Journal of Clinical Epidemiology 137 (2021) 1–13

Journal of Clinical Epidemiology

REVIEW

Why trials lose participants: A multitrial investigation of participants' perspectives using the theoretical domains framework

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Accepted 8 March 2021; Available online 13 March 2021

Abstract

Objectives: To use the Theoretical Domains Framework (TDF) to identify barriers and enablers to participant retention in trials requiring questionnaire return and/or attendance at follow-up clinics.

Study design and setting: We invited participants (n = 607) from five pragmatic effectiveness trials, who missed at least one follow-up time point (by not returning a questionnaire and/or not attending a clinic visit), to take part in semistructured telephone interviews. The TDF informed both data collection and analysis. To establish what barriers and enablers most likely influence the target behavior the domain relevance threshold was set at >75% of participants mentioning the domain.

Results: Sixteen participants (out of 25 showing interest) were interviewed. Overall, seven theoretical domains were identified as both barriers and enablers to the target behaviors of attending clinic appointments and returning postal questionnaires. Barriers frequently reported in relation to both target behaviours stemmed from participants' knowledge, beliefs about their capabilities and the consequences of performing (or not performing) the behavior. Two domains were identified as salient for questionnaire return only: goals; and memory, attention and decision-making. Emotion was identified as relevant for clinic attendance only.

Conclusion: This is the first study informed by behavioural science to explore trial participants' accounts of trial retention. Findings will serve as a guiding framework when designing trials to limit barriers and enhance enablers of retention within clinical trials.

Keywords: Randomized trials; Retention; Follow up; Behavior; Theory

1. Introduction

One of the main threats to the successful delivery of randomised trials is the loss of participants. Poor retention undermines both internal and external validity and is particularly problematic if the data are missing not at random (e.g., there is differential loss to follow-up in the control and intervention arms). However, missingness at random can still cause problems. Approximately 50% of trials lose over 11% of follow-up data [1]. Furthermore, the results of around half of clinical trials could have been overturned if the outcomes from nonretainers were known [2]. This

Declaration of competing interest: The authors have no conflicts of interest

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https://doi.org/10.1016/j.jclinepi.2021.03.007

highlights the critical need to understand how to retain participants in a trial until the end.

Whilst there has been extensive methodological research on recruitment to trials, the same cannot be said for retention. A recent evidence synthesis of qualitative studies identified only 11 studies that had explored any aspect of trial retention with participants who had not completed the trial until the end [3]. While it may be hard to reengage with former participants to understand why trials fail to retain them, the lack of knowledge about this issue is striking. One explanation for this gap may be that, unlike recruitment, the problem of poor retention might look as though it can be adjusted for with statistical methods, such as complete case analysis or imputation. But, as Vickers and Altman argued in 2013, an informed guess, even one based on sophisticated statistical methods, is still a guess [4]. It is more reliable, efficient, and ethical to avoid missing data in the first place by considering aspects of trial design that are amenable to improving trial retention. To date, very few interventions have been shown to improve retention in RCTs, with only moderate certainty evidence available for the use of monetary rewards with a prompts or reminder to improve responses to postal questionnaires [5]. Yet, none of the retention interventions to date has been informed by evidence on the perspectives of participants and/or former participants from a range of trials and what they experience as barriers and enablers to trial retention. Therefore, the acceptability of trial retention interventions to those for whom the interventions are intended remains uncertain.

Retention within clinical trials involves a behavior, with participants asked to complete and return questionnaires and/or attend research visits. Behavior change theories and frameworks can provide a basis for identifying modifiable determinants of nonretention, and for developing a cumulative evidence base of methods that could be used to improve retention within clinical trials. Theory-based interventions for retention show initial promise, such as cover letters with behavior change techniques embedded within them to encourage questionnaire response [6]. One common approach used to apply behavior change theory within health research is the Theoretical Domains Framework (TDF– see Box 1 for domains and definitions) [7,8]. Recent interview studies have utilized the TDF to explore barriers and enablers to enacting behaviors within clinical trials, such as intervention delivery and participant recruitment [9–11]. However, the TDF has not previously been used to identify barriers and enablers to retention in trials from the perspectives of trial participants [12].

The aim of this study was to use this theory-based behavioral framework to identify barriers and enablers to participant retention in trials requiring questionnaire return and/or attendance at follow-up clinics.

2. Methods

The study reported in this manuscript involved a qualitative investigation to identify and assess problems with participant retention in clinical trials by identifying the salient behavioural domains. This work is the first phase in a larger project that aims to develop theoretically informed and participant-centered interventions to target retention [13].

3. Participant recruitment

Five phase III pragmatic effectiveness trials recruiting adults were selected purposively. This trial selection was based on the potential influence of a number of factors on the follow-up of participants (e.g., number of questionnaires or clinic visits). These factors included: variability in trial intervention (e.g., Clinical Trial of an Investigational Medicinal Product (CTIMPs) and non-CTIMPs); and population (e.g., age, gender); trials known to be at risk of poor retention (i.e., online trials); and poor retention (i.e., trials with >15% missing primary outcome data, identified when contacted by STEER study team). Trials currently in active follow-up or recently completed that fulfilled these criteria were identified through the clinical trials units and associated networks linked to the project team. We identified and subsequently invited participants from included trials to take part in a telephone interview study. These participants had discontinued their trial participation for at least one follow-up time point (i.e., they could have missed any/all number of follow ups but had to have missed at least one) either by not returning a questionnaire and/or not attending a clinic visit within the preceding 12 months. We also used social media to invite trial participants from additional trials who met these criteria for discontinued participation.

An invitation letter and participant information leaflet (PIL), co-developed with the project patient partners (J.E. and M.O.), were sent to all potential participants by post or by email, depending on the contact details held for participants. Invitation letters were sent out from each host trial's office to keep personal information of potential participants confidential. A detachable reply-slip to complete and return to the researcher (in a reply-paid envelope) to indicate interest was included. A researcher (R.N.) then contacted the interested participants to discuss the study further. Two attempts were made to engage with potential participants who had expressed interest. An information letter informed by behavioral theory was introduced to encourage participation 4 months into the study. A total of 607 invitations were sent with the aim of interviewing 30 participants (six from each of the five trials) informed by by five key aspects of information power: whether the study aim is broad or narrow (with a focused aim requiring a smaller sample); dense or sparse sample specificity

Box 1. Theoretical domains framework definitions and associated questions. The TDF summarizes 33 behavior change theories – and thus a wide breadth of modifiable factors that have been linked with behavior and behavior change – into 14 theoretical domains [Cane et al 2012].

TDF domain	Definition
Knowledge	An awareness of the existence of something
Skills	An ability or proficiency acquired through practice
Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Optimism	The confidence that things will happen for the best or that desired goals will be attained
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus
Intentions	Conscious decision to perform a behaviour or a resolve to act in a certain way
Goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention, and decision processes	Ability to retain information, focus selectively on aspects of the environment, and choose between 2 or more alternatives
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, an adaptive behavior
Social influences	Interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors
Emotions	Complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Behavioral regulation	Anything aimed at managing or changing objectively observed measured actions

(where dense specificity requires a smaller sample); application or not of established theory (theoretical perspectives requiring smaller sample); quality of the dialogue (with strong clear communication requiring less); and finally, whether case or cross-case analysis (with cross-case requiring more participants) [14].

4. Data generation

We conducted one-to-one semistructured telephone interviews with participants. Interviews explored participants' experiences of the trial, reasons for trial discontinuation, what could have been done to enable them to remain in the trial until its completion (Appendix 1). The topic guide was informed by the TDF, refined by the research team, and used adaptively to ensure interviews were conversational and participants could raise issues that were important from their perspective. Following pilot testing in the first three interviews, the topic guide was further refined to ensure its comprehensibility, acceptability, and theoretical robustness. Follow-up prompts were included when necessary to address specific constructs within the domains.

Interviews were conducted by a researcher (R.N.) who was independent from the trials and who sought verbal informed consent from each participant. All interviews were audio-recorded and transcribed verbatim. The quality of each transcript was checked against the original recordings. The fidelity of the use of the topic guide was checked by another two researchers (K.G. and J.P.) who listened to the first two interview recordings and/or read the transcripts.

5. Data analysis

Anonymized interview transcripts were imported into Vivo qualitative analysis software version 12 to assist data management and coding. A coding guide was developed based on the published definitions and constructs of the TDF domains and agreed (R.N. and J.P.) for the purpose of consistent coding. Three transcripts were randomly selected and coded independently by two researchers (R.N. and J.P.) and discussed during a face-to-face meeting to ensure fidelity of the coding guide. Using the agreed coding guide, verbatim data were first coded (R.N.) to specific theoretical domains of the TDF. Each domain had two behaviors (retention behavior related to: (1) questionnaire return and (2) clinic visit). Next, statements (including both barriers and facilitators, determined by participants framing as positive or negative) related to retention were collated and grouped into sub-themes under each theme (i.e., clinic visit or questionnaire return) of the related domains.

To establish what barriers and enablers influence the target behavior (i.e., participant retention in trials), criteria were developed to determine which domains of the TDF were "relevant'" for this behavior. The predetermined relevance threshold was based on >50% of participants reporting a barrier or facilitator for a given domain, as per criteria from other studies [15,16]. However, on analysis it became apparent this threshold was not specific enough and there-

fore the decision to increase this threshold to >75% was made to allow more defined targeting in later intervention development. Barriers and enablers were considered separately for each domain when considering relevance. Only interviewees' responses on domains determined as relevant to the target behaviors are reported in detail.

6. Patient and public involvement

Two public partners (J.E. and M.O.) were part of the study team and involved at several stages including the development of study protocol, the design of the study materials, ethics application, and discussion at the steering committee's quarterly meetings. They also had considerable input into the phrasing of the topic guide questions. Our public partners have extensive experience of working across a range of health research projects, funding panels, and policy roles (e.g., patient and public involvement lead for the Health Research Authority) and so have an in depth understanding of randomized trials. Whilst the public partners on the study did not have any direct experience of trial participation themselves, the wider STEER project that this study falls within has patient involvement across intervention design and acceptability phases through input into co-design activities.

7. Results

7.1. Sample characteristics

Of the 607 trial participants invited, 25 indications of interests were received (response rate of 4%). From these 25, 16 participants were interviewed between November 2017 and March 2019 with the remaining 9 proving to be uncontactable. Participants' ages ranged from 31 to 90 years (median = 58), and nine were male (56%) and all were White. Participants were from five UK trials with one further participant recruited through social media. Across the sample, 7 of 16 (from two trials) of the interview participants took part in trials that required both questionnaire return and clinic visits to collect outcome data, and 9 of 16 (from four trials) took part in trials where trial questionnaire return only was required. The interviews lasted between 17 and 80 minutes (median 39 minutes). See Table 1 for trial and participant characteristics.

7.2. Interview findings

Overall participants were mostly unaware of being considered by their trial teams as lost to follow-up. The majority presumed that the study was complete, or that they might be still taking part but was not certain about this. Most could not recall the total duration of the trial or the duration of their involvement. When considering their participation in the trial, most participants perceived themselves to be a "private person" as they don't normally disclose health and personal-life related information (i.e., reasons for taking part in the trial and/or not completing all trial related activities) to others. However, they took part in this interview study because they felt it was an opportunity to share experiences and help improve future trials. Participants described taking part in trials as an opportunity to help others, doing a duty, a feeling of peace of mind, and contributing to discovering whether a new treatment/drug was effective.

Behavioural barriers and enablers were identified across the TDF domains for each of the specified behaviors (clinic attendance then returning postal questionnaire). Table 2 presents the factors that influence clinic attendance and questionnaire return across all TDF domains. Overall, there were seven domains that were relevant for both attending clinic appointments and returning postal questionnaires and identified as both barriers and enablers: knowledge; beliefs about capabilities; environmental context and resources; beliefs about consequences; reinforcements; behavioral regulation; and social influences. However, there were two domains that were identified as salient for questionnaire return only: goals; and memory, attention and decision-making (enabler only). Emotion was identified as relevant for clinic attendance only. While the data were analyzed separately for the two behaviors, because the findings were remarkably similar for each, the summarized findings are presented in parallel below for each relevant domain with key contrasts highlighted. Data from participants in the form of quotes can be found in Supplementary Table S1 (attending clinical appointments) and Table S2 (returning questionnaires).

7.2.1. Knowledge

All participants were aware that clinic visits and questionnaire return were involved in the trial they took part in. However, only a minority was aware of the number and frequency of visits or questionnaires involved and whether they managed to attend them all or not. Some did not realize that they had to return an identical questionnaire at every follow-up time point and therefore found it repetitive and boring, and hard to keep track of.

7.2.2. Beliefs about capabilities

Participants perceived themselves as being confident and capable of attending clinic appointments if they were available on a suitable day and time. Enabling factors such as the close proximity of the clinic to the participant's home, combining other activities (e.g., shopping, day out) with the clinic visit and flexible appointment system offered by the clinic (e.g., evening time after work) were mentioned as helpful. Likewise, most participants perceived themselves as capable of completing a questionnaire stating various reasons such as: it was easy to complete and return an online or a postal questionnaire using the pre-paid envelope, clear instructions, not too long, and support from staff to complete it during clinic visits.

Table 1. Host trial and participant characteristics

Trial acronym, ISRCTN, title	Brief description (population, primary outcome, timing of primary outcome, reminders and incentives/rewards)	Number of interviewees (gender, age)	Target behaviour
CGALL: ISRCTN55215960 A UK multicentre RCT comparing laparoscopic cholecystectomy with observation/conservative management for preventing recurrent symptoms and complications in adults with uncomplicated symptomatic gallstones.	- Adults with symptomatic uncomplicated gallstone disease- Primary outcome = self-reported quality of life- 3, 9, 12 and 18 months post randomisation – reminders sent for each time point 2 weeks after due date.- Incentives/Rewards = None	n = 3(male = 1, female = 2 / 53 y, 38 y, 75 y)	Return of postal questionnaires
DISCO: ISRCTN89237370 A UK online RCT of the effects of digital cognitive behavioural therapy (CBT) for insomnia on cognitive function.	-Community participants (age 25 or over) meeting criteria for self-reported Insomnia Disorder -Primary outcome = self-reported cognitive impairment. -Online questionnaires at 10 and 24 weeks post-randomisation. - 10 weeks (£10 gift voucher reward) and 24 weeks (£15 gift voucher reward) questionnaire.	n = 2(female/ 52 y, 57 y)	Online return of questionnaires
MASTER: ISRCTN49212975A UK multicentre RCT evaluating the male synthetic sling versus Artificial urinary Sphincter Trial for men with urodynamic stress incontinence (USI) after prostate surgery.	- Adult men with USI after prostate surgery, for whom surgery is judged appropriate-Primary outcome = self-reported incontinence.-12 and 24 months post-randomization (up to two reminders sent at each time point and 2 weeks after due date).-Incentives/Rewards = None	n = 3(male/ 56 y, 72 y, 75 y))	Return of postal questionnaire
TISU: ISRCTN92289221 A UK multicentre randomised controlled trial of extracorporeal shockwave lithotripsy, as first treatment option, compared with direct progression to ureteroscopic treatment, for ureteric stones.	- Adults (≥16 Y) presenting with a ureteric stone within any segment of the ureter - Primary clinical and economic outcome = stone clearance (self-report of no further intervention) and quality adjusted life years (from EQ-5D self-report). -One week (postintervention), 8 weeks and 6 months post randomisation (up to two reminders sent by post, email or phone, considering any preferences participants had for mode of communication). -Incentives: £10 sent with the 6 month questionnaire	n = 1(male, 60 y)	Return of postal questionnaire
INTERVAL: ISRCTN95933794 A UK multicentre RCT investigating the best dental recall interval for optimum, cost-effective maintenance of oral health in dentate adults attending dental primary care.	- Adults with periodontal disease -Primary outcome = self-reported quality of life and clinical assessment of periodontal disease. -Questionnaire: 3, 6, 12, and 24 months post-randomization (up to two reminders sent at each time point) -Clinic visit: 6 months, 24 months, risk based recall (reminders via letters and/or phone calls sent at each time point). -Reward: £15 vouchers after returning 24 months questionnaire and attending 24 months clinic visit	n = 6(male = 4, female = 2 / 31 y, 34 y, 65 y, 69 y, 71 y, 90 y)	Return of postal questionnaires and clinic visits

(*continued on next page*)

Table 1 (*continued*)

Trial acronym, ISRCTN, title	Brief description (population, primary outcome, timing of primary outcome, reminders and incentives/rewards)	Number of interviewees (gender, age)	Target behaviour
Participant identified through social media (Twitter). Participant reported detail of trial = Multicenter, double- blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of Daclizumab High Yield Process (DAC HYP) versus Avonex® (Interferon β-1a) in patients with relapsing-remitting multiple sclerosis.	Not available	n = 1(female, 46 y)	Return of postal questionnaires and clinic visits

Table 2. Summary of findings across TDF domains

TDF Domain	Target Behaviour			
	Follow-up clinic attendance		Questionnaire return	
	Barrier	Enabler	Barrier	Enabler
Knowledge	✓	✓	✓	✓
example	Unaware still in trial	Understood frequency of visits	Repetitive questionnaires unexpected	Was aware of questionnaires
Beliefs about capabilities	✓	✓	✓	✓
example	Ease and distance of parking	Close to home	Font size too small	Easy to complete and return
Environmental context and resources	✓	✓	✓	✓
example	No childcare	Time	Lack of time	Good questionnaire design and reply paid envelope
Beliefs about consequences	✓	✓	✓	✓
example	Trial takes longer	Access to clinician	Unsure whether they made a difference	Helping a research study or self
Reinforcement	✓	✓	✓	✓
example	Lack of acknowledgment of contribution	Incentives	No response from trial office	Incentives (monetary and non-monetary)
Behavioural regulation	×	✓	✓	✓
example	-	Adding appt date to diary	Mode of delivery	Putting in a visible place
Emotion	✓	✓	N/R	N/R
example	Stressed and anxious about visit	Happy to attend		
Social influences	✓	✓	✓	✓
example	Unhelpful, unfriendly, trial staff	Helpful, friendly, trial staff	Lack of communication from trial staff	Clinician or family members opinion
Intentions	✓	✓	✓	✓
Goals	✓	✓	✓	✓
example			Competing priorities	Important priority
Memory, attention and decision making processes	×	✓	x	✓
example			-	Using post-it notes to remind
Skills	×	✓	N/R	N/R
Optimism	N/R	N/R	N/R	N/R
Social and professional identity	N/R	N/R	N/R	N/R
TOTAL	*9*	*12*	*9*	*10*

× = no data reported, ✓ = data reported, N/R = Not relevant for target behaviour

Determined as relevant due to >75% frequency	Determined as not relevant due to <75% frequency	Data presented within domain not relevant for target behaviour

Barriers that impacted on participants' beliefs about capabilities with regard to clinic visits included: an inability to attend due to needing childcare, distance to travel, availability and location of parking, inflexibility of appointments, and other life events such as attending other health-related appointments (e.g., ante-natal or mental health) or taking part in other research studies. The barriers people cited to questionnaire return were different and included a belief that they were *"not good with paperwork"* with some lacking confidence and believing they were not capable of returning all questionnaires due to a dislike of filling in paper/online forms or worries related to complet-

ing the questionnaire "correctly" for the purpose of the trial. Some discussed preferred options of returning questionnaires including online, postal or both. One practical issue highlighted was the font size being too small.

7.2.3. Environmental context and resources

Participants suggested several situational or environmental barriers related to clinic visits and questionnaire return. These ranged from lack of time due to caring or work commitments, financial issues (e.g., paying for trial related activities such as parking/travel), not seeing any other participants from the trial, disorganized and/or cancelled appointments, duration of visit, and travel time required. Barriers relevant only to questionnaire return related to the design of the questionnaire such as a "*boring," "depressing," "repetitive,"* or *"lengthy"* questionnaires which discouraged them to return.

Enablers that encouraged participants to attend clinic appointments included having plenty of time due to no competing priorities (e.g., retired) and a pleasant clinic atmosphere. Having no competing demands on their time was also raised as an enabler for questionnaire return. Some participants also reported the design and mode of delivery of the questionnaire as enabling return as it was easy to follow, and the online method or reply-paid envelopes supported this.

7.2.4. Beliefs about consequences

Both negative and positive consequences of attending a clinic appointment were reported in this domain. Positives for both behaviors centered on the belief they were helping by taking part in a research study or feeling satisfied that they were making a difference to others and benefitting themselves (e.g., finding a solution for their health issues). In addition, consequences of attending clinic visits were seeing the clinician more often than usual and getting additional clinical tests or checks done again related to a belief of improving their health or care.

The negatives of not attending a clinic appointment or returning a questionnaire were that the trial may take longer to complete, there may be a negative impact on research findings, or participants *"may get struck off"* from the trial. However, some participants could not identify any downsides of not attending a clinic appointment or not returning a questionnaire. This was largely because they believed the trial office would send another questionnaire or the clinic would reschedule their appointment. Finally, while most participants believed their contributions made a difference to the trial, some were unsure, and one mentioned personal disappointment in not finishing.

7.2.5. Reinforcement

When asked about what reinforced their behavior to attend clinic visits or return questionnaires, monetary incentives in the form of vouchers (i.e., if provided by a trial) were well accepted by some participants who thought it was a *"nice gesture."* In contrast, others felt monetary incentives were not expected or needed or indeed felt these were coercive and would deter them from participating or completing the trial tasks. When asked about what incentives would be deemed acceptable both monetary (e.g., cash or vouchers) and nonmonetary (e.g., a thank-you note or additional health check) incentives were proposed. A few interviewees suggested that the offer to receive a summary of the findings following trial completion would have been motivating, potentially encouraging them to take part in future trials as well as complete a trial until the end.

Participants mentioned a number of negative experiences that deterred them from attending clinics, which largely related to the demeanor of the staff and participants not feeling valued. Conversely, clinic staff with a pleasant demeanor encouraged clinic attendance and contributed to a rewarding experience for participants. Participants mentioned that not receiving a response from the trial office to their queries had deterred them from returning questionnaires further highlighting the impact of participants' perceptions of trial staff on retention.

7.2.6. Behavioral regulation

Participants described the strategies (i.e., enablers) they used to attend clinic appointments including arranging childcare, putting the appointment date in the diary, calendar or notes on their phone, arranging a "day out" to coincide with the clinic visit. Strategies used by participants for returning a questionnaire included putting the questionnaire out in a visible place as a visual reminder, allocating time to understand the questions and complete then return it. However, some used no specific strategies simply to complete and return the questionnaire.

When participants were asked about what would have made it easier for them to return the questionnaire, responses were largely linked to mode of delivery. For example, an online questionnaire (compared to postal/paper copy) would have been easier to complete and return to the trial office. However, one participant stated a dislike for online methods due to his older age and lack of competence with technology. A few individuals suggested they would like to complete a questionnaire over the phone but others disliked this option because they would prefer time to consider responses, or commented that they had a call screening service that would screen out the number, or their phone reception was poor. Reminders, such as text messages, email, letters, or a repeat questionnaire, were mentioned as a helpful prompt for both clinic attendance and questionnaire return.

7.2.7. Social influences

As mentioned previously under reinforcement, participants stated that the demeanor of the trial staff (at the study office or at the clinic) impacted attendance at clinical appointments and returning questionnaires. Participants raised barriers such as no communication from the trial

team, uncooperative trial staff (e.g., seemingly not prepared to be flexible with appointments) who provided no support (e.g., guidance on how to complete the questionnaires) and/or no opportunity to discuss concerns. Conversely, participants described helpful clinic staff as an enabler to attend appointments. The lack of opportunities to meet or discuss the trial with other participants was also cited as barrier. A few participants mentioned not receiving any questionnaires from the trial office and then an unexpected call enquiring about the questionnaire, which they sometimes experienced as "unpleasant" and "rude."

Most participants believed that returning a questionnaire was their own decision and that the experiences or views of other people would not impact their own behavior. Some participants thought that their clinicians' and family members' opinion (i.e., whether to continue with the research) was important to them in relation to completing and returning a questionnaire but they didn't feel pressure from anyone to do so. While in most cases participants reported no direct support requirements from others to attend a clinic visits, one participant stated that they had asked a family member for help to complete the questionnaire.

7.2.8. Emotion

Participants required to attend follow up clinic appointments highlighted a number of barriers such as feeling "*stressed," "anxious," "strange,"* or *'nervous"* about attending the clinic. The reasons reported by participants for these emotions were mixed but were largely linked to a lack of contact with other trial participants, unhelpful trial clinic staff, and concerns about whether any treatment would be needed. The converse was also reported with some participants mentioning feeling "*glad"* and *"happy"* to see their friendly healthcare team and/or they wanted to have a health check-up.

7.2.9. Goals

Influences relevant for the goals domain were only identified by participants considering return of questionnaires. A few participants felt that completing a questionnaire was important and hence it was a priority to return it to the trial office. Although most participants had other, potentially competing, commitments a few managed to return some of the questionnaires whether their priorities changed during the trial or not. Most participants mentioned not being able to return the questionnaire as they had other personal priorities such as dealing with health issues, personal life, caring responsibilities, and work pressures.

7.2.10. Memory, attention, and decision processes

Participants did not mention anything related to forgetfulness when considering their ability to return a questionnaire, but instead mentioned needing to remember to return questionnaires. They reported using various strategies to remember to complete and return the questionnaires, which included using "post it notes," "mental notes" and/or leaving the questionnaire in sight as a visual reminder.

Table 3 presents the identified barriers and enablers and provides potential solutions to help optimize their impact on trial retention.

8. Discussion

This is the first study to investigate trial participants' accounts of trial retention through a behavioural perspective and apply a theoretical framework to understand the barriers and enablers [12]. Our key findings are summarized in two tables: Tables 2 and 3. Table 2 helps trial teams to identify potential barriers and enablers. Table 3 gives practical suggestions for what trial teams can do about them. Together we think they will help trial teams to avoid predictable retention problems.

This study has shed light on two often essential trial related retention behaviours: questionnaire return and follow-up clinic attendance; critical activities for collecting participant-reported outcome data. Moreover, this study included participants from a range of host trials with varied experiences. Findings suggest that many domains from the TDF are relevant and important, as enhancers and limiters, for different trial-related retention behaviours such as questionnaire return and clinic attendance. This provides the first step in producing an evidence base from which to develop behavior-change interventions to improve retention in trials.

Common barriers frequently reported in relation to both target behaviors stemmed from participants' knowledge, beliefs about their capabilities and the consequences of performing (or not performing) the behavior. This resonates with the notion that an individual's knowledge (i.e., about how many times they have to complete a task during the trial period) and beliefs often predict behavior, particularly the perceived ability to complete a task in relation to personal capabilities and/or time available amongst other priorities in life and the anticipated consequences of performing a particular action. Another frequent barrier to both behaviours identified within environmental context and resources (and linked to goals) was time. Whether it was the time required to complete a questionnaire or attend a clinic, sometimes by incorporating it as a "day out" (behavioral regulation), ensuring the trial could be accommodated within the lives of participants was key to them completing the trial activities. Of particular note was the belief by some that there are no consequences associated with not performing the behavior which manifested itself as a lack of awareness of their individual contribution. Contrastingly, whilst participants were aware that their noncompletion of the trial might result in the trial taking longer, they were unaware of the impact on trial results from poor retention. Taken together, the findings suggest that effective behavioural interventions to improve retention in trials should provide a clear and realistic timescale for trial participa-

Table 3. Potential solutions to minimize barriers and enhance enablers

TDF Domain	Target Behaviour				Possible solutions
	Follow-up clinic attendance		Questionnaire return		
	Barrier	Enabler	Barrier	Enabler	
Knowledge	✓	✓	✓	✓	• During consent and throughout trial team highlights and reminds how many questionnaires (and whether they will receive the same questionnaire at each time point) to be completed and returned and the timeline for expecting these questionnaires. • Trial team highlights at the beginning of the study how many any clinic attendances would be expected and when. • Trial team stays in touch with participants throughout the trial period and informs them when the trial ends.
Beliefs about capabilities	✓	✓	✓	✓	• Provide clear instructions to participants regarding how to complete and what to do if they need any help to complete a questionnaire. • Give participants choices for mode of delivery e.g. complete and return of a paper or an online version of the questionnaire or whether they would prefer a call from the trial office to complete it over the phone (with help). • Trial team asks participants whether they would prefer to receive and complete a questionnaire with a bigger font size. • Trial team pays for parking and /or travel costs and identifies and suggests free parking near the clinic. • Trial team offers flexible clinic appointments based on participants availability.
Environmental context and resources	✓	✓	✓	✓	• The length of the questionnaires must be adequate e.g. not too long • Any unnecessary (e.g. not relevant to study objectives) questions must be avoided to keep participants motivated to complete and return the questionnaire. • Trial team offers a suitable day and time for clinic appointments. Where possible, home visits could be arranged to avoid any inconveniences. • The duration of an appointment must be adequate with appropriate arrangements in place.
Beliefs about consequences	✓	✓	✓	✓	• Trial team informs participants that their contribution is making a difference and will contribute to the study findings and future health/practice.
Reinforcement	✓	✓	✓	✓	• Trial team prioritises and answers participants queries satisfactorily. • Trial team offers incentives (monetary, such as vouchers, and non-monetary e.g. a free dental check, send a thank you note after receiving a completed questionnaire) to keep participants motivated.
Behavioural regulation	×	✓	✓	✓	• Trial team sends reminders based on participants' preferred modes of communication (e.g. text messages, email) and gives them reminders (e.g. text messages)attend the appointments or return questionnaires.
Emotion	✓	✓	N/R	N/R	• Trial team members are approachable and positive throughout the trial period.
Social influences	✓	✓	✓	✓	• Trial teams provide friendly and helpful support to meet participants' needs and expectations. • Trial teams organise various sessions with participants and staff for support.
Goals	✓	✓	✓	✓	• Trial teams set expectations from the beginning of a trial and highlight that returning all questionnaires is important.
Memory, attention and decision making processes	×	✓	x	✓	• Trial teams provide some tips to complete and return the questionnaires to the trial office.

tion and highlight the importance of continuing through all follow-up phases of the project.

Recent work has highlighted that very little information is given to potential trial participants about trial retention (i.e., what can be expected and when) during the consent process but stating the right to withdraw is commonplace [17,18]. Improving potential participants' knowledge about trial retention could also help to influence beliefs about capabilities and consequences, through intervention approaches such as persuasion, modeling, and enhancement, and as such improve data collection. A potential concern from trial teams might be that improving knowledge and expectations of trial retention at recruitment could negatively impact on recruitment rates. Equally, we could speculate that this impact could be offset by improved retention; if a person is going to drop out, it's better for them to do so at recruitment. However, the net effect is currently a matter of speculation and such hypotheses need to be tested.

Reinforcement, behavioral regulation, and memory were also reported by participants as barriers to retention with key linkages between these domains. A lack of reinforcement (e.g., no appreciation for participants taking part in the trial or no reward provided) was a common barrier to retention, suggesting that a "reward" may have encouraged participants. This was supported by a subset of participants who indicated their appreciation for the shopping vouchers they had received. The Cochrane review of interventions to improve retention to trials has shown that there is moderate certainty evidence to support the use of mon-

etary incentives as reinforcement to improve postal questionnaire responses in trials [5]. However, the studies that evaluate these monetary incentives appear to employ the use of behavior change techniques in both the comparator and control groups suggesting further work to maximize any effect of behavioural components on reinforcement is needed [19]. Social incentives (such as a thank you note) for reinforcement of return of postal questionnaires are currently being investigated [20–22].

Several participants indicated that they would have found it helpful to receive text or phone reminders of upcoming appointments or to schedule questionnaire completion. Other participants reported that they had found their own behavioural strategies to remind them to complete the allocated task, such as leaving the questionnaire in a visible location or logging the date in a diary. Others reported using no strategies to return the questionnaire. It may be valuable for trial offices to routinely send out reminders or encourage participants to adopt behavioural strategies they could use to aid task completion. There is evidence that the use of electronic prompts (e.g., email/text/both) can improve response rates to postal questionnaires [23].

Many of the relevant domains and proposed strategies discussed thus far have related to practical aspects of trial design or conduct. However, a key influence on attendance at clinic appointments and return of questionnaires (albeit less so) was social influence and its direct interplay with emotions. The participants' perceptions of unfriendly or unhelpful trial staff at the clinic or the study office was identified as being important as to whether a participant completed the behavior. Negative emotions experienced by participants due to poor communication and/or motivation from the trial office appeared to be a strong deterrent to retention. Previous studies have highlighted the importance of these relational considerations to influence both recruitment and retention [3,24]. The other relational aspect highlighted by trial participants as being influential for clinic visits was the opportunity to meet other trial participants to discuss the trial. This potential for a sense of community amongst participants and the normalization of trial participation as a behavior has also been highlighted previously [25]. Strengthening relationships between trial participants and trial staff to enable positive experiences may therefore have promise, although the operationalization and implementation of this will likely have its own challenges. It is worth noting, however, that only one trial in our sample included attendance at follow-up clinics as part of its data collection procedure. While this adds to the already scarce evidence base on attendance at follow-up clinics, more research is needed to understand, for example, whether attendance at routine healthcare appointments that coincide with trial follow-up visits compared to visits set up for the purposes of the trial are harder to retain to or indeed influence responsiveness of staff.

Some of the key domains that participants identified as enablers of retention related to participants' belief that their participation was meaningful (beliefs about [positive] consequences), and the belief that they were helping others through their participation. Educating, persuading, modeling, and enabling participants on the value of trials and the importance of retention may be an effective behavioral change strategy. Critiquing what information trial teams share with participants, and when, should be considered. It is notable that interventions to improve trial retention identified to date rarely target such enablers. While interventions more often target the minimization of barriers, these findings indicate that interventions that enhance or amplify what matters to people when taking part in a trial also have potential. Many of the findings identified in this study map onto the priorities for the trial retention research agenda [26]. The top priority identified was "What motivates a participant's decision to complete a clinical trial?" and many of our findings talk to that. However, the second priority was "How can trials make better use of routine clinical care and/or existing data collection to improve retention?" Making better use of routine data collection to minimize problems of poor retention in trials is not a panacea but certainly has potential to mitigate against many of the problems identified with regard to completing and/or attending follow-up. This suggests that considering retention when designing trials is essential irrespective of whether considering routine or trial-specific data.

8.1. Strengths and limitations

This study adds to the scarce literature and enhances knowledge of the common barriers and enablers to trial retention using data from several trials. Exploratory studies of this nature tend to be embedded within one host trial, whereas this study included participants across six trials, so enhancing transferability of findings. This exploration across trials has shown the need to consider the context of the individual trial (i.e., nature of the participant group, degree of fit with the trial and intervention design) when designing interventions to target trial retention. Furthermore, implementing a validated theoretical behavioral framework enables the design of effective interventions aimed at behavior change. Theoretical frameworks allow health researchers to target common determinants of behavior [7,8]. Thus, suggested strategies without a theoretical basis may be less likely to induce effective change. Our focus was solely on Phase III pragmatic effectiveness trials which may limit applicability of our findings to earlier phase trials.

Some have argued that utilizing the TDF to frame interview topic guides is too prescriptive and leads participants to verbalize their views and opinions only about the topics covered in the TDF [27]. However, a previous study compared the use of the TDF with a theoretical methods using qualitative methodology (interviews, questionnaires and focus groups) and established that the TDF uncovered views that were not mentioned in the studies that used a

theoretical topic guides [28]. This highlights that the TDF does not limit responses from participants. We could only interview those participants who responded positively to our letters of invitation (4%) and need to be mindful that their views may have differed from invited nonresponders and those from other trials. Moreover, we did not make special efforts to sample for diversity with regard to characteristics such as ethnicity and socioeconomic status. This means it is unlikely that we have identified the full range of barriers and enablers to trial retention for everyone in our communities. Who our results apply to will become apparent when the interventions based on these accounts are tested for their impact on retention.

Despite these limitations, we were satisfied that our sample size was sufficient as no new concepts were identified within the TDF domains over the last three interviews. This is in line with stopping criterion for theory informed interviews and the guidance on information power [14,29]. However, the full suite of behavioural barriers and facilitators relating to follow-up clinics is limited as only one of the trials used such clinics for its data collection schedule. We note that these TDF-generated findings, resonate with the major themes identified in a qualitative evidence synthesis of trial retention which included studies that were not informed by the TDF [3]. However, the current behavioural analysis has added insights around the potential for reinforcement, behavioural regulation, and environmental context and resource issues and provided more nuanced understanding of the domains identified in the previous synthesis.

8.2. Priorities for further research

One area for future research is to identify the behavioral challenges and enablers for trial participants who do stay in a trial until the end and complete all of the follow-up activities. These behavioral influences could be compared with our findings to identify further retention strategies. There is some suggestion in the literature that people who complete a trial until the end have been influenced by the relationships developed with trial staff [24], the sense of community with other participants [30], and their personal relationships outside the trial [31] – mirroring some of the aspects identified in this study. In addition, further consideration of the duration of follow-up, the type of clinic visit being attended (i.e., routine healthcare as part of a trial or trial-specific), and involvement of individuals often excluded from research (e.g., people from ethnic minority groups and people with cognitive impairments [32]) is warranted.

Future studies aiming to invite participants who have not completed a trial until the end to engage in further research might consider various strategies to improve response, for example, who the invitation letter comes from. In this study invites were issued from the Trial Chief Investigator; it may be that they need to come from an individual the participant has formed a relationship with, for example, the recruiter. The content of the invitation may also need further refinement and the use of incentives to engage in the research way also warrants investigation. The context of the host trial may also influence willingness to participate. As an example, we observed some differences in the uptake rate of participants in our sample, where participants from trials including patients with a "chronic" ongoing condition (e.g., urinary incontinence postsurgery) were more responsive than those in an "acute" condition trial (e.g., treatment for urinary stones).

9. Conclusion

This paper has identified barriers and enablers to trial retention based on participant responses from semi-structured interviews using a behavioural science approach. Researchers can use these findings in two ways. Firstly, it is critical when designing trials to consider barriers and enablers of retention to prevent problems before they arise. Secondly, these findings can be used to develop participant-centered behavioural interventions where uncertainties remain about the most effective ways to increase retention.

Ethics approval and consent to participate

The study was granted ethical approval by the North of Scotland Research Ethics Service (NoSRES) Committee (ref: 17/NS/0086).

Funding

This research is funded by the Chief Scientist Office of the Scottish Government's Health and Social Care Department [HIPS/16/46]. KG held a Medical Research Council UK Methodology Fellowship during the delivery of this project [MR/L01193X/1]. MDW acknowledges support from the NIHR Newcastle Biomedical Research Centre. Infrastructure support for this research was provided by the NIHR Imperial Biomedical Research Centre (BRC) to support MW.

The Health Services Research Unit, Institute of Applied Health Sciences (University of Aberdeen), is core-funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The funders had no involvement in study design, collection, analysis and interpretation of data, reporting or the decision to publish.

CRediT authorship contribution statement

Rumana Newlands: Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Validation, Project administration. **Eilidh Duncan:** Methodology, Investigation, Formal analysis, Writing - review & editing, Validation. **Justin Presseau:** Methodology, Formal analysis, Writing - review & editing, Vali-

dation. **Shaun Treweek:** Methodology, Investigation, Formal analysis, Writing - review & editing, Validation, Funding acquisition. **Louisa Lawrie:** Writing - original draft, Writing - review & editing. **Peter Bower:** Methodology, Writing - review & editing, Funding acquisition. **Jim Elliott:** Methodology, Writing - review & editing. **Jill Francis:** Methodology, Writing - review & editing. **Graeme MacLennan:** Methodology, Writing - review & editing. **Margaret Ogden:** Methodology, Writing - review & editing. **Mary Wells:** Methodology, Writing - review & editing, Funding acquisition. **Miles D. Witham:** Methodology, Writing - review & editing, Funding acquisition. **Bridget Young:** Methodology, Writing - review & editing, Funding acquisition. **Katie Gillies:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Validation, Supervision, Funding acquisition.

Acknowledgments

We would like to thank all of the participants who volunteered and gave up their time to contribute to this study. We would also like to thank all of the teams linked to the host trials we worked with to help identify potential participants.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.03.007.

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