



Clinical trials site recruitment optimisation: Guidance from Clinical Trials: Impact and Quality

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Abstract

Background/Aims: Participants are integral to the success of any clinical research study, yet participant recruitment into clinical trials poses ongoing and complex challenges. It is widely accepted and recognised that clinical trial sites often find it difficult to meet recruitment goals, both in terms of accrual targets and timelines. This can impact the validity of trials or cause major delays for research. There are very few frameworks available to clinical trial sites to improve recruitment. The GREET project (Guidance to Recruitment: Examining Experiences at clinical Trial sites) sought to identify barriers to recruitment and produce formal guidance to optimise recruitment outcomes.

Methods: Clinical Trials: Impact and Quality, a collaborative of sector stakeholders, convened a project team with comprehensive knowledge of the Australian clinical trials sector to undertake the GREET project. The project scope included exploration of recruitment issues at a site level across all phases of clinical trials and all types of trial sites. The scope excluded upstream issues such as protocol design and general public clinical trial awareness, participant retention and elements of recruitment outside a site's capacity to directly influence or control. The project team's extensive knowledge and experience conducting clinical trials in Australia was used to collaboratively identify a list of 24 key barriers and 12 enablers to site recruitment which formed the basis of the project. Key stakeholder groups were surveyed to challenge project team assumptions. A national and international environmental scan and literature review was conducted to identify best-practice recruitment solutions.

Results: A total of 343 people responded to a survey sent to sites, sponsors, and contract research organisations, and 162 people responded to a survey sent to consumers via consumer networks. The key barriers and enablers initially identified by the project team aligned with the key outcomes of the surveys, which in turn assisted in the development of best-practice recommendations in the form of a Clinical Trial Site Recruitment Guide. Recommendations were grouped into four key themes; conducting accurate study feasibility; proactive planning during start-up; selecting optimal recruitment methods; and participant involvement. Early intervention was identified as a key facilitator in maximising improved recruitment outcomes. The GREET Clinical Trial Site Recruitment Guide is publicly accessible on the Clinical Trials: Impact and Quality website.

Conclusion: Participant recruitment challenges experienced at a site level are widespread and varied, and there is no universal recruitment solution. However, this project identified that there are interventions and assessments that can be proactively implemented and selectively applied to facilitate improved recruitment outcomes.

Keywords

Clinical trials, participant recruitment, patient recruitment, site recruitment, enrolment, barriers, enablers, recruitment plan, feasibility

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Introduction

Clinical trials are planned experiments designed to evaluate medical or behavioural therapies or interventions in humans. When properly conducted, they provide the necessary evidence for changes to current standards of care and are crucial to the advancement of disease management. A key factor to the success of clinical trials is participant enrolment, and failure to meet recruitment targets remains an enduring problem.¹ A 2018 Cochrane review concluded that while there is an assortment of ideas in the literature on interventions to improve clinical trial recruitment, they lack any depth.²

Limited reliable and accessible Australian clinical trial participation data are available, with no central point for comprehensively tracking clinical trial activity or recruitment.^{3,4} A report from the Clinical Trial Action Group released by the Australian Government revealed that 90% of trials in Australia experience recruitment delays.⁵ Similarly, it is estimated that around 86% of all clinical trials in the United States,⁶ and 69% of trials in the United Kingdom,¹ also fail to achieve recruitment targets on time. This suggests that while medical systems may vary in different countries, recruitment challenges are common.

Challenges associated with participant recruitment are multifaceted and varied. They include protocol variables, site capabilities and resources, and participant-related barriers. Australia's relatively small population can be a recruitment barrier, particularly in therapeutic areas where there is competition for the same participant population. The problem is compounded by a general lack of referrals to clinical trials by treating clinicians and specialists. Many diseases are managed by General Practitioners with no linkage to clinical research, reducing the likelihood that primary care clinicians will access relevant trial information or assess patients for participation opportunities.⁴

Inadequate recruitment can lead to underpowered trials reducing the validity of study outcomes, thereby contributing to delays in the development and delivery of vital new therapies. It also places an economic burden on sites when there is a failure to recover financial outlay, particularly set-up costs that are often fixed and not per recruited participant.⁴ For sponsors, inadequate recruitment leads to additional costs to initiate new trial sites and to trial delays.

The GREET project aimed to identify recommendations for improving clinical trial recruitment that can be implemented and managed at a research site. It focused on providing guidance that required minimal or no approval from sponsors or regulators. The intention is to empower sites with increased independence and knowledge to more efficiently assess, manage and proactively control recruitment outcomes.

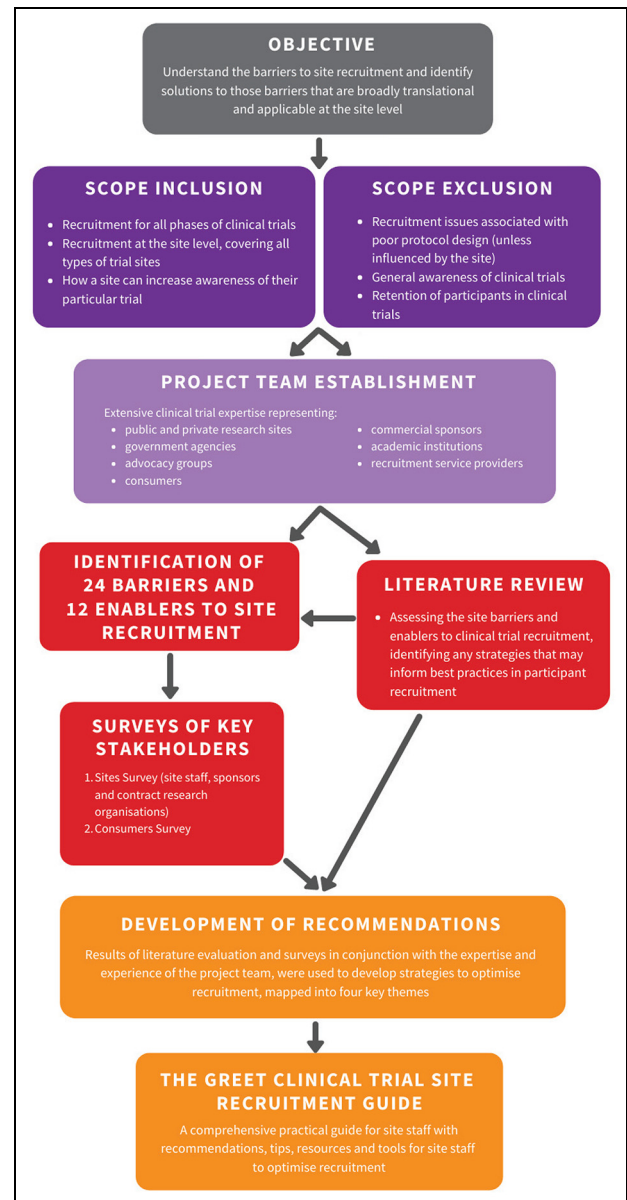


Figure 1. Project flow chart.

Methods

The objective of the project was to understand the barriers to site recruitment and identify solutions to those barriers that are broadly translational and applicable at the site level. Factors such as poor trial design, retention issues and general unawareness of clinical trials were beyond the scope of the project. However, site guidance on how to increase public awareness of a specific trial was considered within scope (Figure 1).

Project establishment

Clinical Trials: Impact and Quality (CT:IQ) is an Australian member-based organisation focused on

improving the impact, quality and efficiency of clinical trials, funded by member contributions and MTPConnect, an Australian Government initiative. In order to achieve the objective a project team of 17 stakeholders with extensive experience in clinical research, clinical operations management, ethics, research governance, participant recruitment, patient education, consumer advocacy and healthcare services, was established.

Twice-monthly teleconferences were scheduled between April 2019 and February 2020 for the project team to meet. The project methodology is shown in a flow chart in Figure 1.

Identification of barriers and enablers

The expertise and experience of the project team was used to develop a list of barriers and enablers to site recruitment that formed the basis of the project.

Literature review

We evaluated the published literature (PubMed, ScienceDirect, ProQuest and Google Scholar), government reports and guidance documents to identify best-practice strategies to overcome participant recruitment barriers. Our searches conducted in May 2019 were limited to English language sources published from 2010 onwards. Search terms included clinical trial recruitment, recruitment barriers, recruitment solutions and best-practice recruitment. Information in the literature was used to confirm the final list of barriers and enablers that were explored in surveys.

Survey development

Two surveys were developed, one for clinical trial sites, sponsors and contract research organisations (referred to as the 'Sites' Survey), and the other for consumers (referred to as the 'Consumers' Survey). The surveys were designed to confirm and rank factors that influence and enhance participant recruitment and to identify additional barriers and enablers. Both surveys included multiple choice, Likert-type scale matrix, and open-ended questions. Information that could potentially identify responders was not collected.

Surveys were conducted using REDCap, a secure web application for building and managing online surveys, specifically designed to support data capture for research studies. Snowball methodology was employed; therefore, there was no denominator of persons polled. Ethics approval was obtained from Macquarie University Medical and Health Sciences Subcommittee, Ethics Approval No: 52019576410973, Project ID: 5764 and was carried out in accordance

with the National Statement on Ethical Conduct in Human Research.⁷

Survey group 1: Sites Survey. The Sites Survey was distributed broadly to advocacy groups representing pharmaceutical and medical device companies, industry groups, associations, organisations and sites involved in clinical research, asking them to share with their networks. The survey contained 46 questions, including questions to rate the significance of identified barriers and enablers, obtain additional barriers and enablers and capture details of possible site recruitment initiatives that may have been successful in the past. The survey targeted 200 responses, was open for 3 weeks in November 2019, and completion time was estimated to be 10–20 min.

Survey group 2: Consumers Survey. Consumers, for the purpose of this project, were defined as clinical trial participants and potential participants, carers, and people who use health care services.⁸ Consumers aged 18 or above were invited to respond to gain their perspective on involvement in clinical trials. Permission was sought from custodians of relevant patient and consumer advocacy and support groups to share the survey with their distribution lists.

The Consumers Survey contained 12–20 questions depending on whether or not the responder had previously participated in a clinical trial, and included questions on their knowledge of how people become aware of clinical trials, reasons for participation, and the enrolment and consent process. More than one answer was allowed. The Consumers Survey targeted 100 responses, was open for 3 weeks in November 2019, and completion time was estimated to be 5–10 min.

Analysis of survey data

SAS version 9.4 was used to retrieve, report and analyse survey data. Results of the Consumers Survey were stratified by whether respondents had ever been enrolled in a trial or not. Quantitative data were summarised as frequencies and percentages, and the denominators were defined as the number of responders who answered the question. Qualitative data were summarised by identifying themes from the free text fields.

Development of recommendations

Evidence from the literature and surveys results were reviewed by the project team and used to identify actionable methods to optimise recruitment. Affinity Mapping was used to organise, consolidate and group

these strategies, based on their relationships, into key themes that formed the basis for the development of the best-practice recommendations. Alternative approaches for presenting the recommendations were explored.

Results

Identification of barriers and enablers

Extensive project team experience in clinical trials was used to develop a list of 24 barriers and 12 enablers to site recruitment, listed in Figures 2 and 3.

Literature review

We reviewed more than 30 publications that focused on solutions to participant recruitment barriers at Australian and international sites. The main avenues in the literature for improving site recruitment were addressing trial feasibility, expanding eligibility criteria, having an experienced principal investigator, ensuring adequate resources for recruitment, simplifying the informed consent process, improving stakeholder engagement and utilising digital health records.

Although many barriers to recruitment were reported in the literature, solutions were mostly trial-specific with limited detail and generalisability for best practice.

The literature reinforced the list of barriers and enablers developed by the project team, with no additional ones identified. These barriers and enablers were explored in the surveys.

Results of Sites Survey

A total of 343 respondents consented to, and commenced the Sites Survey, exceeding the target of 200. However, not all respondents provided responses to all questions. Nearly two-thirds of the respondents worked at a clinical research site with approximately 70% of those research site respondents identified as having the role of a Clinical Trial Coordinator.

Barriers to recruitment. A total of 280 respondents completed all or part of the barriers to recruitment section of the survey, and rated each of the 24 identified barriers in order of significance on a Likert-type scale (Figure 2).

The highest ranking barrier to recruitment identified in this survey was finding eligible participants that meet study inclusion/exclusion criteria (70.0%), followed by an onerous visit schedule pertaining to distance, frequency and time commitments (64.3%), which was consistent with project team experience. The third-ranked barrier was insufficient resources at the site for recruitment activities (61.8%). Time taken for both governance/site review and ethics submission and review,

including amendments (61% and 60%, respectively) were key barriers to recruitment. This was a consistent finding noted by the project team, where the ethics approval process delayed the distribution timeline of the surveys by 3 months. Respondents were also asked to identify barriers that were not considered. Culture of research within an organisation was viewed as a notable barrier.

Enablers to recruitment. A total of 255 respondents completed all or part of the enablers section of the survey. Figure 3 illustrates the ratings in order of importance of each of the 12 identified enablers on a Likert-type scale.

Adequate staff resources to perform recruitment activities were the most important identified enabler to improve recruitment outcomes (91.8%), followed by an adequate budget for recruitment activities (90.2%). The third-highest ranked enabler was having an active principal investigator involved in the recruitment process (87.8%). An engaged and involved principal investigator was strongly supported in the survey comments along with the need for them to build a good rapport with site trial staff. Enablers outlined by respondents that were not considered in the survey were as follows: the need for increased awareness of clinical trials; opportunities for the sponsor to help enable recruitment, such as taking more time to develop the protocol with less amendments; having realistic eligibility criteria; less onerous visit schedules and providing ongoing support to the site research team.

Results of Consumers Survey

A total of 162 consumers consented to and commenced the survey, exceeding the target of 100 responses. Less than half (41%) of all consumer respondents had previously participated in a clinical trial, 31.7% of whom became aware of the trial via a specialist or other health care professional (the highest identified method of awareness), while only 4.8% learnt via their Doctor (General Practitioner) as shown in Figure 4(a).

Of those who had previously participated in a clinical trial, 85% rated the enrolment process as either good or excellent. However, 69% agreed that a simplified participant information and consent form would be helpful to improving the process.

Consumers who had not participated in a clinical trial prioritised learning about relevant opportunities via a doctor or healthcare professional at a similar rate to learning via social media (69% and 68%, respectively; Figure 4(b)). Key factors that would influence participation from those consumers who had never been in a trial included awareness of a relevant clinical trial (88%), personal health gain or benefit (84%) and the importance of contributing to research (71%; Figure 5).

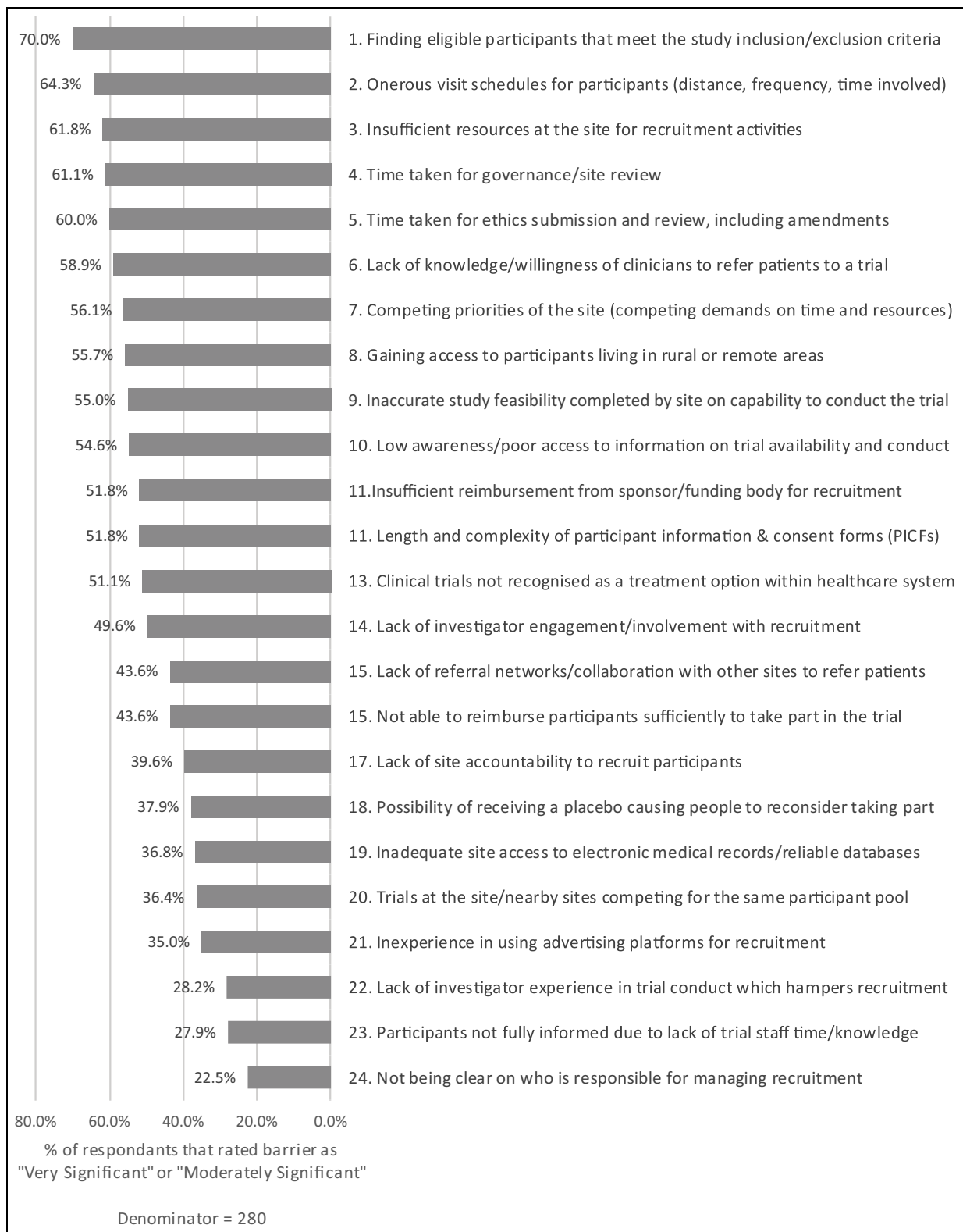


Figure 2. Ranking of the 24 identified barriers to recruitment from the Sites Survey.

Consumers were willing to consider trial participation, 91% of previous participants would consider another trial, and 79% of potential participants would think about taking part.

The Clinical Trial Site Recruitment Guide

The results of the literature evaluation and surveys, as well as mapping of additional ideas and strategies to



Figure 3. Ranking of the 12 identified enablers to recruitment from the Sites Survey.

improve recruitment, were used to develop recommendations under four key themes:

1. **Study feasibility:** accurate study feasibility is essential to determine a trial's importance and relevance for a site and to evaluate a site's capability and recruitment capacity.
2. **Start-up:** proactive planning during the start-up phase is key before recruitment starts, including training finalisation, ethical and regulatory approvals, budgets, contracts and the development of a recruitment plan.
3. **Recruitment methods:** understanding and selecting optimal recruitment methods to identify and attract potential participants must be considered in the context of each specific trial. There is no 'one size fits' all solution.
4. **Participant involvement:** ensuring participants are the priority maximises recruitment outcomes. Considerations relating to consent, education, awareness and communication should be examined and inconveniences minimised.

Alternative methods for presenting the recommendations, including checklists and guidance documents, were explored. It was determined a practical guide with

recommendations and links to useful tools and resources would be most valuable, allowing users to self-select relevant information (summary of guide shown in Figure 6). The full detailed Clinical Trial Site Recruitment Guide is available on the CT:IQ website.⁹

Discussion

The published literature on detailed best practice for recruitment is limited and recommends further research into the development of best practices and specific guidance for clinical trial staff to successfully recruit participants. The GREET project aim was to improve recruitment outcomes through practical guidance for site staff.

While initial project discussions focussed on how to recruit trial participants, as the project evolved it became clear that recruitment needs to be considered well before recruitment starts. Early intervention and planning were identified as key to maximising successful outcomes.

Study feasibility

The project highlighted the need for an accurate feasibility assessment conducted prior to site selection/trial

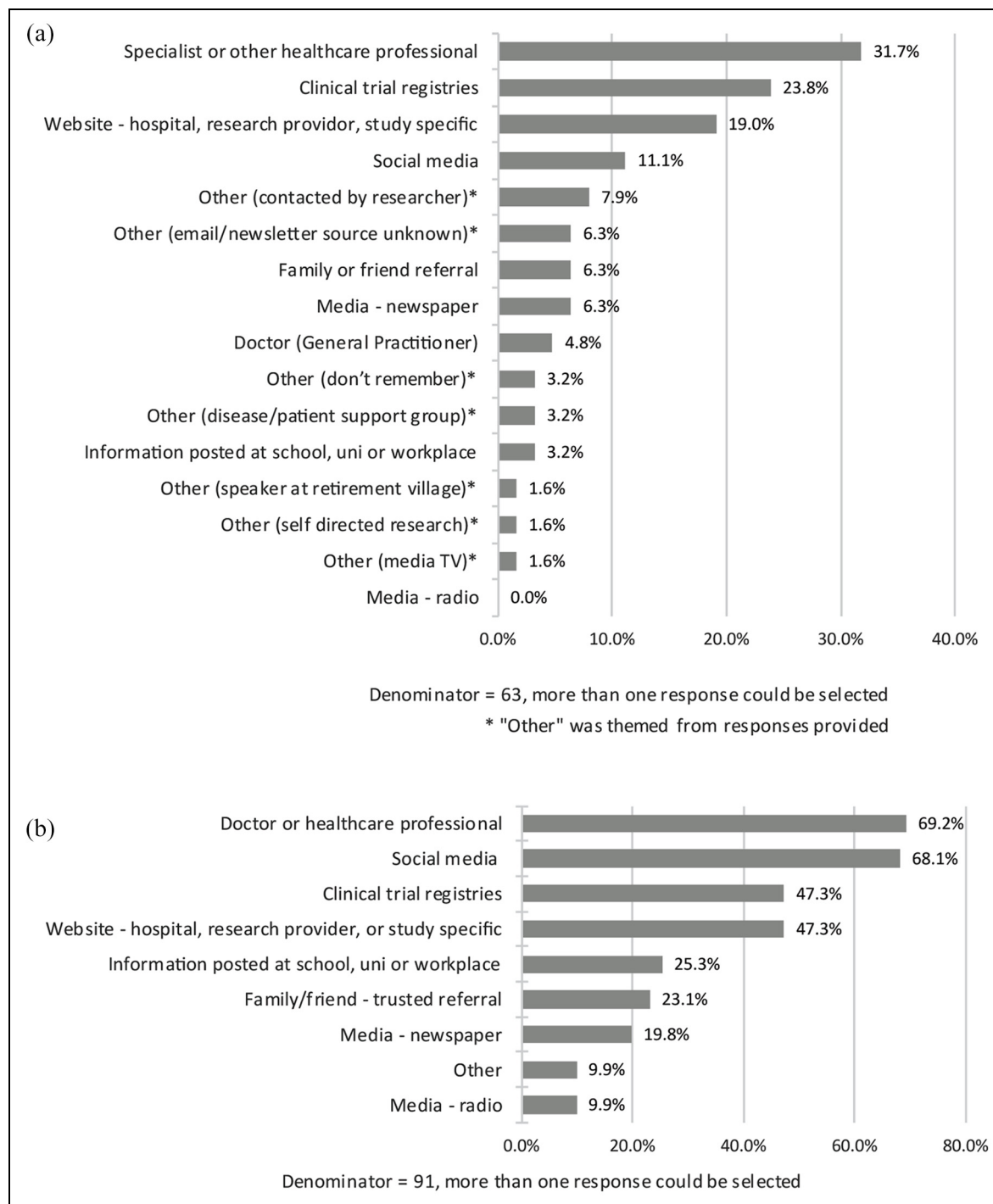


Figure 4. (a) How previous participants were made aware of a clinical trial and (b) how potential participants would prefer to be made aware of a clinical trial.

acceptance. The top three barriers to recruitment identified in the survey (Figure 2) were items that can be assessed and managed during the feasibility stage, suggesting that this was not being undertaken successfully. Feasibility can be a mutually beneficial opportunity for sponsors and sites to determine the capacity for a site to competently undertake a trial. Sites should carefully

assess protocol eligibility criteria during feasibility to ensure they have access to the required participant population,¹ as meeting eligibility criteria have been recognised as a leading barrier to participant accrual.^{6,10,11} While poor protocol design was not within the scope of the project, the project team agreed this was an area that sites could influence at the feasibility stage, and

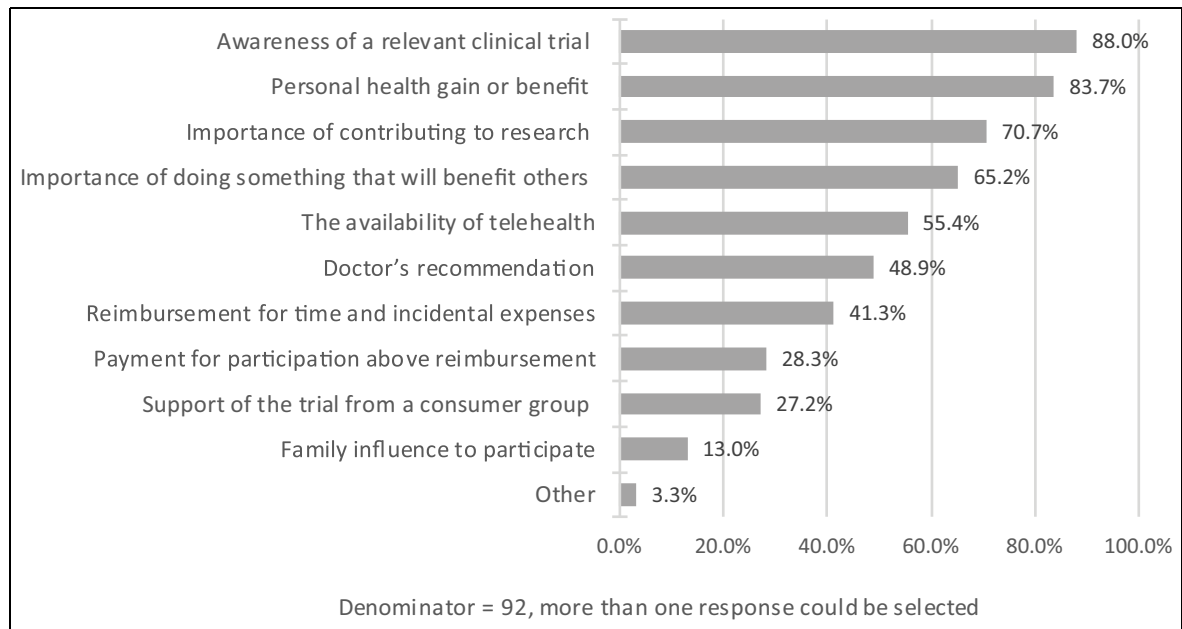


Figure 5. Factors influencing the decision for potential participants to consider participating in a clinical trial.

concerns about protocol design should be expressed to sponsors so that amendments can be considered before the trial starts.

The third highest barrier identified was insufficient site resources (63%). Interestingly, the highest-ranking enabler identified was adequate site staff resources to perform recruitment activities (Figure 3). This aligns with project team experience that resourcing is frequently underestimated and significant resource-related barriers often lead to delays in recruitment as well as trial staff disengagement.¹⁰ Further investigation into resourcing is needed to better understand the specific resourcing challenges, that is, inexperienced staff, competing trial priorities, manual processes and legacy software systems leading to time being used inefficiently.


Study start-up

The project identified that if start-up activities (between site selection and recruitment) are not conducted correctly or efficiently, recruitment will be delayed. These include, ethical and site governance approvals, recruitment budgets and recruitment plans. While sites cannot always control ethical and governance review timelines, it was agreed there are measures that can hasten the review process, including version control and punctual submission of accurate trial documents.

It is important to the success of the trial to establish clear resourcing, a recruitment budget and principal investigator requirements during start-up, as reflected

by the top three enablers. Significant infrastructural and resource-related barriers may lead to delays in recruitment as well as disengagement by senior staff or the principal investigator, who will often defer to junior staff with limited experience.^{10,12} Resource constraints can also lead to time management issues due to research staff's involvement in multiple trials.¹⁰ Adequate site resourcing should be evaluated at both the feasibility and start-up phases. Delays can occur if teams do not have capacity to undertake recruitment activities, and advanced planning, recruiting additional staff where necessary, or engaging external site support services to fill resource gaps, are required. Adequate budget for recruitment activities was also identified in our survey as critical for successful recruitment (Figure 3).

To increase awareness and registrations of interest or referrals, the trial should be promoted to the target participant population and their healthcare providers. The importance of this is often underestimated, and teams can be overly optimistic about how many 'organic' referrals they will get without spending money on recruitment. Based on the data from our Consumers Survey (Figure 4(b)), participants expect to learn about trials primarily from their healthcare professional and social media. For a site to effectively provide trial information via both of these channels, a dedicated budget is required for paid media spending, campaign management, General Practitioner outreach and other related activities. Budgets should be negotiated and approved by sites in the start-up phase prior to ethics submission.



CLINICAL TRIAL SITE RECRUITMENT GUIDE

Summary of Recommendations

<p>STUDY FEASIBILITY: Conduct an accurate feasibility assessment before taking on the trial</p> 	<ul style="list-style-type: none"> Determine if the site has staff with the appropriate expertise and the right facilities and resources Determine if the site can manage the trial in addition to other planned and existing trials/programs Consider the administrative and contractual requirements so there are no surprises Foster open relationships with trial sponsor, communicate concerns early and set realistic goals
<p>START-UP: Undertake up-front trial planning and start-up activities before recruitment commences</p> 	<ul style="list-style-type: none"> Identify key staff and clarify roles and responsibilities Prepare, submit and manage accurate and timely ethics and governance approvals Ensure the budget includes funding for site recruitment activities Develop a realistic and methodical participant recruitment plan
<p>RECRUITMENT METHODS: Identify optimal methods of participant recruitment – no universal approach</p> 	<ul style="list-style-type: none"> Improve awareness with internal advertising Utilise existing databases and electronic medical records Engage the target population from the broader community with external advertising Consider third party vendors to provide recruitment support if site resources are limited Develop and foster clinician referral networks List the trial on all relevant clinical trial registries Regularly review and report recruitment rates, adjust planning as necessary
<p>PARTICIPANT INVOLVEMENT: Consider participants and their needs, be flexible and accommodate where possible</p> 	<ul style="list-style-type: none"> Involve and engage consumers where possible in trial-design phase and trial material content, advertising content and share research findings Ensure trial information is publicly assessable to consumers Proactively educate potential participants about the trial Ensure potential participants are informed of all aspects of the trial that are relevant to a decision to participate in a clear and unambiguous way Communicate clearly and consistently on all aspects of the trial Minimise participant inconveniences

*See [CT:IQ website](https://www.ctiq.org) for a full copy of the Clinical Trial Site Recruitment Guide

Figure 6. CT:IQ GREET project Clinical Trial Site Recruitment Guide summary.

This would facilitate trial advertising and liaising with the relevant providers, and commencement as soon as ethics approval is obtained.

Recruitment methods

The project identified no universal approach to maximising recruitment. Survey respondents commented on strategies that had worked for their site; however, these were noted to be equally ineffective at other sites.

A notable barrier to recruitment that was not part of the Sites Survey was the culture of research within an organisation. This was supported by previous reports that when staff do not view clinical trials as an essential business activity, it can create a detached research culture, and can adversely impact recruitment outcomes.^{10,13,14}

As previously highlighted, an adequate recruitment budget is essential to recruitment success, but having low-cost recruitment options are also important where budget may be limited, and this was included in the recommendations developed.

Another important enabler to recruitment success (79% of survey respondents) was having a clear recruitment strategy upfront and assigned responsibilities for the recruitment plan (Figure 3). The project team broadly categorised recruitment methods into five key areas: internal site advertising; external community advertising; utilising third-party recruitment vendors if limited site resources; promotional activities to raise awareness about a site's trial activities with consumers and clinicians and reviewing each recruitment campaign to improve future campaigns. These different recruitment methods allow sites to more easily undertake a comprehensive option assessment and proactively identify, plan and implement strategies to maximise success.

This project did not explore specific commercially available technology solutions that aim to accelerate and streamline participant recruitment. An opportunity exists for a critical assessment of technology solutions, including artificial intelligence and machine-learning technologies and their respective adoption by sites, contract research organisations, sponsors and clinicians to enhance recruitment methods. Given the number one enabler was adequate site staff resource to perform recruitment activities, technology may play a role in optimising site processes and automating repetitive, low value tasks so that site staff can concentrate on complex, high-value tasks.

Participant involvement

The fourth key theme emerging from the project was around the participants themselves. A noteworthy result emerging from the Consumers Survey was willingness to participate in a trial; over 90% of consumers who had previously participated in a trial indicated

they would consider participating again, and almost 80% of those who had not previously done so indicated they would consider enrolling in a study. However, attracting, identifying and assessing eligible participants to suitable studies remains a challenge.

Key areas of opportunity to improve participant involvement in clinical trials include; engaging consumers and raising awareness of a site's clinical trials, ensuring clear and consistent communication in a courteous and respectful manner, simplifying the consent process and minimising participant inconveniences (such as visit schedules, treatment closer to home, telehealth and considering ethically acceptable reimbursement).

The survey highlighted that consumer's expectations are to learn about trials from their healthcare provider or social media (Figure 4(b)). Considering only 4.8% of consumers who participated in a trial were informed by their General Practitioners (Figure 4(a)), an opportunity exists for improved communication between doctors and patients about participating in trials, and for sites to support General Practitioners in providing trial information. Further research in liaising and supporting General Practitioners may facilitate this unmet need.

Given that 69% of consumers surveyed felt that a simplified information and consent form would be helpful to the recruitment process, this is an area deserving of more attention. A recent method in circumventing complicated participant information and consent forms, is to obtain input from participants and site staff in the drafting phase,¹⁵ to ensure that high-level aspects of the trial, including dose exploration and different treatment arms, can be conveyed as plainly as possible. Although participant information and consent form modification may be out of scope for some sites, our recommendations include tips for engaging with sponsors to seek early input into the information and consent form from consumers. This should be routinely incorporated into trials particularly where site staff have increased autonomy and control on the design and conduct of the study. These findings are in line with other research that demonstrates trials with patient-centric designs had accelerated enrolment times and were more likely to meet recruitment targets.^{16,17} Early consumer engagement and involvement in research presents a clear opportunity for sites to implement and facilitate change that can deliver improved recruitment outcomes.

Since the launch of our Site Recruitment Guide, a 2020 Cochrane review emphasised the need for recruitment approaches that focus on the participant, exploring the multifaceted reasons that influence trial participation, and producing a list of key questions to help trial staff.¹⁸

Our literature search did not identify any detailed practical recruitment guides or tools that were targeted specifically at research site staff. The Clinical Trials

Transformation Initiative (CTTI) published a Framework in 2018 which proposes an upstream approach to recruitment planning in the protocol writing phase.⁶ CTTI and other groups have also called for a more patient-centric approach to optimise recruitment.^{6,16,19} Both methods are approaches are valuable, but they contrast with the practical and more prescriptive nature of our guide, and target a wider audience.

Conclusion

There is no universal approach to optimising participant recruitment in clinical trials that can be applied across all types of sites, studies and disciplines with guaranteed success. Several factors affect recruitment outcomes, which can broadly be defined as those that can or cannot be controlled by sites. While there are many factors that are beyond a site's ability to alter, there are numerous opportunities where sites can exercise autonomy in shaping outcomes.

There is a lack of detailed centralised guidance and strategies that can be implemented and controlled at a site level. The GREET project delivers a unique framework of practical recommendations to support sites in optimising participant recruitment outcomes.

The GREET Clinical Trial Site Recruitment Guide provides comprehensive guidance, tips, resources, and tools for site staff to optimise recruitment (summarised in Figure 6). Launched in April 2020, the full guide is accessible via a free third-party online learning platform (Teachable), and as a downloadable PDF document, both available from the <https://ctiq.com.au/current-projects/project-4-2/>.⁹

We envision that the Clinical Trial Site Recruitment Guide could be adopted by sites to support decision-making, planning and to enhance overall clinical trial recruitment performance. The recommendations provide solid and practical solutions, intended to be used as a guide to provide sites with options that should be selectively and pragmatically applied where appropriate.

The Guide was designed for the Australian research sector; however, as many of the recruitment barriers are a universal challenge, these recommendations will be translatable to the international context, providing a template for the development of local guides.

Opportunity exists to further evaluate the effectiveness and uptake of the recommendations in a second-stage project. In addition, further research into the major barriers and enablers as well as exploring how technology can play a role is an area worthy of further investigation.

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