CT:IQ Early Phase Best Practice project

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).

Review of site practices and guidelines for best practice approaches in the conduct of early phase clinical trials. May 2019

Introduction

Early phase clinical trials (EPCTs) are crucial in the development of new treatment options. For the purpose of this literature review early phase studies encompass all clinical trials up to Phase II, including studies with any Phase I component, or pre-pivotal medical device studies.

Early phase pharmaceutical studies are non-therapeutic in intent and aim to assess the human pharmacology, tolerability and safety of investigational medicinal products (IMPs). Early medical device studies are similar in focus but aim to produce data relevant to the performance of the device, as well as safety. For the purpose of this review, reference to IMPs includes investigational drugs, biological compounds and medical devices. EPCTs, especially those that represent first-in-human (FIH) studies, have the largest degree of uncertainty in terms of risk to participants, whether they be healthy participants as is the case in most pharmaceutical studies or participants with the target indication, which is typical of device studies [1].

There are important points of variance between early phase pharmaceutical and medical device studies. There are distinctions in terminology, such as pharmaceutical studies working from a Trial Protocol, and device studies from a Clinical Investigation Plan. As well

as clear differences in the participant population, as above. Additionally, there are substantially different regulatory requirements for different products, which is why pharmaceutical studies are guided primarily by ICH GCP [2], whereas medical devices are conducted under ISO14155 [3]. However, both guidelines were ultimately developed from the principles of Good Clinical Practice and the Declaration of Helsinki. Many elements of this review can be generalised to both pharmaceutical and medical device studies, but points of significant difference are highlighted throughout.

While the safety profile of early phase trials is largely acceptable, the occurrence of possibly preventable fatal and life-threatening serious unexpected severe adverse reactions (SUSARs) in two European trials (TeGenero 2006 and Bial 2016) has placed a focus on the conduct of clinical trials at clinical research sites, henceforth referred to as “site(s)”. As site practices vary, insufficient site processes have significant potential to impact on participant safety [4-7]. These studies highlighted the imperative of robust communication processes, particularly in regard to dissemination of urgent safety information.

Although limited international guidance regarding best practice recommendations for the conduct of EPCTs at research sites exists, the guidance is not adequately generalisable to the Australian context [8]. The aim of this review is to evaluate the existing recommendations and guidance, and in alignment with Australian regulations, consolidate recommendations regarding best practice for sites conducting EPCTs. This includes establishing a reference point for the development of guidance, including a site self-assessment checklist and resource toolkit, specific to the conduct of clinical trials at sites within Australia.

This review, and corresponding recommendations and resources, intends to build upon guidance and regulatory recommendations such as International Conference on Harmonisation-Good Clinical Practice (ICH-GCP). The review will focus solely on the conduct of clinical trials at clinical research sites and discussing particularly the areas of identified need.

Risk Assessment and Mitigation

Given EPCT participants typically do not derive any therapeutic benefit from participation, the risk of harm to the trial participants must be minimised for the study to be ethically justifiable [1,9]. Even in device studies utilising the target population, therapeutic benefit may not be a primary endpoint, and cannot be guaranteed. Therefore, a risk assessment coupled with a risk management/mitigation plan is an important harm minimisation strategy [1]. While it is the responsibility of the trial sponsor to undertake a detailed risk assessment of the protocol design and implications, clinical researchers at each site should also perform an independent and formalised risk assessment prior to study commencement [10-12]. Sites should be comfortable that trial design is compatible with site resourcing capabilities before proceeding to ethical review of the study’s conduct at their sites.

A well-informed site-specific risk assessment should include a review of the protocol, investigator’s brochure(s) (IB(s)), IMP dossier (including pre-clinical data, IMP mode of action, and a good understanding of the IMPs safety profile) as well as any relevant medical and scientific literature within the context of the study being conducted at that site and within the population the site accommodates [9]. A survey in 2017 of European Principal Investigators (PIs) conducting early phase research found that 19% did not, or only

sometimes, felt that they were adequately informed about the non-clinical data for an IMP, which is problematic given that this information forms the basis of participant dosing schedules, and can also impact trial design, dose escalation proposals, stopping criteria and subject selection considerations [10,13,14].

Thus, an understanding of the risks associated with the conduct of an early phase trial is an important aspect of the risk identification and mitigation process. Sites should have in place appropriate strategies to mitigate identified risks and to respond to unplanned events, with these processes practiced and documented at the site [1,10,11]. Examples of site-based risk mitigation activities include requiring a physician to be on site during and for a designated time period following dosing and ensuring specific equipment, procedures and staff training are available to handle expected and unexpected adverse events [14].

Furthermore, sites should have specific SOP's and strategies for off-site follow up. Pharmaceutical studies are often shorter in duration, with most assessments conducted on-site, utilising pharmacokinetic and pharmacodynamic analysis. However, some pharmaceutical studies do need ongoing administration or longer-term follow-up and medical device studies often require ongoing usage of a device, resulting in a follow-up period of months or even years. Therefore, the risk assessment/mitigation process is essential to the follow-up phase as well. It is ultimately a site responsibility to have documented processes and contact details for participants in the case of emergency or issue once off-site.

A common finding from inspections of Phase I sites was the failure to adequately document the risk assessment/mitigation process, in addition to this, evaluation being updated based on receipt of new information, such as a modified IB or protocol [14]. Hence, it is recommended that sites should undertake regular review and updates of risk assessment/mitigation processes throughout the lifespan of the trial to integrate all new clinical trial data throughout the conduct of the trial, and to document associated training [10,15]. To ensure that the most current information about the trial has been considered, it should also be made clear which version of documents were used to inform the risk assessment/mitigation plan and conduct associated training [14].

Quality Assurance

Another under resourced process identified at sites conducting EPCTs is site specific quality assurance (QA) programs, independent of sponsor or other regulatory authorities [11,16-19]. A site's QA program should consist of planned and systematic actions that ensure their processes are performed in compliance with GCP, approved protocols and their risk management strategies [11,16-19]. These processes should correspond with, and closely reference, either ICH GCP E6 for pharmaceutical studies or ISO 14155 for medical device studies.

In a survey of nearly 400 clinical trial staff, consisting mainly of co-ordinators, site managers, directors and investigators from sites in North America, factors that were found to contribute to low levels of satisfaction included the lack of a formal QA program at their site [20]. Sufficient resources should be allocated to provide an evolving QA program at the site, including internal audits, self-assessment, complaints management, protocol deviations management, adverse events review and training processes [11].

One of the key activities that promotes QA is the generation of standard operating procedures (SOPs), which provide detailed written instructions for all the activities undertaken at the site [9,10,19]. A non-exclusive list of recommended SOPs is outlined in the British requirements for Medicines & Healthcare products Regulatory Agency (MHRA) accreditation of Phase I sites. This includes processes for handling medical emergencies, staffing level/resourcing and dose escalation, as described below [10]. Although core SOPs relative to the conduct of clinical trials at Australian research sites are publicly available, issues with the dose escalation process, including the absence of a clear procedure, is by far the most common finding from MHRA inspections of Phase I sites [14]. This is concerning given that they were found to be a key contributor to the 2016 Bial tragedy [6,21].

Another recommended SOP is for an information management/documentation plan that details how all the data is to be collected, securely maintained, and what quality control measures will be performed to substantiate data [11,22]. Considering the failure to communicate safety information in real time contributed to the Bial 2016 incident [7,21], it is recommended that sites have a formalised communication plan, and corresponding SOP, that includes an approved procedure for reporting Serious Adverse Events (SAEs) to the PI (if not the treating physician at the time of the event), sponsor and regulatory authorities [11].

To improve familiarity and compliance with SOPs by site staff members, it is recommended that current SOPs are communicated and readily available, with appropriate training available [9]. Furthermore, SOPs should be regularly reviewed and updated as required [9,17,19]. As part of ongoing QA and site management, sites should consider their medical oversight arrangements, staffing numbers, experience and communication processes to ensure they meet the needs of the clinical trial, the unit and participant numbers. Sites should have documented practices for the reporting of medical events outside of their standard business hours, and participants should be aware of who to contact and what action to take should they require medical care outside of these operating hours. Ideally, the site should give the participant an emergency contact card as a resource to both themselves and emergency medical personnel. The card should contain contacts who can also expedite contact with the sponsor for further medical guidance into possible interactions, or treatment restrictions, due to the IMP.

Additionally, sites should proactively identify and respond to site specific issues, including protocol deviations or issues with site procedures [11,12,16,18]. Suggested methods for identifying potential site-level issues include managerial oversight of site-based monitoring and audit findings, and random review of source data and documentation practices related to a specific participant [18]. Furthermore, protocol deviations and other issues should be reviewed by the QA team at the site and corrective and preventive action plans (CAPAs), implemented to address immediate quality issues and minimise recurrence [11,12,16,18,19]. This process should be documented for auditing purposes and any learnings or alterations that result from this process should be communicated to all relevant staff, including documented training [11,19]. It is also recommended that the site initiate periodic external audits [9,17,18]. Furthermore, SOPs establishing communications and reporting timeframes between medical staff, PIs and sponsors should also be in place, with particular respect to immediate reporting of SAEs to the PI, if not the treating physician.

Emergencies

Though emergency situations can occur in any clinical trial phase, the potential risk is elevated in early phase clinical research where the emergence of unexpected serious events are more prevalent due to the inherent risk of early phase research. Sites must have adequate procedures, equipment, facilities, qualified staff, training and external support to handle any potential medical emergencies [1,9,10]. To ensure staff can be immediately notified of a medical emergency, the unit should be equipped with alarms in all areas frequented by participants, including bathrooms and common areas, and regular, documented checks of the alarm system should be performed [9,10]. In addition, the bathroom doors should be able to be opened from the outside by staff in the case of an emergency [10]. An emergency trolley must be available in each main area of the facility so that it can quickly and easily be brought to where it is needed [9,10]. The Australian Resuscitation Council Guidelines recommend the contents of an emergency trolley [23]. However additional rescue medicines for common adverse events and antidotes for the IMP, where applicable, should also be readily available, either on the trolley or within close proximity in the treatment area, and known and easily accessible by staff and emergency responders [1,9]. Audits by MHRA inspections of Phase I units frequently identified items on emergency trolleys that were expired or missing, therefore a frequent inventory check is recommended [9,10]. In addition, participant beds and chairs within the facility should have sufficient access surrounding them to accommodate the emergency trolley and required staff in the case of a medical event, which in the UK is recommended to be 3.6m (width) by 3.7m (depth) [24]. It is also recommended that the beds and treatment chairs be height and position adjustable to facilitate procedures during a medical emergency [10]. Medical device studies are often conducted in established medical facilities, specific to the target indication. Despite this, the facilities must still be evaluated against any potential emergencies related to the study device. This is particularly important given the increased risk of Serious Adverse Device Effects compared to approved devices, which the site may be more familiar with. The tendency for medical devices to undergo design changes during the course of the investigation makes re-evaluation of the facilities of particular importance throughout the study [3].

It is an imperative that early phase clinical research sites have documented and practiced procedures for dealing with medical emergencies, including the resuscitation, stabilisation and transfer of participants to an emergency or intensive care unit (ICU) [10]. SOPs relating to medical emergencies should include anticipated SAEs that were identified as part of the risk assessment of the trial [9]. The site should have a pre-existing agreement with the emergency department to provide support for medical emergencies, including ensuring access to ICU services [1,10]. The current international recommendations do not stipulate any minimum proximity from the research site to emergency medical care however the transfer should be tested under varying conditions and documented as part of the risk assessment [14].

Facilities

The group of participants, and therefore the site and facilities, is an important variance between early phase pharmaceutical and medical device studies. Phase I pharmaceutical studies typically start with a small group of healthy volunteers, moving onto greater sized cohorts as the study progresses. Whereas medical device trials begin testing in a small group of patients with the target indication. Therefore, medical device trials require a site specialised in the target indication, while pharmaceutical studies can be conducted in dedicated early phase clinical trial facilities.

Each site determines the facilities and equipment that is required to conduct high-quality and safe trials [11]. These needs vary depending on the number of trials, the number of participants per trial and the types of trials undertaken at the site [11]. Although not specific to clinical research sites, investigations into the best layout for a medical facility, including single/double corridor, L-shaped, T-shaped, Y-shaped, triangular and cruciform, found that none were universally superior [25]. Hence, the facility's layout can be based on service needs and optimised workflow [25]. The types of rooms that may be required in an early phase clinical research site include consultation rooms that can provide participants with privacy during examinations/procedures, private interview rooms for obtaining a medical history/informed consent and meeting rooms for conducting staff training, sponsor meetings, monitoring and audits by external monitors [12,26]. The site should also have adequate space to store all study documents as well as appropriate archiving procedures to facilitate secure storage of trial documents following study closure [12,19]. The ideal configuration of chairs, beds, rooms and wards will depend on several factors, including the length of stay and the need for observation/lines of sight, as stipulated in the trial protocol and risk management plan [25]. Design features such as glazed walls or large windows with blinds can promote good observation, while also providing privacy [24]. In order to promote subject wellbeing within the site, as many rooms as possible should receive natural light [24,25]. Amenities that enhance the experience of the participants, such as a lounge, are worth considering depending on participants' length of stay and probable acuity [25]. The Australasian Health Facility Guidelines contain Standard Components that detail the recommended dimensions, features and finishes of various specific room types in medical facilities [25].

EPCTs must have continuous monitoring equipment available, including machines that measure vital signs and perform electrocardiograms and pulse oximetry [10,12]. All medical equipment at the site should be regularly inventoried and subject to a formalised and documented maintenance plan that details the frequency of maintenance and calibration required for each item and the person(s) responsible for these activities [11,16]. It is also crucial that the site has adequate facilities, equipment, quality systems, documentation, and records for storing, preparing, releasing, administering and where applicable returning or destroying unused IMPs [27]. The site must have adequate facilities to store the IMP securely, separately and under the correct conditions [12,16]. There should also be a robust SOP for handling the IMP at the site that includes processes for receipt, storage, monitoring expiry, keeping inventory records, stock control and return to sponsor/disposal [11]Robust tracking logs should ideally be tailored to each study. This is particularly important for medical devices whereby a proportion of IP (investigational product) may be kept on site, while other critical components may be brought in on the day of implant or administered later

to the participant. Laboratory facilities, which may be internal or external, should have the relevant accreditation (e.g. NATA), follow SOPs, be regularly inspected and undertake maintenance and calibration of equipment [9]. When outsourcing services, the site should ensure there is a contract in place that includes robust procedures and clearly delineates responsibilities [11].

Additional considerations for Medical Devices

Clinical trials for medical devices are regulated with published requirements and guidelines by well-established regulatory authorities such as Australian TGA [28], U.S. FDA [29] and the European Commission [30]. In addition, international standard 'ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice' defines best practice requirements for running medical device clinical trials [3].

Medical devices requiring direct evidence of safety and performance obtained from pre-market pivotal clinical trials typically involve moderate to high risk device categories (such as class IIb class III and class AIMD). Investigational devices must undergo a risk assessment according to 'ISO 14971 Medical devices – Application of risk management to medical devices' and must pass applicable bench testing with positive results before being used in patients [31].

Design and manufacturing changes during a clinical trial, including early phase trials, are not unusual and must be well documented and, if significant, approved by and notified to the ethics committee and/or the regulatory authority as applicable.

Staff

Due to the complexity of EPCTs an adequate number of staff at the site are required to ensure the safety and quality conduct of trials [9,10,12,16]. It is recommended that sites conducting EPCTs have a SOP that outlines procedures to ensure there is continuous medical coverage, including ensuring the required number and mix of qualified staff for responding to a medical emergency [9,10,27]. Periodic skill mix reviews by site management may be useful in determining whether the current numbers and types of staff members at the site meet the requirements for successful clinical trial delivery [11]. Minimum staffing levels may need to be revised depending on the number of participants and the risk assessment associated with a protocol, for example, a risk mitigation strategy may have increased medical staff present for a defined period following dosing [14, 32]. The staffing level SOP should also include procedures for dealing with unexpected short-term absences or resignations of staff [12,14,19]. In addition, it is recommended that the site considers having a 'spare' member of staff who is not allocated specific tasks and can assist with any issues or delays that may pose a risk to protocol compliance [14]. The staffing levels at the site should be documented so that there is evidence that the predetermined minimum requirements have been met [10,14]. Medical device studies often require a sponsor representative, engineer or technician to attend study visits and calibrate the device directly with the participant. The site should have adequate staffing, SOPs, rooms and time to facilitate these requirements and ensure the participants privacy and comfort are not compromised.

An important factor for maximising the performance and retention of quality staff at a research site is managing workload [33,34]. It is necessary that the PI and other staff, especially those that do both research and clinical practice, have sufficient time for research activities [18,35]. For the PI this includes having sufficient time to effectively supervise the trial [12,18,19]. The experience and supervisory role of the PI was identified as the most important factor in determining staff performance, hence the number of trials per PI also requires careful management [32,36]. As EPCTs are more complex and labour-intensive than later phase trials, managing the workload of other site staff, particularly clinical research nurses and study coordinators, is crucial for supporting the safe conduct of a clinical trial [37]. Workload concerns were identified as one of the key stressors for CRNs/CRCs, which can lead to burnout and staff turnover [37,38]. Staff turnover has a negative impact on the trial in terms of increasing delays, costs and inconsistencies [39]. Hence, it is recommended that staff turnover at the site is tracked and an exit survey administered to leaving staff to identify any areas of dissatisfaction that may need to be addressed [12]. In order to assist with staff workload management, a number of different tools have been developed to measure protocol acuity, trial complexity and/or task frequency. Participant enrolment numbers can be incorporated into this tool to objectively calculate each CRNs/CRCs workload [39-41]. This information can then be used flexibly to make data-driven decisions regarding the allocation of tasks to staff members and to assess and justify the need for additional resources [40]. The use of acuity algorithms to evenly distribute complex and/or high-risk trials between CRNs/CRCs was found to improve their performance at Phase I cancer research sites [36,39]. Notably, all of the protocol acuity tools that have been developed to date are specific to oncology trials and not to early phase trials. In addition to adequately managing staff workloads, other recommended ways to maximise staff satisfaction and minimise turnover at clinical research sites include engaging staff in decision making, supporting professional development and providing co-authoring opportunities [35].

Sites must ensure that the PI and staff have the relevant skills, knowledge, qualifications and experience required to support the safe and high-quality conduct of trials. Staff require ongoing training to maintain credentials and optimise their skills [1,10,12,16,18,32]. It is recommended that the site has formal procedures for ensuring that a PI has the requisite training and experience to be made responsible for a specific trial [14]. Sites should have a documented training plan that ensures all staff, including agency staff and specialist consultants, have the relevant skills, knowledge and experience for their designated responsibilities, a requirement to document training in GCP, site-specific SOPs (emergency responses), protocol-specific SOPs and the IMP itself [1,11,12]. To be prepared for unexpected staff absences or departures, the site training plan should include procedures for cross training staff so that multiple people are competent in each task [35]. One of the main areas of dissatisfaction in regard to training amongst staff was insufficient time to reinforce training, which suggests that opportunities to implement new learnings should form part of the training plan [20]. It is recommended that a site-level training log/competency register is established and regularly updated for all staff [9,11,35]. This will enable site compliance with the training plan to be assessed by internal and external stakeholders. Furthermore, there should be a thorough onboarding procedure for new staff that involves site orientation and training, including being made aware of site policies and procedures [11,42].

The staffing structure at an early phase clinical research site is another area of consideration in regard to best practice. The University of Leeds Clinical Trials Research Unit, which had

been exclusively undertaking Phase III trials, successfully established a unit for early phase oncology trials and recommended creating a core team dedicated to such trials, which facilitated the development of appropriate expertise [43]. They also recommended limiting the number of trials per Phase I staff member through combining trial and data management roles to strengthen detailed protocol knowledge within a smaller team [43]. A study of sixteen more established sites undertaking Phase I oncology trials found that having disease-oriented teams also increased the number of trials and participant accruals [36]. The Department of Investigational Cancer Therapeutics (ICT) at MD Anderson Cancer Center (Houston, TX), which primarily undertakes early phase trials, employs an investigator-centred team structure in which individual PIs head a consistent group of staff [44]. Compared to other departments that did not have this structure, trial development time and participant accrual was greater at the ICT, which they attributed to enhanced relationships between team members [44]. Similarly, a cancer Phase I research site was able to reduce detrimental staff turnover by implementing a staffing structure in which consistent teams worked together on a small number of trials (average of 8) [36]. Together, this suggests that best practice in most early phase oncology trials is for each PI at the site to lead a consistent team that works on disease-specific trials. However, evidence is lacking as to whether this structure is also optimal for non-cancer early phase trials in healthy volunteers.

A culture that facilitates open communication and collaboration among staff can benefit the operations of an early phase clinical research site [11]. The Australian Government, through the National Health and Medical Research Council (NHMRC) developed a Good Practice Process (GPP) to enable efficient and effective site assessment and authorisation of clinical trials [45]. A key initiative in the GPP was the provision of a dedicated Clinical Trial Liaison Officer to act as a central point of contact to improve communication between the site, the sponsor and regulatory bodies [45]. A trial of the GPP across 16 sites (not necessarily early phase) resulted in a reduction in the time taken for clinical trial commencement by 100 days (19%) [46]. This suggests that early phase research sites may be able to increase their efficiency by employing a specific individual to undertake this role for all trials or splitting this role amongst existing staff on a trial-specific basis. In addition, it is recommended that sites foster a culture of open and transparent communication amongst staff [11,42]. Cooperative knowledge sharing should also be encouraged between staff at all levels to enable the site to learn from any mistakes and support continuous process improvement [11,42].

Subject management system

Sites require a method of study and participant management, and while Investigator Site Files can accommodate this on an individual study level, where sites are conducting multiple studies, and particularly in the early phase setting, an electronic site management system is essential. Electronic site management systems afford a number of aspects for the management and coordination of a study, or multiple studies at a site, including site-based metrics, project level and participant level information. Some systems include study budget and invoice generation capabilities which can assist with the accurate tracking of invoiceables.

Conclusion

Safe and high-quality operational conduct of EPCTs is dependent on the practices of sites and their investigators. Existing best practice guidelines for research units undertaking EPCTs include conducting a thorough and independent risk assessment prior to trial commencement, implementing a continuous internal QA program committed to process improvement, providing facilities, resources and procedures capable of handling medical emergencies and the proposed protocol, and delegating an adequate number of appropriately trained staff to complete trial tasks. However, there are still significant gaps in knowledge relating to early phase trial best practices within Australia, particularly within the non-oncology trials landscape, which warrants further investigation. Assisting early phase clinical research sites in Australia to develop safe, efficient and effective evidence-based practices for early phase research should be a focus of future endeavours. Development of best practice recommendations through a checklist or guidance document may be an appropriate means of communicating this information to prospective study teams.

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