Australian Government
Department of Health
Therapeutic Goods Administration

Good Clinical Practice (GCP) Inspections Program

Consultation paper

Version 1.0, December 2018

TGA Health Safety Regulation

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

Introduction

Purpose

To introduce a pilot Good Clinical Practice (GCP) Inspections Program of 12 months duration that will inform a routine GCP Inspections Program.

Scope

The scope of this paper is to:

- Outline the rationale for introducing a domestic GCP Inspections Program for clinical trials conducted in Australia under the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes.
- Provide preliminary information on a risk-based approach to selection of inspection sites, and the management of findings of non-compliance, including the release of inspection findings to the approving Human Research Ethics Committee and/or authorising institution.
- Seek feedback from clinical investigators, clinical trial sponsors, and other stakeholders on a pilot GCP Inspections Program.
- Seek volunteers for a pilot program of GCP inspections of clinical trial investigator sites.

Background

Australia's CTN scheme provides advantages in speed, cost and access. However, unlike comparable medicines regulatory schemes in other countries, it devolves primary responsibility for assessing the scientific validity of the trial design, safety and efficacy of the medicine or device, and approval of the trial protocol to the approving Human Research Ethics Committee (HREC). This approach impacts on the TGA's ability to identify risk over the life of the clinical trial, and is compounded by the absence of a routine GCP inspections program to determine whether the conduct of the trial complies with international GCP guidelines and *Therapeutic Goods Regulations 1990*.

The Australian Government is working collaboratively with jurisdictions to progress a clinical trials agenda and related initiatives, through the COAG Health Council. In addition, the Government has established a Clinical Trials Collaborative Forum as an important engagement mechanism for shared problem solving. Development of a National Clinical Trials Governance Framework aligns with the Government's $7 million Encouraging More Clinical Trials in Australia initiative.

As announced in the 2018-19 Budget, the Australian Government's work with jurisdictions to develop a National Clinical Trials Front Door concept will integrate key clinical trial approval and reporting processes. Australia's position in a globally competitive clinical trial environment is predicated on international recognition of clinical trial data quality and integrity, which would be improved by a regulatory GCP inspections program. These initiatives build and protect our competitive advantages in this sector.

A pilot GCP inspection program

The TGA is planning to conduct a pilot program of voluntary GCP inspections, initially restricted to investigator sites of clinical trials involving pharmaceuticals. The pilot program seeks to inform the progress of a proposal to implement a routine GCP inspection program in Australia.

A domestic regulatory GCP inspections program will strengthen Australia as an attractive clinical trial research destination for both the local medical technologies, biotechnology and pharmaceuticals sector, when deciding where to conduct their trials, and in attracting internationally sponsored clinical trials. It will address the potential risk of a decline in international recognition of Australian clinical trial data quality and integrity, and underpin creation of a highly productive commercialisation environment.

A GCP inspections program will also encourage compliance and provide the TGA with a capability to investigate non-compliance should it be reported (e.g., triggered inspections). The future selection of trials for a routine GCP inspections program is likely to be based on the approach currently used in other jurisdictions, i.e., to select a small percentage of regulated clinical trials, however with a focus on higher-risk clinical trials, e.g., early phase trials of new medicines or of combinations of medicines, where there may be possible safety concerns.

What are your thoughts on a pilot GCP inspections program and proposed establishment of a routine program following the pilot?

Conduct of the pilot program

The procedures for the conduct of regulatory GCP inspections have been modelled on those in use by the European Medicines Agency (EMA)[1] with specific items to be verified by interviews, reviews of documentation and inspection of facilities. Inspections will include the review of:

- Legal and Administrative – examination of aspects related to the implementation, progress and termination of the clinical trial, including evidence of communication with the HREC and regulatory authorities;
- Organisational – examination of the implementation of the trial at the site, including qualifications and experience of site personnel, delegation of authority, standard operating procedures, facilities and equipment, source of the investigational medicinal product, monitoring and auditing records;
- Informed Consent – determine whether patient consent was obtained in accordance with GCP Guidelines;
- Clinical Trial Data – review whether the trial was conducted according to the study protocol by source data verification (SDV), particularly inclusion/exclusion criteria; and
- Management of the Investigational Medicinal Product (IMP) used in the trial.

A 12-month pilot program of voluntary inspections will help obtain stakeholder feedback on GCP inspections and in the development of systems and process for an ongoing inspections program.

[1] EMEA/INS/GCP/197219/2005 Annex I Procedure for Conducting GCP Inspections Requested by EMEA; Investigator Site.

The inspections in the pilot program will be announced inspections and suitable inspection times will be negotiated with the volunteer sites. Inspections include opening meetings where the plan for the inspection is discussed. The source documents for the clinical trial included in the scope of the inspection would need to made available to the inspectors for review and personnel involved in the conduct of the clinical trial may need to be available to answer questions regarding the information. There will be a closing meeting at the end of the inspection and an opportunity to discuss any observations made in the review of the data. Volunteer sites will receive an inspection report that provides information on the areas reviewed during the inspection and any issues identified.

Would you consider volunteering to be a clinical trial site inspected under the pilot program?

Although inspections conducted as part of the pilot program will be strongly collaborative, deficiencies found during inspections will be graded and reported at 3 levels, minor, major, or critical, based on the approach taken by the EMA.[2] A number of remedial actions may be recommended depending on the deficiencies identified and the impact on public safety and data integrity.

If an inspection of a clinical trial identifies serious issues with the conduct of the trial or data integrity then information of the observed issues would be released to the HREC and/or Authorising Institution. Where an inspection identifies issues that might be seen to have a public safety risk for participants then various compliance powers may be considered.

Would the release of inspection findings to the approving HREC and/or Authorising Institution be an appropriate mechanism for managing issues relating to the conduct of the trial or data integrity?

Rationale for a Australian domestic GCP inspections program

An Australian domestic regulatory GCP inspections program will strengthen Australia as an attractive clinical trial research destination for both the local medical technologies, biotechnology and pharmaceuticals sector, when deciding where to conduct their trials, and in attracting internationally sponsored clinical trials. It will address the potential risk of a decline in international recognition of Australian clinical trial data quality and integrity, and underpin creation of a highly productive commercialisation environment.

A GCP inspections program will encourage compliance and provide the TGA with a capability to investigate non-compliance should it be reported (e.g., triggered inspections). It is not planned at this time for TGA to undertake GCP inspections outside Australia.

[2] EMA/INS/GCP/158549/2016 Rev.1

Strengthen clinical trials environment

A domestic GCP inspections program will address a gap in the current regulatory oversight of the conduct of Australian clinical trials. It will support the TGA's ability to identify and manage risk under the CTN and CTX schemes, and enhance the reputation of Australian clinical trials for quality and integrity. An internationally aligned regulatory framework will support Australia's position in a competitive global clinical research market.

Mitigate potential risks

A domestic GCP inspections program will play an important role in assuring human subject protection in clinical studies, and data quality, reliability and acceptability upon which international regulatory approval decisions are made. Consultation with the UK Medical and Healthcare products Regulatory Agency (MHRA) has highlighted that a domestic GCP inspections program in the United Kingdom raised the standard of conduct and quality of clinical trials - particularly those sponsored by non-commercial organisations - and reduced the risk of GCP non-compliance.

Benefits to those conducting clinical trials

A domestic GCP inspections program will play a role in improving stakeholder understanding of GCP, encourage compliance, and ultimately raise the standard of conduct and quality of clinical trials conducted in Australia. Local clinical sponsors and investigators will have greater confidence that their trials are conducted in a manner that meets international requirements relating to the rights, safety and well-being of trials subjects, and that the results of their trials are credible.

Amending the Therapeutic Goods Regulations to formalise inspections powers for clinical trials conducted under the CTN scheme will provide clarity to the sector and further encourage compliance. Similarly, providing clearer powers to manage findings of non-compliance, such as the release of inspection findings to the approving HREC and/or authorising institution, will benefit all those involved in clinical trials in Australia.

What impact, if any, would a domestic GCP inspections program have on Australia's competitiveness as a place to conduct clinical trials?

Further considerations

Although a number of Australian clinical trial investigative sites may have been inspected at some time in the past by an international regulatory agency, the great majority may not. In implementing a pilot GCP Inspections Program, the TGA will be taking a collaborative approach, in part, to educate stakeholders involved in the clinical trial sector, but to also provide the opportunity for feedback as systems and processes are refined.

International approaches regarding fees for domestic GCP Inspections

Domestic clinical trial inspection programs for compliance with GCP standards are in operation in the USA, European Union, Canada, and several other countries with comparable regulatory frameworks. While taking various forms, these programs are designed to investigate that GCP standards are being adhered to in the local conduct of clinical trials. In addition, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) conduct a small number of clinical trial GCP inspections in Australia, mostly, of investigative sites.

GCP inspections conducted by comparable agencies are, with the exception of the MHRA, at no fee. For example, the GCP inspection program in the USA does not incur a fee to the entity inspected, and is funded via Federal budget allocation. Clinical trial fees for GCP inspections performed by MHRA were met (at establishment) with resistance by the academic clinical research sector. They started with a tiered fee model, charged to the clinical trial sponsor, based on an organisation's size.

Funding options

The cost of the TGA's regulatory services are recovered by the fees and charges levied on Australian Manufacturers and Sponsors. No fees will be applied to the pilot on ongoing GCP inspections programs, rather the costs will be absorbed by TGA's general charges revenue.

Timelines and implementation

A Pilot GCP Inspections Program, of 12 months duration is proposed, commencing in early 2019, and conducted at no charge to those inspected. The pilot GCP Inspections Program will provide an opportunity to gauge stakeholder response in further developing an ongoing routine inspections program. At the completion of the pilot program further consultation will take place regarding a possible ongoing routine GCP Inspections Program with finalised guidance to be published immediately thereafter.

Providing feedback

Stakeholders are invited to provide feedback on the proposals outlined in this paper including;

- The proposal to conduct a pilot program of GCP inspections; and
- The formalisation and clarification of inspection process, including a proposal to release inspection findings to the approving HREC and/or Authorising Institution.

Appendix 1

Background

Clinical trials in Australia

Clinical trials are an integral part of the research and development process for therapeutic goods, the refinements of existing standards of care and clinical practices, and ultimately, via evidence-based clinical practice, better health outcomes. Without clinical trials, it cannot be determined whether new treatments are effective or safe or whether a diagnostic test is effective. Clinical trials also help to improve health care services by raising standards of treatment and by exposing clinical research staff and patients to clinical trial methodology, and innovative services and therapeutics. Australian clinical trials are recognised internationally as providing high quality patient care and generating reliable clinical trial data.

Through the efforts of the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), European Committee for Standardization (CEN), and the International Organization for Standardization (ISO), standards of conduct for clinical trials (and clinical investigations) have been determined that provide the basis for regulation across most regions under the remit of the major regulatory agencies world-wide. These comprise the so-called principles of "Good Clinical Practice" or GCP.[3] Although the methods for implementing and enforcing these principles vary, the main objective is a global environment in which trials collect high quality, credible data that contribute to the answering of specific scientific questions, while most importantly protecting the rights, safety and well-being of clinical trial participants.

Clinical trial sponsorship

Clinical trials can be considered as two interdependent segments based on sponsorship type; (1) industry sponsored clinical trials, and (2) non-industry sponsored clinical trials (investigator-initiated, academic, or public good trials). Both segments rely heavily on a skilled, reputable, and efficient clinical trials system, covering workforce and infrastructure, and contribute to the significant value that the sector creates for the wider economy and society.

Industry-sponsored clinical trials are sponsored, funded and managed by medical technology, biotechnology or pharmaceutical companies with a commercial agenda focused on the regulatory requirements for the marketing of the therapeutic goods investigated. The great majority of industry-sponsored studies conducted in Australia are carried out under the CTN scheme.

By contrast, non-industry sponsored clinical trials are conducted for the public good by investigating clinically relevant questions to identify the best treatment irrespective of its commercial value. They include trials to evaluate therapeutic goods available commercially, or common procedures for comparative effectiveness, or explore new uses for old drugs (some of which would be conducted under the CTN scheme), or broader models of care or implementation science. They often result in changes to the standard of care or treatment methods, ultimately improving patient outcomes and cost effectiveness across the health

[3] Integrated Addendum to ICH E6(R1): Guidelines for Good Clinical Practice E6(R2),2016 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

system. A report[4] commissioned by the Australian Commission on Safety and Quality in Health Care evaluated the potential health and economic benefits of twenty five (25) high-impact clinical non-industry sponsored clinical trials and found a gross benefit of approximately $2 billion (2014 dollars) measured through better health outcomes and reduced health service costs. Clinical trials of this type (e.g., ARCH, ENCHANTED, ACHOIS, COIN, ARISE, CHEST, NICE-SUGAR) are of critical importance to patients who receive care within the health system, and to the functioning of the health system itself, because they address these important gaps in knowledge and deliver significant benefits measured through better health outcomes and reduced health service costs.

Clinical trial risks

Clinical trials are essential for evidence-based medicine, yet all clinical research involves some risk. The risks associated with clinical trials are assessed and managed at different levels and in a number of ways involving international, national and jurisdictional frameworks and approaches. Australia's CTN scheme provides advantages in speed and access as there is not an approval processes required from the regulator. Instead the Human Research Ethics Committee (HREC) is solely responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device, the ethical acceptability of the trial process, and for the approval of the trial protocol. However there are also some risks in this approach as, for the great majority of clinical trials conducted in Australia, there is currently no mechanism for a routine regulatory inspections program to ensure the conduct of the trial protects the safety of the participants and the integrity of the data.

Clinical trial oversight

The oversight of clinical research is multifactorial and addresses protection of research participants, the safety and quality of research, privacy and confidentiality, financial probity, legal and regulatory matters, risk management and monitoring arrangements and promotes good research culture and practice.

In recent years, the imperative to properly oversee the conduct of human research in Australia has generated frameworks for governance of research at jurisdictional and institutional levels.[5] These research governance frameworks are targeted at institutions, but recognise sponsors of research as having parallel responsibilities to properly govern research with which they are associated and that the sponsor's obligations are independent of the institution's research governance framework.

Accordingly, for research that will be conducted at more than one site, both a HREC and each participating institution must assess the proposed project and, if appropriate, provide ethical approval (HREC) and project authorisation (Authorising Institution). The evolution of the concept and scope of research governance and the advent of models of single ethical review mean that some of the monitoring responsibilities that may have been previously attributed to a HREC are now best understood as the responsibility of the institution where the research is being conducted.

[4] Economic evaluation of investigator-initiated clinical trials conducted by networks. July 2017 Australian Commission on Safety and Quality in Health Care.
[5] Research Governance Handbook: Guidance for the national approach to single ethical review 2011, NHMRC

Parties responsible for oversight of human research

Parties responsible for the oversight of human research include researchers, institutions, reviewing HRECs and sponsors of research, including any expert committees that may be established to assist any of these parties in the fulfilment of their responsibilities. For some types of clinical research, medicines regulatory agencies (are also responsible for some aspect of oversight and involved in inspection activity.

Timeline for oversight of research projects

Prior to authorisation of a research project, oversight includes developmental aspects of the research (including commercial aspects, when relevant), ethical and scientific review and assessment of the project by participating sites (sometimes referred to as "governance review").

All clinical trials in Australia require review and approval of trial proposals by an ethics committee. In many cases the committee must be registered with, and report annually to, the National Health and Medical Research Council (NHMRC). Ethics committees in Australia provide a combined ethical and scientific review process, which may be supplemented on an as-needed basis by external expert advice as the committee(s) concerned see fit.

In a small number of trials, (namely that require approval under the CTX Scheme), the TGA has a direct role in review of trial scientific data and must give an "approval" for the proposed trial program to go ahead; however, ethics committee review is still required.

Based on site assessment and ethical approval, a project may then be authorised by either the participating institution(s) or a jurisdictional body such as a health district, area health service or local health network. Responsibility for monitoring a research project begins upon authorisation of the project and continues through all phases of the conduct of the research project, including the closure of the research project and, in some cases even beyond the cessation of activity related to the project *per se*.

An illustration of the timeline for monitoring research can be drawn from the various types of reports that are traditionally considered requirements associated with the conduct of a research project. These reports include: safety reports, progress reports, annual reports and final reports. Matters such as communication of individual research results and publication of outcomes, both of which generally occur after the closure of a research project, can also be considered subject to monitoring and are included as components of monitoring in the framework.

Regulation of clinical trials in Australia

Clinical trials in Australia are regulated at a number of levels under both Commonwealth and State and Territory legislation. At the Commonwealth level, TGA is responsible for regulating therapeutic goods. The use of unapproved therapeutic goods in a clinical trial requires an exemption under the CTN or CTX schemes. National laws governing the use and sale of therapeutic goods are supported by State and Territory laws that prohibit the possession of certain types of therapeutic goods without permission.

Framework for monitoring

The identification and allocation of monitoring responsibilities related to research conducted in Australia is derived from a set of regulatory provisions, national and international codes and guidelines promulgated by the Australian government and higher education authorities, industry groups, and representative bodies. Policies and guidelines established by Australian states and territories are also, to differing degrees, either binding or persuasive.

Overlapping accountabilities between these entities poses a risk to effective monitoring of compliance with regulations, and various standards and codes, including GCP standards, particularly for non-industry sponsored trials.

Monitoring of clinical trials

Monitoring has been defined as the "act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP) and regulatory requirements." The National Statement refers to monitoring as the process of verifying that the conduct of research conforms to the approved proposal (and includes "random inspections of research sites, data, or consent documentation" under the mechanisms for monitoring.) So, although regulatory GCP inspections meet the definition(s) of monitoring it is advisable to distinguish between regulatory inspections and study sponsor directed clinical trial monitoring activities (including remote and on-site monitoring activities). Indeed such a distinction is important in the understanding of the objectives and remit of the oversight responsibilities attributable to different parties so as to avoid convolving them into a single function or activity.

Good Clinical Practice

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with the standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of the original and subsequent ICH GCP guidance documents was to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions. The guidance was developed with consideration of the good clinical practices at the time, of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO). The guidance was to be followed when generating clinical trial data intended to be submitted to regulatory authorities. The principles established in the guidance could also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

In much the same way experts from the United States, Europe, and Japan agreed on a standard ISO 14155 that, at minimum, met the regulatory requirements that already existed in their respective countries. The National Statement is particularly important in the Australia context of GCP, as ethics committees in Australia have the primary role of assessing and approving trial proposals. The assessment of initial trial documentation is a key milestone where all necessary documentation and logistical requirements of a trial are reviewed for compliance by the ethics committee(s) concerned. Hence, proper planning and the provision of comprehensive documentation are necessary to achieve approval.

The use of the GCP guideline and the NHMRC National Statement provide the basis for a standardised approach to clinical research in Australia that equates to a level of research rigor comparable with that in any other major regulatory jurisdiction. The requirements are extensive and require significant resources on the part of the trial sponsor (whether industry, or non-industry). When assured by a domestic GCP inspections program conducted by the TGA, they result in a standard of research that other countries as well as major regulatory agencies can have confidence in when the data form part of either a marketing submission to a regulatory body, or a submission to a peer- reviewed journal. Most of all, they ensure that subjects have had their well-being considered paramount in the trial process, with mandatory fully-informed consent and ongoing medical care.

Current state

What is currently done and by whom

In the Australian context, the NHMRC plays a major role in providing guidance and registration to HRECs (and certification of the HREC's hosting institution) for the pivotal role they play in reviewing the scientific and ethical aspects of clinical trial proposals and undertaking a role in the ongoing monitoring of such research. This is crucial in delivering a number of the requirements of GCP-standard research, and highlights one way in which Australia differs from other countries in the provision of GCP standards, with many other jurisdictions using the national regulatory agency for initial trial documentation review.

The Australian Code for the Responsible Conduct of Research 2018[6] (the Code) encourages and promotes integrity in research. It provides a framework for managing breaches of the Code and allegations of research misconduct, managing research data and materials, publishing and disseminating research findings, including proper attribution of authorship, conducting effective peer review and managing conflicts of interest. It also explains the responsibilities and rights of researchers if they witness research misconduct.

NHMRC takes all matters related to research integrity very seriously, and all research funded by NHMRC is required to comply with the Code. It is important to note, however, that NHMRC does not investigate allegations of research misconduct. This is the responsibility of the relevant research institution, as stated in the Code.

Human Research Ethics Committees (HRECs)

Reviewing HRECs have a clearly defined responsibility for monitoring the conduct of a research project in accordance with an approved protocol. In order to ensure that research projects that they approve are conducted ethically, the HREC must:

- ensure that it is notified of any changes to the protocol and that it has an opportunity to consider any substantive changes to the protocol that would implicate the continued ethical conduct of the project;
- have some role in protecting the safety and welfare of participants in the research via notification or review of relevant information from appropriate parties in keeping with national and local regulations, guidance and policies related to safety reporting;
- ensure that it is notified of and, where appropriate, has an opportunity to retrospectively consider protocol violations or prospectively approve requests for the waiver of a protocol requirement;
- oversee the conduct of the project via receipt of progress reports on at least an annual basis during (at a minimum) the active phases of the research project;
- ensure that any agreements by researchers to communicate individual research results are honoured; and
- ensure that any special conditions that it has imposed at the time of project approval are met.

Other activity previously defined as 'HREC monitoring' is more appropriately handled, at least initially, by institutions under a single ethical review model. In private sector research, the

[6] Australian Code for the Responsible Conduct of Research, 2018, NHMRC.

reviewing HREC may need to take on a larger monitoring responsibility to replace absent structures or limited resources at the institutional level.

The primary modes of oversight that HRECs use to monitor approved research are amendments and reports from researchers – or reports from sponsors submitted via researchers. Certification under the National Certification Scheme provides some assurance that the policies, processes and procedures of an institution and its HREC comply with an agreed set of national criteria for the conduct of an ethics review of multi-centre human research, however, participation is voluntary, and there are over 40 institutions with certified HRECs. As an indirect measure, industry sponsored on-site monitoring of investigative sites routinely includes an assessment of correspondence between the investigative site and the approving HREC for initial and ongoing approval, amendments, annual reports, protocol deviations and safety reporting as required by the HREC. If extrapolated from the findings identified by international regulatory inspections of Australian investigative sites, the frequency of non-compliance in this regard across industry-sponsored clinical trials is low. Unfortunately, non-industry sponsored clinical trials do not enjoy the same level of on-site monitoring either in Australia or in any other jurisdiction, and the level of compliance is unknown.

Institutions/Organisations

Institutions have a substantial monitoring role and significant monitoring responsibilities. In accordance with the institution's research governance framework, institutions are obliged to ensure the integrity of their research programs and their researchers and the individual projects that those researchers conduct. In addition, institutions have a responsibility to protect the safety and welfare of participants in research conducted under their auspices, particularly, in the health context, those participants who are also being treated or cared for at those institutions.

Under a system of single ethical review the oversight and governance roles translate into specific institutional monitoring responsibilities as a function of the removal of all but one local HREC from responsibilities related to any multi-centre research project.

Authorising institutions have a responsibility for monitoring the conduct of a research project in order to ensure that projects that they authorise are conducted with integrity and in compliance with relevant requirements. Consequently, each institution should:

- ensure that it exercises appropriate quality control over a research project such that researchers or other staff over whom it has authority conform to any contracts and agreements and comply with any relevant internal or applicable external policies;
- ensure that it has an opportunity to consider any changes to a research project that have implications for its capacity to support the conduct of the project in accordance with any ethical and administrative requirements;
- have some role in protecting the safety and welfare of participants in the research via notification of relevant information from appropriate parties;
- ensure that data collected and used are properly secured and that project records are properly kept;
- ensure that financial matters related to a research project (e.g., budgets and grants) are being properly managed;
- oversee the conduct of the project via receipt of progress reports on at least an annual basis (at a minimum) during the active phases of the research project;
- oversee the conduct of the project via receipt of final reports on the research project;

- ensure that project closure proceeds in accordance with any contractual or internal site requirements;
- ensure that research outcomes that are published are notified to the institution;
- ensure that any complaints raised by participants in the research, allegations of research misconduct or potential post-project authorisation conflicts of interest are properly investigated and that any resulting recommendations are implemented and, if appropriate, notified to the reviewing HREC and/or the NHMRC as appropriate; and
- ensure that any special conditions that it has imposed at the time of project authorisation are met.

To carry out their oversight role, many Australian institutions have developed administrative units such as Offices of Research with dedicated staff employed for this purpose. However, it is acknowledged that many Australian institutions have insufficient resources to meet all of their monitoring obligations.

Researchers/Principal Investigators

Researchers have a responsibility to ensure the integrity and ethical appropriateness of the individual projects that they conduct. This responsibility covers all aspects of the research project and is an ongoing responsibility, sometimes requiring monitoring activity long after a research project has formally closed.

The principal way in which researchers fulfil their monitoring responsibilities is via reporting to other parties or by forwarding on reports provided to them by sponsors of the research. Different types of reports require differing reporting pathways; however, in most cases, it is the role of the researcher with primary responsibility for the project at his or her site, the 'principal investigator' or 'PI' in the health research context, to complete and submit the reports.

Sponsors

Sponsors of research have a responsibility to ensure the integrity and ethical appropriateness of each research project that they sponsor, including protecting the safety and welfare of participants in their research. Sponsors of research can be commercial companies, collaborative research groups, government entities, individual investigators, or universities.

The responsibilities attributable to the sponsors of clinical trials involving unapproved therapeutic goods, as mentioned above, are articulated in ISO 14155 and the ICH Guideline for Good Clinical Practice E6 (and revisions), as follows;

> 5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
>
> 5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.
>
> 6.10 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, Institutional Review Boards (IRB)/ Independent Ethics Committee (IEC) review, and regulatory inspection(s), providing direct access to source data/documents.

There are differences between industry-sponsored and non-industry sponsored clinical trials in how those responsibilities and obligations are met. Industry sponsors of clinical trials typically commit significant resources to meeting their responsibilities including costly[7] on-site monitoring of investigative sites. If based only on the observations reported from a small number of Australian site inspections conducted by international regulators,[8] is not unreasonable to suggest that larger-sized industry sponsors, are aware of the various codes, regulations and guidelines, in a manner consistent with their international peers. Smaller and less-experienced industry sponsors are unlikely to have access to the same level of resources in this area.[9] This is demonstrated by the findings of GCP inspections of non-industry sponsors reported by international regulators.[10]

It is important to note that non-industry sponsored clinical trials make up a significant proportion of all the trials conducted each year which involve the use of therapeutic goods. However in those trials the clinical trial sponsor is not the "sponsor" as defined by the TGA (for the purposes of the Australian Register of Therapeutic Goods - ARTG).

Therapeutic Goods Administration (TGA)

TGA's role in monitoring clinical trials is limited to those trials involving use of an unapproved product via one of two pathways, the CTN scheme or the CTX scheme, with the latter accounting for less than 1% of the total number of trials conducted under the two schemes. Although the number of CTXs is predicted to increase with the requirement that clinical trials of Class IV biologicals be conducted under the CTX scheme, the significant majority of clinical trials will continue to be conducted under the CTN scheme. The conduct of higher-risk early-phase studies under the CTN scheme poses a challenge to TGA's ability to identify risk early in the clinical trial process, to identify non-compliance, and to respond to reports of adverse drug reactions (and medical device adverse events).

TGA's powers to inspect clinical trial sites, or revoke approval of clinical trials in the public interest are clear for those approved under the CTX scheme. Inspections may be "random" (simply chosen without favour from those trials that are subject to regulation); "for cause" (inspected as a result of information the regulator may have received from someone involved with the trial, or a third party); or "targeted" (chosen for inspection as it represents a likelihood of maximising inspection resources).

TGA has in the past conducted "for-cause" inspections but does not currently operate a routine clinical trial GCP inspection program, unlike international counterparts. Not only do other comparable regulators conduct GCP inspection programs, and have done so for a number of years, but they have programs, in planning and/or in place, to share their findings to avoid duplication, decrease the regulatory burden on sponsors and make best use of their resources and capabilities. With the increasing global use of third country clinical trial data the attention of regulators and sponsors is being drawn to the oversight of clinical trials, with potential impact on Australia's reputation as a clinical trial environment of choice.

Other regulators

Domestic clinical trial inspection programs for compliance with GCP standards are in operation in the USA, European Union, Canada, and other countries with comparable regulatory

[7] Collier R. Rapidly rising clinical trial costs worry researchers. CMAJ : Canadian Medical Association Journal. 2009; 180(3):277-278. doi:10.1503/cmaj.082041.
[8] GCP Inspections Metrics Report, July 2017, MHRA.
[9] McMahon AD, Conway DI, MacDonald TM, McInnes GT (2009) The Unintended Consequences of Clinical Trials Regulations. PLoS Med6(11): e1000131. https://doi.org/10.1371/journal.pmed.1000131
[10] GCP Inspections Metrics Report, July 2017, MHR.

frameworks. While taking various forms, these programs are designed to investigate that GCP standards are being adhered to in the local conduct of clinical trials. In addition, some regulators, namely, United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) conduct a small number of clinical trial GCP inspections in Australia, mostly, of investigative sites rather than other entities.

International GCP Inspection Schemes

International cooperation

International cooperation has been clearly identified as a key foundation in developing a robust international framework for the conduct of clinical trials. As more and more clinical trials on medicinal products marketed in the EU are performed in countries outside of the EU, enhanced international cooperation is seen as essential to ensure that, as far as possible, there is a common international approach to the oversight of clinical trials. In addition the establishment of an international network of clinical trial regulators should therefore be a fundamental objective. The ultimate objective is to have a system for regulators of clinical trials i) with harmonised approach for clinical trial oversight, ii) with strengthened efficiency of the controls by exchange of information and implementation of synergies between countries.

The EMA's GCP inspection policy for centralised procedures - medicinal products for human use (EMA/INS/GCP/572210/2012) gives priority to clinical studies performed outside European Union/European Economic Area/European Free Trade Association (EU/EEA/EFTA) that may give rise to special ethical concerns (e.g., informed consent process, inclusion of vulnerable population, use of placebo etc.), and, to sites located outside EU/EEA in order to have reassurance that these studies have been conducted in accordance with the principles of GCP. As reported in the GCP Inspectors Working Group Annual reports, approximately 58% of GCP inspections were carried out in regions outside the EU/EEA/EFTA (in 2016).[11]

United States of America

The FDA conducts inspections of clinical investigators under the Bioresearch Monitoring (BIMO) Program in accordance with the agency's regulations on Good Clinical Practices (21 CFR 10.115).

The FDA developed its BIMO Program to help ensure the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of clinical trial data submitted to the FDA in support of research or marketing applications, and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical trials. Among other activities, the FDA BIMO Program involves site visits to clinical investigators, trial sponsors, monitors, contract research organisations, IRBs, nonclinical (animal) laboratories, and bioequivalence analytical laboratories.

The FDA's inspection of clinical investigators is not limited to the United States of America. International inspections are generally conducted when the studies are part of a marketing application submitted to FDA and provide data critical to decision making on product approval. Such assignments include studies that are conducted under (or in support of) an FDA investigational new drug application (IND), as well as studies at non-US sites that are not conducted under an IND or under an investigational device exemption (IDE).

[11] Annual report of the Good Clinical Practice Inspectors Working Group 2016,EMA/INS/GCP/763873/2016

Canada

In Canada, clinical trials of drugs are regulated by Health Canada under the *Food and Drugs Act and Part C, Division 5 of the Food and Drug Regulations: Drugs for Clinical Trials Involving Human Subjects*. These laws allow Health Canada to regulate the sale and importation of drugs used in clinical trials, and to enforce good clinical practices. Inspectors assess whether sites comply with legal requirements. The main goal of these inspections is to protect the rights, safety and well-being of the human subjects enrolled in clinical trials. Inspections are also conducted to verify the integrity of data collected in clinical trials.

Japan

In Japan, clinical trials of drugs are regulated by the PMDA under the Pharmaceutical and Medical Devices Act and GCP inspections conducted by the Office of Conformity Audit in accordance with the Ministerial Ordinance concerning the Standard for the Performance of Clinical Trials of Drugs (GCP Ministerial Ordinance). Both document based conformity inspections and on-site GCP inspections are conducted across both domestic and international clinical trials.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	10/12/2018

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #