

**CT:IQ GREET project**

(**G**uidance to **R**ecruitment: **E**xamining **E**xperiences at clinical **T**rial sites)

**Literature Review**

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On behalf of CT:IQ (a collaborative of Australian clinical trial stakeholders who aim to develop and implement recommendations that will improve the impact, quality and efficiency of clinical trials).

**Assessing the site barriers and enablers to clinical trial recruitment, identifying any strategies that may inform best practises in participant recruitment.**

**Abstract**

Adequate participants in a clinical trial is the defining measure of trial success and statistical validity. There are many site barriers existing within the current research landscape that are a direct result of the stringent regulatory requirements. This affects recruitment at multiple stages in the process where site staff encounter difficulties engaging participants and conveying trial information plainly due to participant diversity, including those identifying as Aboriginal or Torres Strait Islander, and education-level. Increased workload and lack of enrolment can present as burdensome to the site and can result in disengagement and subsequent lack of leadership oversight. Further, clinical trial registries are difficult to navigate and rarely provide specific information regarding point of contact. To streamline the recruitment process incorporating Electronic Health Records (EHRs) to inform participant population, potential trial design and to conduct pre-screening would be highly beneficial to recruitment timelines. Additionally, conducting pilot studies to analyse feasibility and protocol design work to highlight unforeseen barriers, which can be addressed strategically. Expanding eligibility criteria to obtain complete safety data would allow for trial generalisability, therefore careful inclusion of participants with comorbidities such as Human Immunodeficiency Virus (HIV) is valuable. Active revision of eligibility criteria using an adaptive trial design maintains the statistical integrity and promotes evidence-based modifications of trial design.

**Introduction**

Globally, clinical trials serve as a method towards developing new medications, detecting prevention methods and producing scientifically sound data. Achieving sufficient recruitment of participants to a trial is a crucial factor that can determine the statistical and scientific validity of a trial (1). Although many of the barriers impacting clinical trial recruitment require changes in legislature, there are challenges associated with trial management, interoperability of trial and hospital systems and coordination of resources (13). Insufficient recruitments rates increase trial costs, workload and may also lead to early termination of the trial. Although, there is a regulatory push for standardisation across the industry, for site staff standardisation is not an accurate reflection of reality (2). This review will assess the more site-specific barriers of recruitment to clinical trials while highlighting solutions suggested in the literature that may be translated into best practise. Most factors that act as barriers to recruitment are multifaceted and require a pragmatic approach that can be adapted and applied across all clinical trials.

Educating participants about the target disease and related treatment helps to address low health literacy. Further, simplification of the informed consent process to maximise inclusion of Indigenous populations and minority groups will benefit recruitment (3). Despite existing health and socioeconomic disparities, it is important that trial medications are communicated to vulnerable participants as potential treatment options. This requires general practitioner’s (GPs) awareness and willingness to refer participants to trials, and the collaboration between research and non-research staff (4). At the site level, there are significant infrastructural and resource related barriers that often lead to a delay in recruitment and trial staff disengagement. In the early stages, addressing trial feasibility through effective methods that accurately assess the trial’s viability, help to identify potential clinical trial barriers (5). Therefore, incorporating constructive pilot studies or using an adaptive trial design allows active assessment of trial procedures, eligibility and participant population. Subsequently, strengthening clinical trial registries, such as the Australia and New Zealand Clinical Trial Registry (ANZCTR), to provide site-specific information and including more lay language will improve accessibility and readability (4). Inability to recruit participants within the planned timeframe delays other dependent trial milestones which further delays participant’s access to medication. Therefore, including stakeholders in the trial design process as key partners will inform best practice and strategies to execute recruitment activities efficiently and successfully (6).

**Informed Consent Process**

The aim of informed consent is to inform potential research participants of possible risks and benefits of a clinical trial. Site staff are tasked with engaging the participants and are often required to play educator roles when explaining the treatment and the trial design to the participant (2). As this is a critical process that directly effects recruitment, sites and even the sponsor are required to develop a targeted and strategic approach based on the trial population. The inclusion of legal and privacy wording is perceived as intimidating and overwhelming by participants and can often results in disengagement. Researchers have highlighted the importance of simplifying the language within informed consent forms by presenting trial requirements, benefits and associated risks separate to detailed legal and privacy language (2). Although privacy and legal disclaimers are necessary to satisfy regulatory standards and reduce sponsor/site liability, extended and complex ICFs, such as those used in oncology studies, increases the barrier associated with readability of Informed Consent Forms (ICFs) (8). Simplification of ICFs by altering the format to include diagrams, shorter sentences and flowcharts has been seen to increase comprehension especially in participants with low literacy levels (9). Further, the push for standardising documentation such as ICFs disallows customisation based on the participant and the trial objectives.

Researchers have stressed that obtaining informed consent is a process that is delivered differently to every participant due to varying levels of health literacy, language barriers and visual/hearing impairment (9). A recent method that has proved functional in circumventing complicated ICFs, is to obtain input from participants and site staff in the development of the document (10). This works to tailor the ICF to the specific trial and related treatment such that high-level aspects of the trial i.e. dose exploration and different treatment arms can be conveyed as plainly as possible. An oncology trial conducted by *Maughan et al. 2014*, devised a four-step informed consent process that provided trial-specific information to participants at separate stages of the trial. There were four Patient Information Sheets (PISs) used: PIS1 comprised of a diagram outlining the tests to be conducted on the participant’s tumour tissue, PIS2 was provided before screening results were obtained and explained the different trial arms and treatment-related adverse events, PISs3 described the randomisation process and was provided to participants prior to randomisation, finally PISs4 offered detailed information of the treatments regimens. Follow-up interviews and participant comprehension questionnaires were used to measure understanding of the trial where over 90% of respondents expressed full trial comprehension (10). Thus, the use of tiered PISs at specific treatment milestones provided tailored and relevant information to participants and avoided the burden of excess information. This method can be applied to the delivery of ICF documentation to participants, specifically in studies with complex designs and multiple treatment arms, to ensure relevant and concise information is provided to participants.

**Informed Consent for Aboriginal and Torres Strait Islanders**

A significant barrier to recruitment in Australia is engaging Aboriginal and Torres Strait Islander populations in clinical research and developing an adequate level of research comprehension during the informed consent process (3). A recent trial conducted by The Picture Talk Project interviewed Indigenous peoples as part of a focus group from Fitzroy Valley in Western Australia (3). The group was questioned regarding their experience and opinions of the standard informed consent process and how likely they were to participate in a trial. The respondents expressed the importance of the organisation’s reputation within the Aboriginal community, for example Marninwarntikura Women’s Resource Centre is regarded highly within the community and including their logo on research documentation holds as much value as the trial-specific information within the document (3). Participants also highlighted that English and health literacy is a significant barrier to recruitment in older Aboriginal members of the community, which hinders the comprehension of complex, lengthy informed consent documents. Although this layout may satisfy regulatory requirements, respondents suggested that the inclusion of visual diagrams, less wordy documents and translation of English text to their native language would be more interactive (3). As visual communication is essential to Aboriginal and Torres Strait Islander culture, minimising texts while increasing the use of flipcharts and other visual aids while maintaining content that are culturally appropriate are important; but may prove challenging for the sponsor (7). Therefore, increased collaboration with Aboriginal and Torres Strait Islander leaders to inform trial design and provide cultural guidance is required.

**eConsent**

TransCelerate Biopharma published a guidance document regarding electronic consent as a method to facilitate recruitment and reduce the burden on sites and the sponsor (11). The document contends that eConsent is complementary to Risk-Based Monitoring and allows for central and remote risk analysis of the consent process. This method also works to reduce printed paperwork and associated quality risks such as missing signatures and version control (11). For the participant, eConsent will increase trial comprehension as complex procedures and information can be relayed visually through multimedia use. The document also condones the use of a tiered eConsent approach whereby participants can navigate to more relevant information as they approach a specific milestone within trial (11). As the sites essentially own the consenting process, eConsent enables sites staff to address more high-priority trial activities and participant queries, which aids in the process to retain participants on the trials.

**Stakeholder engagement**

Maintaining site staff engagement in recruitment-specific activities while ensuring active communication between research and non-research staff has proved challenging (15). Research staff are often juggling multiple trials, and due to resource constraints, have limited time. In the hospital setting, non-research staff may fail to refer and identify potential trial participants to clinical research, as they too, suffer time-constraints (13). Insufficient staffing models and unsuccessful resource allocation hampers effective cross-functional collaboration between research and non-research staff. Although sites may be optimistic about recruitment numbers at the initial stages of a trial, lack of participant enrolment reduces morale and increases staff disengagement. The ASPREE trial conducted in Australia, included GPs as ‘co-investigators’ in the trial, in an effort to increase recruitment and community engagement in both regional and metropolitan areas (12). GPs were reimbursed for their participation and the trial did not require lengthy time commitments, which further incentivised participation. The inclusion of GPs from regional areas around Australia saw 45% increase in recruitment of participants to be successfully randomised (12). This strongly suggests that the GP-participant relationship is essential when enrolling participants of remote and regional areas. However, the trial also noted that co-investigators who joined the ASPREE trial were less likely to achieve successful randomisations when enrolment activity was slow or took more than 8 months (12). This implies that slow accrual rates may lead to investigators deprioritising the trial and gradually withdrawing oversight of recruitment activities.

**Principle Investigator Experience**

In many cases, lack of experience as a Principle Investigator (PI) hinders the ability to foresee forthcoming issues that may present as barriers to trial recruitment (15, 17). Experienced trial investigators reported that obtaining funding from the sponsor to cover research costs was not a barrier compared to inexperienced investigators (15). Moreover, research conducted by *Adams et al. 2015* found that senior research staff were effective at recruiting participants to studies due to the utilisation of established networks and extensive experience in participants communication (15). However, senior staff such as the PI rarely take part in recruitment activities, due to lack of resource, and often defer to junior staff who have limited experience (15). Another study surveyed GPs and assessed trends around perceived barriers to recruitment (17). The common barriers expressed by GPs were limited access to qualifying participants and the excessive time taken to recruit their first participant. Failure to recruit participants is attributed to lack of experience and/or lack of effective communication style when relaying trial information to the participant (17). Thus, there are calls for constructive training as an intervention allowing site staff to increase participant-centric communication skills, while developing proactive methods for strengthening the researcher-relationship (14).

**Site Staff Engagement**

These interactions between the doctor and the participant are essential in the process of building the participant’s awareness and education of a trial. As previously mentioned, low participant accrual rates lead to loss of PI oversight and additionally reduces study coordinator support, placing added pressure on an already limited unit (13) Consequently, clinical trials may not be viewed by site staff as essential business, which creates a detached research culture and further disengagement. A pragmatic approach is required to boost research culture through the provision of the necessary support functions and even the restructure of staffing models. Encouraging the perception that clinical trials are core business during training and equipping staff with tools to combat disengagement is be beneficial (16). To drive this concept, the relationship between the study coordinator and the PI should be maximised where discussions regarding site staff feedback, trial design and recruitment activities can be conducted (13). Further increasing the trial budget as necessary to accommodate for challenges presented when attempting to recruit participants, especially those of minority and specials-needs groups, will allow for the mitigation of communication barriers and lend support to recruitment staff.

**Pilot Studies**

As site staff remain at the forefront of the clinical trial it is important that they are included in the trial design to ensure they are adequately qualified for recruitment activities. Conducting a pilot phase as a method of measuring operational uncertainties surrounding the main trial, while seeking input of stakeholders can work to optimise recruitment. An internal pilot trial conducted by *Bertram et al. 2019* aimed to identify unforeseen recruitment barriers specific to the trial design (18). The results of the internal pilot trial were assessed with the contribution of a trial-specific participant working group, regarding the improvement and modification of trial documentations i.e. questionnaires. These findings were also discussed with site staff as a means of training to incorporate these learnings into future recruitment activities. The group met regularly throughout the trial and provided participants -centred advice such as simplification of ICFs and made recommendations regarding the updating of the recruitment Standard Operating Procedures (SOPs) (18). In another trial, participants potentially satisfying the eligibility criteria were calculated to be 60%, however the internal pilot trial found that 74% of participants were indeed eligible to join the trial (19).

In some cases, pilot studies can also be employed to determine proof of concept and efficacy of a treatment in a participant population. Smaller participant cohorts (which are easier to obtain) allow for adequate assessment of efficacy which counteracts early termination of larger, main studies (20). The pilot phase also works to determine whether the investigator estimate of disease population, incidence and prevalence is reflected in the number of participants screened for eligibility (20,21). Overestimation of these numbers can often result in trial delays and off-track recruitment. Therefore, conducting internal pilot studies allows for the predetermination of potential barriers, incorporating a viability assessment of recruitment, and overall trial design (21). The active inclusion of site staff in the trial design and subsequent design modification, is a practical approach to maintaining engagement in recruitment activities and benefits the delivery of a trial (18).

**Digital health records**

The process of information exchange between the participants and researcher (sponsor included) is tedious, slow and often involves copious amounts of paperwork. This takes up a significant amount of time and delays high-priority tasks, which adds to trial workload. Moreover, optimising the use of hospital/clinic systems and records such that interact directly with sponsor systems would serve as an enabler to recruitment. Since the development of electronic Health Records (EHRs), there has been speculation as to whether EHRs can be used to facilitate the exchange of information in clinical trials (24). EHRs could be used to analyse feasibility of a trial, given the participant population, and assess eligibility (22). Although incomplete records may pose as a challenge, EHRs allow for the pre-screening of potential participants through the analysis of diagnostic records, pathology reports, age and gender. Practical use of EHRs, such as My Health Record, may reduce the burden on site staff as screening information such as concomitant medications and comorbidities can be recorded directly by health professionals and therefore do not have to be duplicated into electronic Case Report Forms (CRFs) by trial staff. Research conducted by *Marceglia et al. 2017* devised a system that incorporated participant generated data from eDiaries into eCRFs and EHRs. This method addresses the lack of inter-functionality associated with hospital/clinic systems and would allow for the rapid detection of non-compliant participants (23). Often poor compliance to treatment schedules is risk factor for withdrawing from studies, and thus rapid detection would allow for staff to communicate with the participant and determine any underlying deterrents to administering the treatment(s). Additionally, this information can also be viewed by the sponsor directly which provides the opportunity for remote monitoring, reducing the number of site visits required and the overall trial cost (23).

However, there are challenges related to the implementation of EHRs in clinical trials such as capturing complete data and ensuring the data is to the ICH GCP (International Conference on Harmonisation-Good Clinical Practice) quality standard (23). Ensuring source data captured is aligned with the ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles will require that all medical staff are trained in ICH GCP, otherwise this data cannot be used directly in clinical trials (24). In Australia, using the My Heath Record system for recruitment purposes will require a specific consent mechanism which has not yet been developed (25). Constructive collaboration between site staff, sponsors and regulatory health bodies is beneficial to develop a standardised method of employing digital health records in clinical trials to streamline recruitment and monitoring activities.

**Clinical trial registries**

Clinical trial registries are a platform where sponsors publish information on current or recent trials and provide an educational space for participants and other individuals such as carers or HCPs to express their interest (32). Online registries are an effective way to relay up-to-date trial information to potential participants and HCPs. However, navigating these registries may prove difficult as essential information such as the trial location and a local point of contact is either not published or located ‘centrally’ (4). This poses an awareness gap between potential participants, Health Care Providers (HCPs) and the trial. TransCelerate Biopharma Inc conducted a global survey including participants, health care practitioners, sponsors and other trial stakeholders. The survey sought to obtain information that would enable participants to gain better access to trial information while assessing health care practitioner’s knowledge of registries. Results from the sponsor survey suggested that despite all sponsors having Standard Operating Procedures (SOPs) stating that trials should be listed on registries 77% of sponsors do not upload site-specific contact details (4). Despite seeking the approval of sites, less than half of responding companies rarely posted/updated registries with site-specific information (4). There are challenges around resource allocation that need to be considered if information on registries were made site-specific and publicly available. Disclosing contact numbers publicly would require availability of site staff/researchers to answer enquiries. Most studies list central contact numbers which are often located off-shore and are difficult to contact, which deters participant engagement.

In addition, more than 50% of HCPs failed to discuss and refer participants to clinical trials (4). Even fewer knew where to access clinical trial information in terms of locations and these numbers were even lower amongst inexperienced practitioners. Respondents in the Site Advisory Board expressed that the sponsor should allow sites to decide which method of contact should be made available on public registry (4). This would allow for sites to adequately develop staffing and infrastructure to handle enquire volume and can be assessed on a site-by-site basis. The participant survey revealed that participants prefer using online and electronic notifications when trial information is available. Participant respondents expressed an appreciation for making trial details publicly available and 72% were enthusiastic about contacting the site directly. However, a mere 16% currently used registries to search for trials (4).

**ANZCTR Compatibility and Accessibility**

Further, clinical registries such as ANZCTR and clinicaltrial.gov are not compatible with smart phones and tablets and reduce portability (26). The information in the ANZCTR is only available in English and does not provide the option for trial description to be read in any other language. To optimise user friendliness, ANZCTR should include a map service and provide transport options to attend sites listed. The website does not contain pages tailored to each type of user i.e. participants and HCPs, this would ensure information available is specific to health-literacy levels (26). There is limited information on how to apply for clinical trials, with no links provided to websites that contain disease information i.e. incidence and prevalence (26). The implementation of local clinical trial registries that focus on a single disease area can present trial information in a simplified format that is readily accessible by potential participants (27). The Australian Cancer Trials website feeds directly from ANZCTR and ClinicalTrials.gov, providing specific information relating to oncology trials in participant-friendly manner. The website/registry was developed with the input of consumer representatives which advocated the inclusion of lay language (27). Further, the website also provides a ‘Specific Questions Prompts List’ which participants can take to their physicians and inquire further about the trial. Local registries are an effective method of specifying trial information based on therapeutic area, this improves user-friendliness as information is not presented in an overwhelming manner. This layout may be useful in informing the redesign of ANZCTR to increase accessibility on portable devices, include language tailored to varying health literacy levels and include translation functions to streamline access to trial information.

**Eligibility Criteria**

Eligibility criteria are used in clinical trials to define the trial population and remaining protective of participants safety. Currently, excessive exclusion criteria are a leading barrier to clinical trial accrual. For example, many oncology studies exclude participant’s with HIV, despite cancer being the leading cause of death for HIV patients (27). Excluding potential participants due to HIV limits evidence-based treatment options for this population and reduces trial generalisability. The American Society of Clinical Oncology (ASCO) in collaboration with the Friends of Cancer Research and the Food and Drug Administration (FDA) in the United States analysed the main concerns that would regularly result in participant exclusion, these included (but not limited to); HIV, organ failure or dysfunction and previous malignancies (29). The project devised several recommendations for the inclusion of participants with specific comorbidities. Of the HIV population, the inclusion criteria should be focused on CD4 and T-cell counts and whether the participant is at low risk of AIDS-associated conditions prior to treatment (29). An oncology trial conducted by *Ulderick et al. 2017* involved the participation of HIV-infected participants to analyse tumour histogenesis in large B-cell lymphoma (30). As the trial was investigating the effects of combination chemotherapy on this type of lymphoma, HIV treatment was suspended to reduce immunosuppression and other related adverse events. Further, treatment cycles were reduced for HIV-positive participants through dose modifications based on blood toxicity (30). Once HIV-treatment was resumed, the trial found that participants made a full CD4 cell count recovery, no deaths were associated with treatment and there were no new Acquired Immunodeficiency Syndrome (AIDS) related infections (30). This demonstrates that in specific cases, inclusion of participants effected by HIV is relatively safe compared to participants without HIV (30). To accommodate this, increased site staff support, infrastructure and resourcing is required to maintain adequate monitoring of these participants.

**Adaptive Clinical Trial Designs**

Modern oncology trials are working to utilise biomarkers and targeted therapy methods where a heterogenic trial population is desirable to obtain more complete safety data (31). Adaptive trial strategies use cumulative data from the trial itself to make statistic-based modifications without compromising the integrity of the trial. This design would serve as beneficial for biomarker-driven trials as the trial design can be adjusted based on biomarker data and response (31). Many studies tend to use previous eligibility criteria as a template for newer studies, however the criteria should be evaluated based on the Investigational Product (IP) and the prospect of heterogenous disease population (29). In combination with an adaptive trial design, expanding eligibility criteria would allow for early detection of efficacy and/or dose-limiting toxicity data and therefore earlier development of mitigation strategies (29, 31). For the development of realistic eligibility criteria, engagement and collaboration with multiple stakeholders such as PIs, site staff and sponsor staff is essential to allow for successful recruitment rates and effective analysis of toxicities across the trial population. Although expansion of eligibility criteria will require increased site staff infrastructure and resource, an adaptive trial design may be beneficial to recruitment as it will allow for active assessment of inclusion/exclusion criteria (29).

**Conclusion**

Ultimately the existing barriers to recruitment require specific strategies based on active collaboration with site staff, participants, HCPs and other stakeholders. Implementation of strategies to expedite recruitment, specifically in Australia, are dependent on understanding research attitudes at an individual level, providing resource to site staff and active revision of clinical trial documentation and design. This will support the efforts to increase awareness of ongoing and recruiting trials to physicians, participants and potential participants in the community. Adequately resourcing staff will enable the prioritisation of participant-researcher dialogue, recruitment activities and improving health literacy. Further, incorporating the use of more modern, portable technology when publicising trial information will allow increase access to participants and referring HCPs. Although there may be concerns about the analytical capability of incorporating EHRs, coordination with necessary stakeholders may inform effective management of this data, ensuring that the principals of informed consent are upheld.

**Acronyms**

AIDS – Acquired Immunodeficiency Syndrome

ALCOA – Attributable, Legible, Contemporaneous, Original, Accurate

ANZCTR – Australia and New Zealand Clinical Trials Registry

ASCO – American Society of Clinical Oncology

CD4 – Cluster of Differentiation 4

eCRF – electronic Case Report Form

EHR – Electronic Health Record

FDA – Food and Drug Administration

GP – General Practitioner

HCP – Health Care Provider

HIV – Human Immunodeficiency Virus

ICF – Informed Consent Form

ICH GCP – International Conference on Harmonisation-Good Clinical Practice

IP – Investigational Product

PIS – Patient Information Sheet

PI – Principal Investigator

SOP – Standard Operating Procedure

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