to answer questions •Treat all participants with respect and value, not as a number or a guinea pig •Highlight expertise of research team
	Cultural appropriateness	•Where appropriate, include people from study cohort in research team e.g. representation increases willingness to participate of some minorities •Make an effort to be culturally aware and appropriate e.g. people from some cultures may be more comfortable with a researcher of the same gender or ethnicity •Demonstrate a willingness to be accepting of different cultures
	My doctor knows best	•Involve participants own medical team in recruitment; endorsement from participant's personal doctor was a powerful motivator to participate •Where appropriate, incorporate participant's medical team into the research team
Trust	Research is not exploitation	•Strongly highlight no conflicts of interest if none exist •Disclose conflicts of interest and how they are mitigated •Explain how researchers are not exploiting participants for their own gain •Address erroneous or conspiratorial beliefs about research
	Track record and reputation	•Promote the expertise and track record of the research team
		•Highlight trustworthiness of research team •Highlight ethical approval •Highlight any endorsement from significant external sources or stakeholders e.g. trial has government funding and/or approval [59] •Provide positive research experience; increases likelihood of further research involvement

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