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National Health and Medical Research Council

Good Practice Process for Site Assessment and Authorisation Phases of Clinical Trial Research Governance

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Introduction

Clinical trials are an important element of health and medical research and are required for the evaluation of the safety and effectiveness of interventions or treatments. To ensure the safety of research participants, the integrity of each research project, the effective use of research funds and the responsible conduct of research, all clinical trials are subject to a process of institutional assessment prior to their commencement. The framework, systems and processes leading to the authorisation and commencement of a clinical trial at a research site are commonly referred to as 'research governance'.

A wide range of stakeholders, including the pharmaceutical industry and clinical trial practitioners have raised concerns about the length of time taken to commence clinical trials in Australia, and particularly about the time taken to complete research governance in Australia. Reducing delays in the commencement of clinical trials will help to increase Australia's attractiveness as a destination for global sponsors to conduct clinical trials.

In order to alleviate this situation, the Australian Government, through the National Health and Medical Research Council (NHMRC) is taking steps to streamline the research governance process in order to reduce delays in clinical trial commencement. The expertise of key stakeholders from public and private hospitals, jurisdictions, industry, academia and medical research institutes, and organisations involved in conducting clinical trials in Australia has been utilised to develop a Good Practice Process to enable efficient and effective site assessment and authorisation of clinical trials. It is believed that if this Process is adopted, it will lead to a decrease in the time taken for clinical trials commencement.

In developing the Good Practice Process, two key improvements that would reduce the time taken to commence clinical trials have been proposed by the development group:

1. An increased commitment to planning, preparation and ongoing support for clinical trials within those institutions where clinical trials are conducted; and
2. A change to the order in which the activities within the assessment and authorisation process are conducted, whereby key assessment activities occur much earlier.

The proposed order in which activities can be completed in the Good Practice Process represents a paradigm shift from the way in which the site assessment and authorisation process has traditionally been conducted. The majority of site assessment activities can be completed not just at the same time as, but prior to, ethical review being undertaken, rather than be delayed until all documentation is submitted. In this way, ethics and governance review can be carried out in parallel rather than sequentially.

The Good Practice Process comprises three parts:

- Principles and Critical Success Factors: A set of high-level principles and critical success factors that set out the ideal features of a research governance process.
- Planning and Preparation activities: A group of activities that apply to all clinical trials rather than be specific for a given clinical trial, and support the site's ability to attract, accept and promptly commence clinical trials.
- Site Assessment and Authorisation activities: Activities that set out a process that will streamline the review and approval of a clinical trial.

To ensure the Good Practice Process is both implementable and realises improvements in clinical trial start-up times, NHMRC has piloted the Good Practice Process in 16 clinical trial sites across 7 states and territories.

As part of the pilot program, NHMRC also provided each site with seed funding to employ a Clinical Trial Liaison Officer. The role of the Clinical Trial Liaison Officer includes reviewing and streamlining the site's clinical trial start-up processes, providing a central point of contact between sponsors, researchers and site administrative staff and 'shepherding' applications through the site assessment and authorisation process.

The pilot program has demonstrated that implementing the Good Practice Process, including employing a Clinical Trial Liaison Officer, can significantly improve clinical trial start-up times. A report detailing the improvements realised under the Good Practice Process is available at <https://www.nhmrc.gov.au/research/clinical-trials/development-good-practice-process-site-assessment-and-authorisation-clinica>.

Definitions

Site - an institution (or group of institutions) that resource, conduct and manage clinical trials that come under one final research governance authorisation sign off.

Sponsor – an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study.

Research Governance - a process used by an organisation for the oversight, assessment, authorisation and monitoring of research conducted at one or more of its sites or under its auspices¹.

Site Assessment - a process that assesses research against institutional requirements.

Site Authorisation - a determination by an organisation that a research project to be conducted at one or more of its sites or under its auspices satisfies organisational requirements and may commence at the site/s over which it exercises its authority. Site authorisation is the outcome of the site assessment process.

Ethical review - a process to explore the ethical issues presented by, and implications of, a research project.

Ethical approval - a determination by an ethics review body that a research project satisfies ethical standards and requirements, including, but not limited to, the NHMRC/ARC/AVCC National Statement on Ethical Conduct in Human Research.

Feasibility Assessment- a process to determine whether a clinical trial site has the capacity and capability, including resources, expertise and participant pool to carry out a specific clinical trial.

¹ A research governance framework includes good research culture and practice, organisational strategy, role definition and accountabilities, risk, resource and financial assessment and management, compliance with legal, regulatory and contractual requirements, competencies and training of personnel, site assessment, scientific review, ethical review and approval, site authorisation, monitoring of research, and management of conflicts of interest, complaints and allegations of research misconduct.

Principles and Critical Success Factors

Overview

A number of principles and critical success factors underpin the Good Practice Process. These are relevant to any existing research governance process, and are intended to address key areas to improve the research governance approval process.

Principles

Timeliness

Principle: Minimise timeframes.

Sites should seek to minimise the timeframes for activities undertaken during the research governance process. By recording the time taken for key components of the research governance process to take place, sites can use empirical measurements to identify where delays occur, and the impact of subsequent measures to reduce them. Forward planning of all activities can help to reduce the timeframes for the research governance process.

Transparency and communication

Principle: There should be open, transparent and effective communication between all stakeholders involved in the clinical trial and associated governance activities.

Open and effective communication both between sites and sponsors and within a site, is a key feature of an effective and efficient site assessment process. This can be implemented by activities such as:

- providing sponsors with a dedicated contact person at the site (the Clinical Trial Liaison Officer);
- providing sponsors with regular updates on the progress of the site assessment and authorisation for their clinical trial;
- developing an internal communication plan;
- sponsors providing as much information and documentation prior to the site assessment process;
- developing and using Standard Operating Procedures;
- reaching early agreement about costs that may be incurred in the trial and the costs that will be paid for by the sponsor, including what constitutes standard care; and
- transparency in the calculation of costs associated with conducting clinical trials at the site.

Critical Success Factors

1. Clearly documented roles and responsibilities.

Clearly documented roles and responsibilities will:

- help avoid the duplication and/or omission of activities within the research governance process;
- identify people who can provide guidance on different aspects of the governance process; and
- identify when delegated responsibilities are required to avoid delays in the governance process.

2. Early assessment of the feasibility of the clinical trial with applicable service areas.

Delays in the site authorisation process can occur when the feasibility is not confirmed with appropriate service areas (pharmacy, radiology, pathology etc.) early on, even during the concept development stage. These service areas often have competing priorities, and clinical trials may require specialist services that are outside the normal activities of the service area. As negotiating these services can take some time, commencing a feasibility assessment as early as possible allows other aspects of feasibility to be determined in parallel.

3. Conduct of site assessment, where possible before, or in parallel with, ethics review.

Under the Good Practice Process (Figure 1) ethics review and the site assessment are essentially independent processes up until the final site assessment activity. As such, the preparation of site assessment documentation should take place before, or in parallel with, the preparation of ethics review documentation. Similarly, site assessment should take place before, or in parallel with, the ethics review.

4. Completion of as many site assessment activities as possible in parallel.

A number of site assessment activities are independent of one another. As such, these activities can be carried out in parallel. By having a clearly mapped process these independent activities can be identified. Carrying out as many activities in parallel should reduce the time taken for site assessment and authorisation.

5. Minimisation of unnecessary re-review of documentation.

By clearly outlining and promulgating the roles and responsibilities associated with the research governance process, unnecessary re-reviewing of documentation can be avoided. An example of where there may be an opportunity to obviate the need for a re-review of documentation is where patient information and consent forms are considered by the research governance office prior to review by an ethics committee to ensure that they reflect how the trial was going to be conducted.

6. Implement and review clinical trial planning and preparation activities.

The planning and preparation activities are ongoing activities that, rather than being specific to any given clinical trial, are aimed at ensuring the site is 'ready, willing and able' to carry out clinical trials. These include ensuring appropriate resourcing for clinical trials is in place and that appropriate processes and procedures to ensure that clinical trials can take place effectively and efficiently are in place. Appropriate review of relevant processes will ensure they are in place and fit for purpose.

7. Use active management strategies for key steps in the clinical trial start-up process.

Applying active management strategies, such as employing dedicated personnel to manage the site assessment and authorisation process can reduce the time taken for site assessment and authorisation.

The role of the Clinical Trial Liaison Officer (CTLO)

The role of the Clinical Trial Liaison Officer is central to the Good Practice Process. By focusing on three key activities, the CTLO can greatly improve the clinical trial start-up timeframe. These activities are detailed below, and should be considered when developing a job description for a CTLO position.

Reviewing and streamlining a site's clinical trial start-up processes.

- Working with site staff to assess infrastructure and staff availability required for the conduct of clinical trials with each department.
- Implementing the Good Practice Process and monitoring progress, including performance measurements.
- Developing resources related to the Good Practice Process and clinical trial start-up process, including Standard Operating Procedures and Key Performance Indicators.

Providing a central point of contact and information, and improving communication between sponsors, researchers and site administrative staff.

- Working to establish a central repository for the documentation required by external sponsors.
- Working to communicate site research capabilities and interests to clinical trial sponsors.
- Establish contacts and relationships with all key stakeholders, including clinical trial sponsors, contract research organisations, researchers and administrators.

'Shepherding' applications through the site assessment and authorisation process.

- Working with the Principal Investigator and Site Staff to ensure they can demonstrate that they can recruit sufficient numbers of participants.
- Working with clinical trial sponsors to ensure all relevant documentation is available to conduct the capacity planning exercise with local service departments.
- Working with the Principal Investigator and site staff to assess the proposed budget and clinical trial agreement.
- Tracking the progress of individual applications through the site assessment and authorisation process and intervening as necessary to minimise delays.

Planning and Preparation

Overview

The planning and preparation activities are not specific to a particular clinical trial. Rather, they are ongoing activities that ensure the institution is best placed to attract, accept and promptly commence clinical trials. For example, ensuring relevant staff have current Good Clinical Practice certification reduces delays in clinical trial start-up times resulting from researchers having to renew their certification before commencing the trial.

The planning and preparation activities have been listed according to the person or entity responsible. Depending on the structure of a specific organisation, there may be some overlap in the responsibilities. Institutions should use the responsibilities as a guide and implement the activities as appropriate for them.

Activities and responsibilities

Sponsor/Contract Research Organisation

- Use standard research agreements/contracts (such as those available from Medicines Australia, <http://medicinesaustralia.com.au/issues-information/clinical-trials/clinical-trials-research-agreements/>).
- Review trial protocols, patient information and consent forms and other appropriate documentation to ensure it is compatible with the Australian context before providing to investigators.
- Maintain adequate training and an experienced clinical trials team.

Principal investigator and other researchers as applicable

- Complete and maintain current and acceptable Good Clinical Practice training.
- Maintain a current CV in an institutional database.
- Maintain professional registrations.
- Maintain professional indemnity insurance.

Human Research Ethics Committee/Ethics office

- Document and promote processes to efficiently manage clinical trial ethics applications.
- Use certified ethical review processes for multi-centre clinical trials and single site trials as appropriate.
- Utilise the current national ethics application form.
- Adopt standardised ethical review forms, templates and processes.
- Publish HREC meeting dates and deadlines.
- Encourage the use of standard patient information and consent form templates.

Institution/Research office

- Establish and communicate clinical research priorities and objectives.
- Promote capacity to conduct clinical trials.
- Have clearly documented roles and responsibilities.
- Put in place ongoing clinical trial planning and preparation activities and review as appropriate.
- Maintain certification for ethics review processes related to multi-centre clinical trials and single site trials as appropriate.

- Make template documents, standard operating procedures, policies and other guidance available on an institutional website and ensure any changes are widely disseminated.
- Accept single ethics review without further ethics review (unless an additional specialist HREC review is required).
- Comply with national standards and processes for research governance frameworks including, as far as possible, the Good Practice Process.
- Ensure all staff involved in clinical trials have the appropriate training.
- Use active management strategies to ensure that the various steps in the clinical trial start-up process occur within mandated timeframes.
- Use nationally agreed site assessment document templates when available.
- Use standard research agreements/contracts (such as those available from Medicines Australia, <http://medicinesaustralia.com.au/issues-information/clinical-trials/clinical-trials-research-agreements/>) in accordance with applicable State or Territory requirements.
- Develop and report on clinical trials key performance indicators.
- Provide the infrastructure for and promote the electronic submission of documents.
- Utilise (or incorporate into existing documents) national standard operating procedures for site assessment, where available.
- Publish costs for clinical trial-related activities and services (with reference to Independent Hospital Pricing Authority advice where applicable).

Implementation of the planning and preparation activities

In order to implement the above planning and preparation activities, sponsors and sites should:

1. Review current clinical trial planning and preparation activities and responsibilities.
2. Compare current planning and preparation activities and responsibilities to those detailed in the Good Practice Process.
3. Identify which planning and preparation activities can be, and need to be implemented.
4. Develop an implementation plan, including timeframes, responsibilities, measures of success and provision for periodic review.
5. Implement the appropriate planning and preparation activities.
6. Carry out a periodic review of the implementation status and impact of the planning and preparation activities.

Site Assessment and Authorisation for each clinical trial

Overview

For the purposes of the Good Practice Process, the site assessment and authorisation process commences when a sponsor is considering a site for a clinical trial (the beginning of the Feasibility Assessment stage) and ends when site authorisation has been granted (the end of the Site Authorisation stage).

Figure 1 outlines the high level activities, roles and responsibilities for the various components of the site assessment and authorisation process. This should be used as an overview of the clinical trial start-up process and a guide to the general responsibilities of the various stakeholder groups, which may vary between institutions.

Figure 2 expands on the information in Figure 1, and details a proposed workflow and responsibilities for an institution carrying out a site assessment for an individual trial. In this detailed workflow, a number of activities should be carried out in parallel – this will increase the efficiency of the assessment and authorisation process. However, some activities are dependent on the outcome of previous activities, and are depicted as such.

Clinical Trial – Feasibility Assessment to Site Authorisation					
	Feasibility Assessment	Document Preparation	Document Submission	Site Assessment and Ethics Review	Site Authorisation
Commercial Sponsor / CRO	<ul style="list-style-type: none"> Identify and decide on potential trial sites, Principal Investigators, Coordinating Principal Investigator and lead HREC Consider patient recruitment requirements and sample size required for protocol Establish if potential sites are using nationally agreed standards, guidelines, contracts, standard costs etc, and, if not, identify any issues that might have an impact on the suitability of a potential site 	<ul style="list-style-type: none"> Develop/provide research protocol and draft contract/budget Recommend standard of care definition(s) in the research protocol Submit a Non-Disclosure Agreement or Confidentiality Agreement to the PI Finalise all documents required by PIs and CPIs to fulfil ethics and site assessment requirements 		<ul style="list-style-type: none"> Receive copy of ethics approval certificate/letter and approved documents from CPI or HREC 	<ul style="list-style-type: none"> Receive site authorisation/s from PIs Register trial with clinical trials registry if not previously registered Notify trial to TGA if required
Principal Investigator/s	<p>In association with institution (as appropriate):</p> <ul style="list-style-type: none"> Determine whether participation requirements are acceptable Determine capacity of proposed project team to participate in a trial within the proposed time frame Determine whether sufficient participant recruitment can take place at site 	<ul style="list-style-type: none"> Determine institutional requirements for site assessment and authorisation Communicate with sponsor re. document requirements Finalise all documents for site assessment Review documents with institution as necessary 	<ul style="list-style-type: none"> Submit site assessment documents to institution 	<ul style="list-style-type: none"> Receive copy of ethics approval certificate/letter from CPI and provide to institution 	<ul style="list-style-type: none"> Receive notification of site authorisation from institution and provide to sponsor
CPI/delegate	<ul style="list-style-type: none"> Determine capacity and time required to prepare ethics application 	<ul style="list-style-type: none"> Finalise documents for submission to HREC Review ethics application documents with HREC administrator (or equivalent) as necessary 	<ul style="list-style-type: none"> Submit ethics application to HREC 	<ul style="list-style-type: none"> Receive HREC approval certificate/letter and approved documents and provide to PIs 	
HREC			<ul style="list-style-type: none"> Accept ethics application and record in database 	<ul style="list-style-type: none"> Conduct ethics review (including preceding or concurrent scientific review) Communicate with CPI if further information or amendments are required during review Provide approval letter and documents to CPI or CRO/Sponsor 	
Institution (RGO, Research Director, CFO etc)	<p>In association with the Principal Investigator/s (as appropriate):</p> <ul style="list-style-type: none"> Determine if clinical trial is consistent with institution's mission and research priorities Assess availability of required institutional resources Identify any other contribution the institution may make to the clinical trial Communicate any special requirements that are specific to the institution and/or jurisdiction to the Sponsor 	<ul style="list-style-type: none"> Approve proposed contract and budget Engage early with relevant support departments or equivalent Provide advice on institutional requirements for site assessment and authorisation as required 	<ul style="list-style-type: none"> Accept documents for site assessment and record in database 	<ul style="list-style-type: none"> Assess site assessment documents Monitor or coordinate delegate review/s and approval/s Receive HREC approval certificate/letter and approved documents from the PI Liaise with PIs as required regarding any further required documentation Complete assessment 	<ul style="list-style-type: none"> Authorise clinical trial (CEO or delegate) Notify PI of site authorisation

Figure 1. The high level activities, roles and responsibilities for the various components of the site assessment and authorisation process

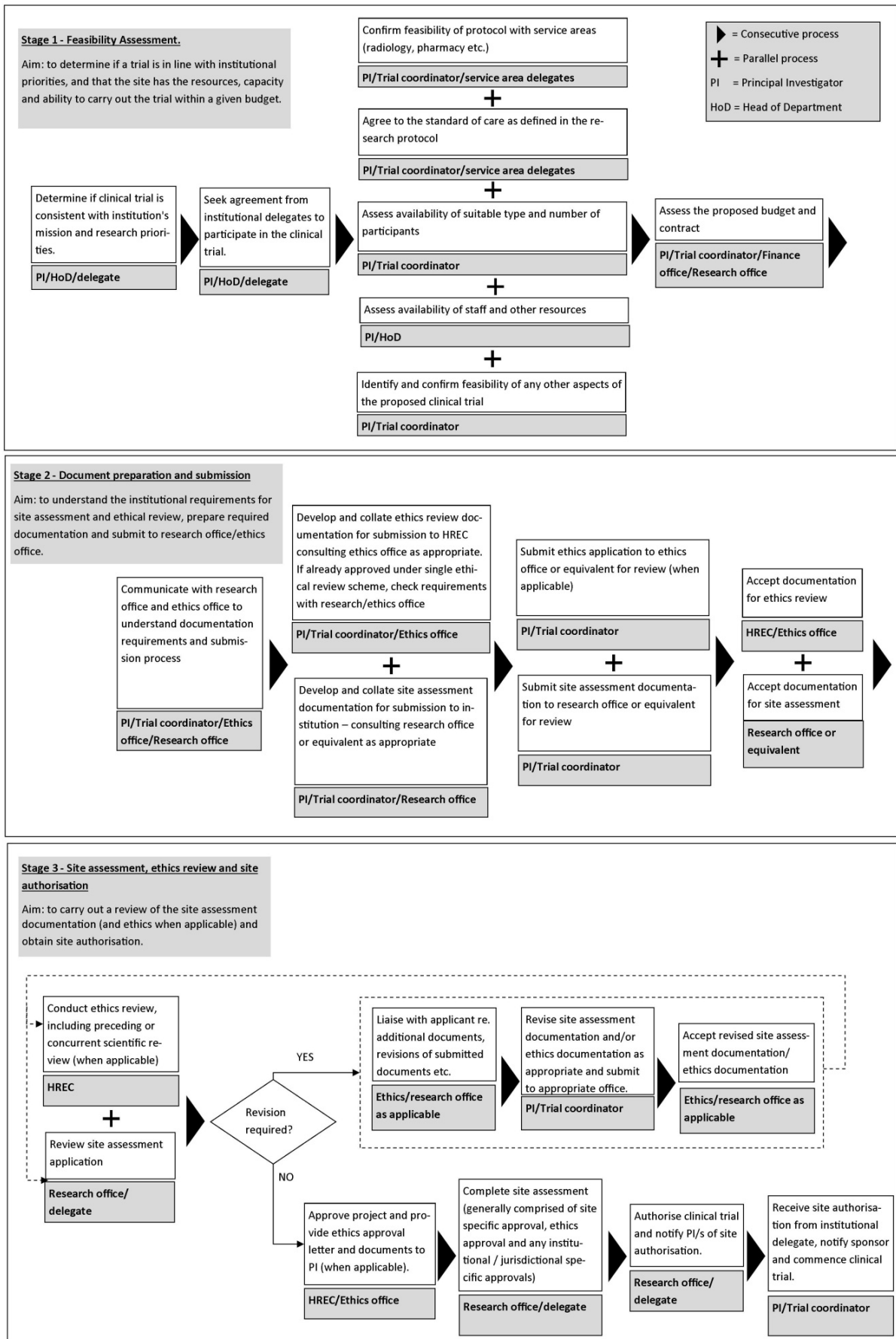


Figure 2. Proposed workflow and responsibilities for carrying out a site assessment for an individual trial.

Stage 1 - Feasibility Assessment

The aim of this stage is for the site to determine if a proposed trial is consistent with institutional mission, values and priorities, and that the site has the resources, capacity, including the participant population, and ability to carry out the trial on time, to recruitment target and within a given budget.

The Feasibility Assessment stage spans the activities from when a sponsor approaches an institution or individual investigator with a clinical trial proposal until the review of the proposed budget and contract to ensure they are appropriate.

The desired outcome is agreement between all stakeholders that all aspects of a trial are feasible, the trial budget is acceptable to all stakeholders and that a draft contract is agreed upon.

Stage 2 - Document Preparation and Submission

The Document Preparation and Submission stage spans the activities from when the Principal Investigator (or equivalent) determines the site requirements for documentation to the submission of ethics review and site assessment documents to the reviewing offices.

The aim of the Document Preparation and Submission stage is for the Principal investigator/s or other appropriate stakeholders to understand what documentation and supporting evidence is required for institutional site assessment and ethics review, prepare the required documentation and submit that documentation to the institutional research office and ethics office as appropriate.

The desired outcome is the submission, within an appropriate timeframe, of a complete and accurate set of site assessment and ethics review documentation to the appropriate institutional offices.

Stage 3 - Site Assessment, Ethics Review & Site Authorisation

The Site Assessment, Ethics Review and Site Authorisation stage spans the activities from when the appropriate bodies review the site assessment documentation and ethics application to the final granting of site authorisation.

The aim of the Site Assessment, Ethics Review and Site Authorisation stage is for a review of the site assessment documentation and, when applicable, ethics documentation to be carried out, revised when necessary, and for the clinical trial to be granted site authorisation.

Implementation

In order to implement the site assessment and authorisation activities outlined in the Good Practice Process, it is recommended that institutions carry out the following process:

1. Review the current institutional site assessment and authorisation process;
2. Compare the current institutional site assessment and authorisation process to that detailed in the Good Practice Process;
3. Identify which components of the Good Practice Process are not currently in place;
4. Develop an implementation plan, including timeframes, responsibilities, measures of success and provision for periodic review;
5. Develop and/or modify existing Standard Operating Procedures that accompany each stage of the site assessment and authorisation process;
6. Put appropriate performance measurements in place;
7. Implement site assessment and authorisation activities; and
8. Carry out periodic review as appropriate.