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Clinical trials best practice checklist: Guidance for Australian clinical research sites from CT:IQ

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ABSTRACT

The Australian clinical trials sector has grown steadily over the past decade, particularly with respect to early phase trials where Australia's research capacity, capability and quality of research is revered. With an increase in the number of internationally sponsored clinical research projects being conducted in Australia, particularly in the early phase setting, there has been a corresponding growth in the number of clinical research sites conducting early phase clinical trials. Australian researchers are guided by a multitude of research codes, guidance and statements which govern the conduct of clinical trials. Although international guidance regarding the conduct of early phase clinical trials exists, there is currently no single source outlining best practice recommendations for the conduct of early phase clinical trials in Australia.

In recognition of this Clinical Trials: Impact & Quality (CT:IQ), a collaborative of sector stakeholders, convened a project team with comprehensive knowledge of the Australian clinical trials sector and particularly early phase research, to evaluate and collate broadly applicable and implementable guidance for the conduct of early phase clinical trials. Although the initial intent was to create guidance specific to early phase, we recognize the project outcomes are more broadly implementable irrespective of the research phase and are intended to support all clinical research sites to conduct high-quality clinical trials in Australia.

1. Introduction

Early phase clinical trials (EPCTs[1]) are crucial in the exploration and development of potential new treatment options. For the purpose of this project, EPCTs were defined as studies up to Phase II, including studies with any Phase I or early device feasibility component.

The primary objective of early phase studies is non-therapeutic in intent, with outcomes predominantly focused on the establishment of the early safety profile of investigational medical products, which for the purpose of this project includes investigational drugs, biological compounds and medical devices [1].

EPCTs, especially those that represent first-in-human studies, have the largest degree of uncertainty in terms of risk to participants, whether they be healthy participants or participants with the target indication [1–5]. The occurrence of potentially avoidable life-threatening or fatal severe adverse events in two relatively recent European trials highlighted the importance of both clinical trial design and conduct of a clinical trial at a research site [2–5], specifically with respect to the

Abbreviations: CT:IQ, Clinical Trials: Impact & Quality.

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[1] EPCT - Early Phase Clinical Trial.

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communication processes at sites, and particularly in relation to emerging safety information.

Although some international guidance and recommendations have been published outlining best practice recommendations or requirements for the conduct of EPCTs at research sites, the available guidance is largely developed in consideration of the developing body's respective country and therefore their recommendations are not wholly transferable to the Australian context [1,5–14].

2. Methods

The Clinical Trials: Impact & Quality (CT:IQ^2) EPCTs Best Practice Project Team was convened to assess this need and involved a multi-stakeholder group of experts in clinical trial conduct representing clinical research sites, medical device organizations, human research ethics committees, patient advocacy groups, academic institutions, government agencies and clinical research organizations. The goals of the project included identifying and concisely presenting key aspects of existing national and international recommendations on EPCT best practices and incorporating the knowledge and expertise of best practice conduct from the project team.

2.1. Literature review

To identify current relevant best practice guidance for the conduct of EPCTs, and more broadly clinical trials, both in Australia and globally we searched Medline, Embase and Cochrane databases, in addition to online resources for publications that addressed the conduct of clinical trials at research sites. The publications were limited to those available in English and published between January 1, 2009 to May 31, 2019 to adequately represent current practices. Publications that met these criteria were then reviewed to establish whether they described appropriate content concerned with the conduct of clinical trials at research sites. Publications that were no longer in keeping with updated regulations were not included. The references of included articles were reviewed to identify any relevant additional guidance, which identified a number of further articles, two of which did not meet the eligibility date range however were included as an exception due to their pertinence.

A postdoctoral researcher, in collaboration with the project team, was engaged to assist with the identification and review of publications. More than 40 publications including international guidance, peer-reviewed journal articles and Australian regulations were deemed eligible and were reviewed.

Review of the publications identified that current recommendations and guidance are presented as lengthy documents, which are an impediment for their implementation at clinical research sites [15]. This observation inspired the project team to consider alternative representations of this information. In tandem with the recognition that many sites have a reasonable understanding of best practices, a checklist presented a different way to present this information which permitted the user to explore in more detail aspects which they identify as areas of need.

The literature review's key findings did however contribute to the formation of checklist items. Of significance, this literature review identified the importance that clinical research sites conduct continuous and thorough risk and quality assurance (QA) programs, an activity that clinical research sites often under-resource and underutilize [15].

2.2. Checklist development

The checklist was developed with the aim of promoting the safety of clinical trial participants; supporting efforts to further improve the quality of Australian research; creating public confidence in EPCTs and striving to maintain consistency in EPCTs across clinical research sites. The scope of the project covered all EPCTs across all forms of investigational medical products and explored the conduct of EPCTs at all types of clinical research sites, and focused upon Australian laws, regulations and practical considerations, though may inform progress in other countries.

The project team met remotely each fortnight between April and December 2019, with an additional face-to-face expert meeting held in August 2019, to develop the considerations and recommendations for inclusion in the checklist.

3. Results

Drawing on the findings of the literature review and the experience and knowledge of the project team, the essential elements for the conduct of EPCTs at clinical research sites were explored and grouped into ten distinct categories (Fig. 1).

Hundreds of hours were spent developing the specific content of the checklist within each of the 10 categories, the final checklist containing 100 questions. Reflecting on the key observation identified by the literature review, the project team purposefully designed the checklist considerations and recommendations as concise questions. The project team was conscious that the length of the checklist should not present a barrier to its adoption and utilization. Wherever possible questions were framed in a manner that could be applied to a variety of circumstances to avoid repetition or a high degree of irrelevance when broadly applied. A rationale or description was included to provide context for each question, and where available practical tools and links to useful, relevant resources were provided. Where resources were not publicly available, but identified as adding sector value, resource templates were created to further enhance the checklist and its associated resource toolkit.

Excel was chosen as the platform for the checklist primarily due to budgetary limitations, the widespread familiarity of this application within clinical research sites, and a high level of application skills within the project team. The functionality of the checklist was maximized within Excel to create a simple, yet practical tool aimed at clinical

Category Heading	Category Description
1. Research Guidance Documents	Does the site have access to and regularly review the relevant guidance documents and is the site aware of future developments in research policy?
2. Safety Management	Does the site have access to appropriate safety measures and is the site proficient in clinical safety data management and aware of the reporting requirements?
3. Staffing	Does the site comply with safe workplace practices and do staff have the appropriate training and experience?
4. Facilities	Does the site have processes in place to manage site equipment and have adequate participant and office/administration facilities?
5. Device Handling	Does the site have appropriate investigational device handling practices in place?
6. Quality Assurance and Quality Measures	Does the site have an internal Quality Assurance procedure, evaluation processes in place and a corrective and preventive action (CAPA) procedure?
7. Participant Engagement	Does the site conduct participant orientation, provide general information to participants and have relevant participant SOPs in place?
8. Pharmacy	Does the site's pharmacy support and have the capability to meet study requirements?
9. Laboratory Requirements	Will the site be responsible for processing biological samples and does the laboratory utilize safe laboratory practices, have the right equipment on site and follow correct sample handling procedures?
10. CTRA (Clinical Trial Research Agreements)	Does the site utilize standard templates for agreements, indemnities, sponsor specific clauses, third party vendors and does the site have an appropriate budget to cover research costs?

Fig. 1. Ten categories in the CT:IQ Early Phase Trials Best Practice checklist.

research site staff, that could be hosted on the CT:IQ website and easily downloaded and utilized [16]. Each category is represented as a separate tab within the Excel checklist, accessed from the Checklist Home Page, as shown in Fig. 2.

The Excel checklist homepage provides an interface to each checklist category and allows users to work through the entire checklist or select categories of interest that they wish to specifically focus on. Acknowledging that questions associated with investigational devices may be distinct to the considerations of investigational medicines, the checklist allows the user to filter questions by devices (79 questions) or investigational products (IP) (94 questions) to remove those questions which may not be applicable, however those that are applicable to both categories will still be visible. Fig. 3 illustrates the checklist items associated within the clinical research Staff category.

The checklist was tested at a broad range of clinical research sites. Ten clinical research sites volunteered to evaluate the checklist, ranging in institution size and structure, experience and clinical focus. Following the user acceptance testing, minor changes were made to some questions and to improve functionality.

As part of the user acceptance testing, we were able to measure the average time to complete the checklist, which typically ranged from 30 to 60 min, dependent on whether associated resource links are accessed for review. As the Excel checklist is downloaded from the host CT:IQ website, completion of the checklist can be saved by the user and completed over several sessions.

The checklist is now available to the Australian clinical trials sector following its launch in March 2020 [16]. Recognizing the dynamic nature of clinical research, we are actively encouraging users to provide feedback to ensure the checklist remains current, relevant, and implantable to promote the safe and effective operation of EPCTs in Australia. To date the checklist has been accessed by a number of clinical research sites who have provided predominantly positive feedback, acknowledging the value in either self-validating their operations or identifying areas of further development.

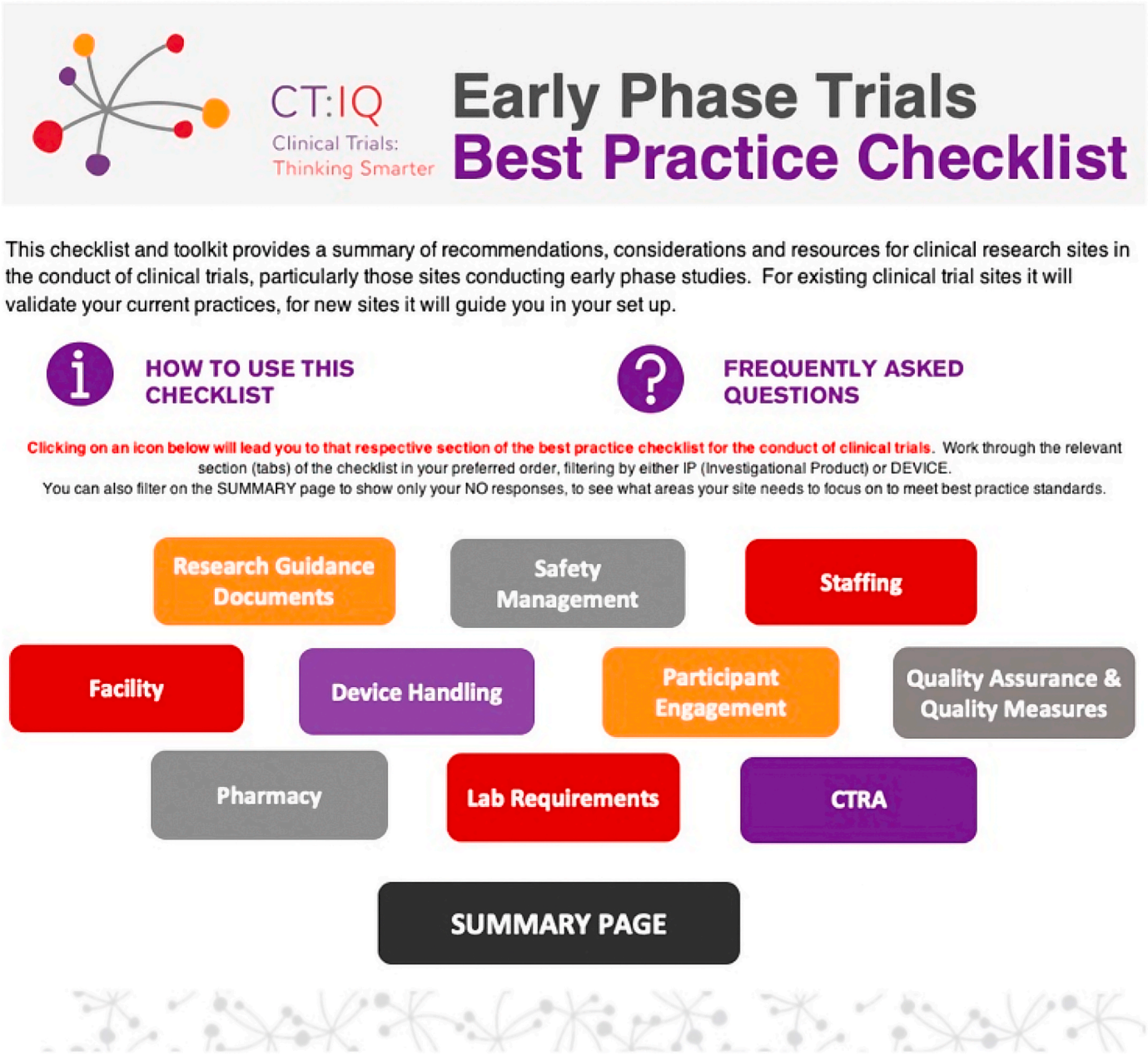
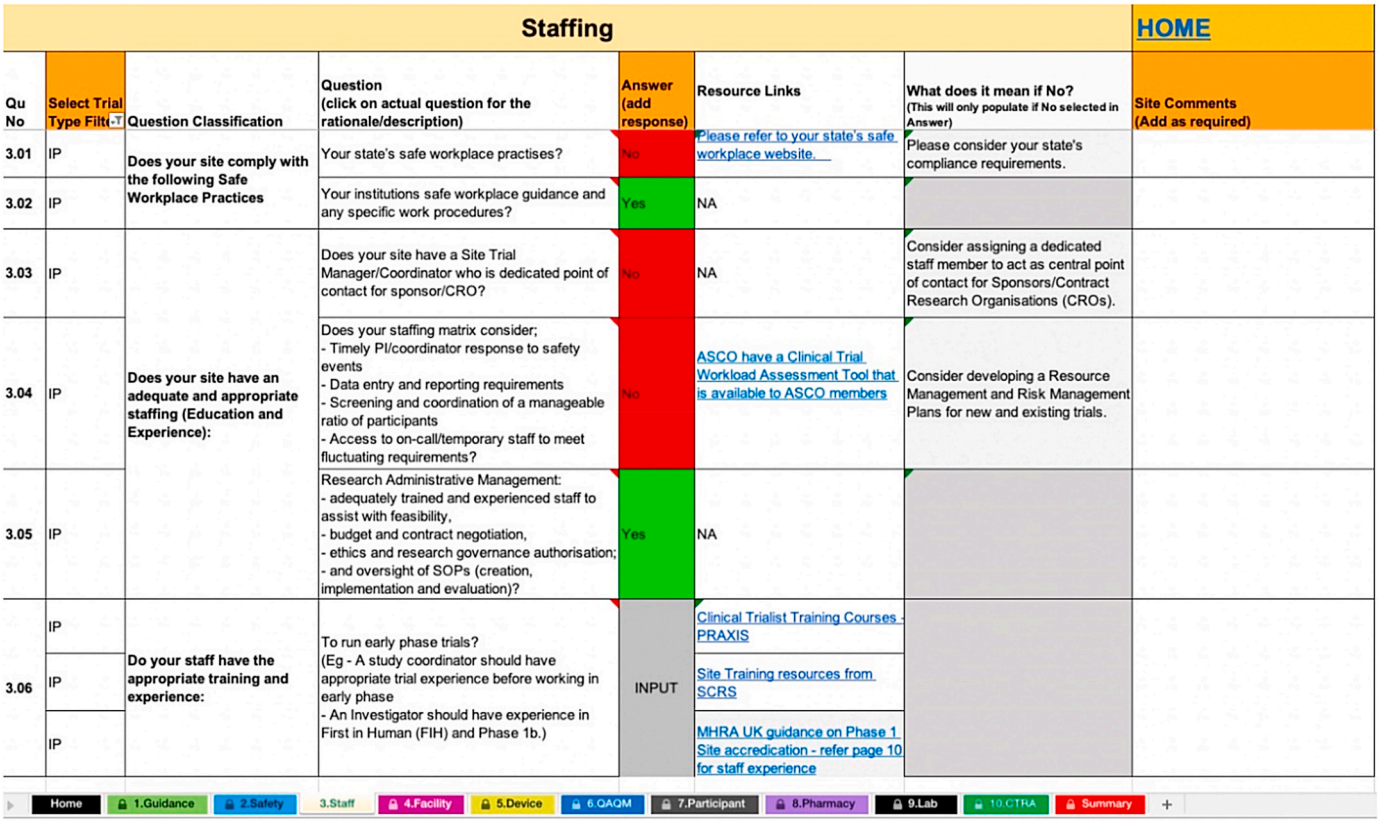


Fig. 2. Excel homepage of the CT:IQ Early Phase Trials Best Practice checklist.



Staffing — HOME

Qu No	Select Trial Type Filter	Question Classification	Question (click on actual question for the rationale/description)	Answer (add response)	Resource Links	What does it mean if No? (This will only populate if No selected in Answer)	Site Comments (Add as required)
3.01	IP	Does your site comply with the following Safe Workplace Practices	Your state's safe workplace practises?	No	Please refer to your state's safe workplace website.	Please consider your state's compliance requirements.	
3.02	IP		Your institutions safe workplace guidance and any specific work procedures?	Yes	NA		
3.03	IP	Does your site have an adequate and appropriate staffing (Education and Experience):	Does your site have a Site Trial Manager/Coordinator who is dedicated point of contact for sponsor/CRO?	No	NA	Consider assigning a dedicated staff member to act as central point of contact for Sponsors/Contract Research Organisations (CROs).	
3.04	IP		Does your staffing matrix consider; - Timely PI/coordinator response to safety events - Data entry and reporting requirements - Screening and coordination of a manageable ratio of participants - Access to on-call/temporary staff to meet fluctuating requirements?	No	ASCO have a Clinical Trial Workload Assessment Tool that is available to ASCO members	Consider developing a Resource Management and Risk Management Plans for new and existing trials.	
3.05	IP		Research Administrative Management: - adequately trained and experienced staff to assist with feasibility, - budget and contract negotiation, - ethics and research governance authorisation; - and oversight of SOPs (creation, implementation and evaluation)?	Yes	NA		
3.06	IP	Do your staff have the appropriate training and experience:	To run early phase trials? (Eg - A study coordinator should have appropriate trial experience before working in early phase - An Investigator should have experience in First in Human (FIH) and Phase 1b.)	INPUT	Clinical Trialist Training Courses - PRAXIS		
	IP				Site Training resources from SCRS		
	IP				MHRA UK guidance on Phase 1 Site accredication - refer page 10 for staff experience		

Home | 1.Guidance | 2.Safety | 3.Staff | 4.Facility | 5.Device | 6.QAQM | 7.Participant | 8.Pharmacy | 9.Lab | 10.CTRA | Summary | +

Fig. 3. Snapshot of the Staff category within the CT:IQ Early Phase Trials Best Practice checklist.

4. Discussion

At the outset of this project there was the intent to provide clear and concise guidance for the conduct of early phase research at clinical research sites in Australia to promote participant safety and the quality of the research conducted in Australia.

As the project evolved, it quickly became apparent that the checklist had broader relevance to other phases of clinical research, with only a minority of specific questions targeting early phase trials. Therefore, whilst the checklist is branded as an early phase checklist it can be used for all phases of clinical trials. For well-established clinical research sites, the checklist can be utilized to validate current practices, whilst other clinical research sites may find value in identifying areas of further consideration and development of their processes.

The project team encountered numerous challenges during the checklist's development, particularly with respect to balancing the level of information and detail to maintain pertinence for sites and in creating a format that is both visually acceptable and functionally useful across the varied clinical research sites within Australia.

Excel is a spreadsheet program and the checklist assumes a reasonable understanding of Excel operation, and whilst the checklist maximizes Excel software functionality the project team acknowledge the limitations it can present. User acceptance feedback noted the checklist as cumbersome in areas, predominantly due to the volume of information present. With the foundation set in the original Excel version, there is an opportunity to maximize user adoption by developing a bespoke online solution in order to enable easy usage and further track uptake.

5. Conclusion

Best practice recommendations for the conduct of early phase trials in Australia are limited and there is currently no single source of best practice information. This inevitably leads to variations in practices which have the potential to introduce risks to the safe and effective operation of early phase trials.

There was a need for a practical tool that could be implemented by clinical research staff to provide QA for the set up and conduct of early phase trials at Australian clinical research sites. The checklist developed by CT:IQ and the project team, provides guidance and resources to promote quality research practice and outcomes. The checklist is applicable across both investigational products and medical devices, at all types of clinical research sites, and across all phases of clinical research.

We consider this checklist to add value to the Australian research sector in promoting quality research outcomes at clinical research sites.

Author statements

Jerneen Williams: Conceptualization, Methodology, Investigation, Formal Analysis, Writing - Review & Editing, Supervision.

Leanne Weekes: Conceptualization, Writing - Review & Editing, Funding acquisition.

Sonia Harvey: Conceptualization, Methodology, Software, Writing - Review & Editing, Visualization, Project administration.

Ashika Kumar: Investigation, Formal Analysis, Writing - Review & Editing.

Meghan Leigh: Investigation, Formal Analysis, Writing - Review & Editing.

Falko Thiele: Investigation, Formal Analysis, Writing - Review & Editing.

Dhanusha Sabanathan: Writing - Original Draft.

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Declaration of competing interest

The authors declare no known conflict of interest.

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