Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Consultation on proposed regulatory changes for clinical trials of medical devices

August 2022

TGA Health Safety Regulation

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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.

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Introduction

The Australian Government is undertaking a program of reform to improve the safety, performance, and quality of medical devices in Australia and improve health outcomes and confidence in products for those patients who require medical devices. As part of the Australian Government Department of Health and Aged Care, the Therapeutic Goods Administration (TGA) regulates therapeutic goods and is responsible for implementing these reforms.

As part of this reform program, the TGA wishes to consult on two approaches that would strengthen safety oversight of clinical trials for medical devices:

1. To increase the degree of regulatory oversight of clinical trials of certain **unapproved, high-risk medical devices**.
2. To include clinical trials of **all** medical devices in **Australia's Good Clinical Practice Inspection Program** (to enable selected trials and documentation supporting these trials to be inspected).

This consultation paper outlines the two potential changes and seeks feedback to inform improvements to the regulatory framework.

Background

Clinical trials regulation in Australia

Clinical trials greatly benefit patients, advance medical knowledge and are estimated to be worth around $1 billion to the Australian economy each year. The environment in which clinical trials are conducted is complex, often occurring across multiple jurisdictions and with every study needing ethics and governance approvals before it can commence.

Within this framework, the TGA is responsible for regulation of import, export and/or supply of medical devices for use in clinical trials in Australia under the therapeutic goods legislation[1]. There are two pathways administered by the TGA that allow use of investigational products (i.e. unapproved products, including those intended for first use in humans) in clinical trials [2]:

- CTN – Clinical Trial Notification scheme
- CTA – Clinical Trial Approval scheme

Detailed information about the difference between the CTN and CTA schemes is available on the TGA website[3] and in the Clinical Trials Handbook.[4] The key difference is the extent of TGA's oversight of the investigational products being studied in proposed trials.

The TGA does not perform an assessment of the medical device to be used in the clinical trial under the CTN scheme. The sponsor[5] is only required to notify the TGA a clinical trial will be conducted. In the CTA scheme, the TGA evaluates information about the device, including scientific data, and grants approval for the trial to proceed, if appropriate. Importantly, the trial

[1] s41HA and s41HB of the *Therapeutic Goods Act 1989* and Division 7.2 of the Therapeutic Goods (Medical Devices) Regulations 2002.
[2] Australian clinical trial handbook
[3] www.tga.gov.au/sme-assist/which-clinical-trial-scheme-should-i-choose
[4] www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf
[5] The sponsor of a clinical trial is defined as 'an individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study'.

sponsor is responsible for selecting the appropriate pathway; there is no current legislation dictating when to choose one over the other.

All medical device trials have occurred through the CTN pathway in the last 5 years (between 120-210 per year) and the TGA has received no CTA applications. While this may be appropriate in many instances, it allows novel permanently implantable investigational medical devices to be used in humans without review by the TGA. This is despite potentially high risks in trials with implantable devices. Whereas if a trial of a new medicine shows that it is producing significant and obvious side effects, or interim analyses of the treated groups shows that the medicine is not effective, the trial can be terminated simply by immediate discontinuation of the medicine. In contrast, unsafe or ineffective implanted clinical devices usually require surgery to remove them, and such surgery (e.g. of the heart or brain) can in itself be risky. However, current arrangements mean that the TGA is not involved in reviewing scientific information about the medical device to be used.

Instead, the Human Research Ethics Committee (HREC) reviews the scientific validity of the trial design, the balance of risk versus harm of the device, the ethical acceptability of the trial process, and is solely responsible for approving the trial. While some HRECs have solid expertise relating to medical devices, a number of others do not, as members are drawn from pharmacology, specialist medicine and ethics backgrounds.

This level of oversight is in contrast with comparable regulators overseas (Europe, UK, USA, Canada and Japan) where the medical device regulator is typically involved in the approval process for medical devices clinical trials, particularly for higher risk implantable products. The Australian regulations affecting medical devices have been amended in recent years to account for advances in technology, including the materials and manufacturing, together with their interaction with software, yet similar regulatory safeguards do not exist for devices used in an investigational context.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials. Clinical trials of medicines and biologicals (but not currently medical devices) are legally required to comply with GCP, and this is actively monitored and enforced by the TGA through the GCP Inspection Program (GCPIP). The GCPIP enables the TGA to conduct physical inspections of clinical trial sites to ensure that trials are being conducted in accordance with GCP standards. Compliance with GCP provides assurance that the rights, safety, and well-being of clinical trial participants are protected and that the trial data generated are credible.

Clinical trials for medical devices are **not** currently included in this program. While clinical trials of medical devices are legally required to comply with the NHMRC National Statement on Ethical Conduct in Human Research (which requires research to meet the requirements of ISO 14155 - the GCP-equivalent standard for medical devices),[6] this is currently not monitored or enforced by the TGA.

[6] www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018#toc_48

Proposed changes

CTA approval for clinical trials of certain high-risk devices

We propose that certain invasive or implantable medical devices that have not previously been used or studied in people would be required to obtain TGA approval through the CTA pathway – the CTN would not be an available option.

Owing to the invasive nature of many medical devices, special consideration is warranted, as in the event of a device failure a potentially major surgical procedure may be required to remove a faulty experimental device or repair damage caused. Over time, medical devices have increased in their complexity, with advances in technology such as the materials used (including 3D printed materials), and the interaction with software. Many regulators, including the TGA have identified that some emerging medical devices are posing an increasing higher risk to patient safety and whilst regulatory changes have been implemented affecting the regulation of devices with these innovations that are marketed, no oversight is mandated for these devices used in the context of clinical trials.

The means the TGA would assess the device's scientific evidence, including but not limited to biological safety testing and functional performance testing prior to use in any clinical trial. HREC review of the trial protocol and scientific data would still be required. Once the approval from TGA was obtained and the sponsor has received other relevant approvals, including the ethics approval by the relevant HREC, the sponsor could initiate the clinical trial.

The current fee for a CTA is $19,699 and it is estimated that it would take the TGA approximately three months to conduct a review and issue an approval, if appropriate. **If agreed, it is estimated that less than 10 per cent of device clinical trials (i.e. 20 or less per year) would be affected by the proposal**. The other 90 percent of medical device clinical trials could continue to submit a CTN notification to the TGA.

The anticipated change in regulatory burden is minimal. This is because information required to be submitted to the TGA as part of a CTA is already held by the manufacturer, no additional effort is required to gather data and the CTA process can be performed in parallel with the submission to and ethics committee and the review by the HREC. Occasionally, HRECs do not possess the required expertise to issue an approval for a clinical trial, meaning they must either seek external specialist advice, or the trial sponsor must seek a different HREC opinion. This process itself takes time and delays trial start-ups – review by the TGA under a CTA would reduce or eliminate this requirement.

Therefore, while there may be a slight delay whilst the TGA completes the scientific data review, this is offset by reduced burden on the HREC and an additional layer of assurance that novel, high-risk devices have been assessed by an authority with the expertise to do so. As described above, there is a significant burden placed on HRECs to approve and oversee clinical trials, and there is scope to further mitigate risk, share responsibility for oversight and bring the TGA into alignment with international best practice.

Include medical devices in the GCP Inspection Program

We are proposing that medical devices be included in the current GCP Inspection Program. This program was introduced in 2022 following piloting since 2018 and currently only applies to clinical trials of medicines and biologicals. It aims to verify compliance of clinical trial sites with Australian and internationally accepted standards, protecting public health.

Clinical trials of medical devices are already legally required to comply with the medical device GCP standard, known as ISO 14155, however the TGA does not currently conduct inspections of these sites, as they do for medicines and biologicals, so there are no effective checks of compliance at present with this existing legal requirement. Again, this contrasts with comparable regulators (US, Canada, UK and Japan), all of which include medical devices in their inspection program.

It is anticipated that only a limited number (10-15 a year) of medical device clinical trials would undergo GCP inspections by the TGA. As for the current approach for medicines and biologicals, these would be selected based on potential risk, by assessment of factor such as whether the trial of the device is 'first in human', safety record of similar products, the experience of the group conducting the trial, and the compliance record of the group undertaking the trial. Therefore, prioritisation of sites for routine inspection is based on an assessment of risk. Non-routine inspections, otherwise known as 'all-cause' inspections are initiated in response to intelligence about non-compliance.

Given that TGA would select the trials to be inspected, as for medicine and biological trials it is anticipated that there would not be a fee to the site for inspections. (Neither would the TGA reimburse investigator sites for their time dedicated to inspection preparation or attendance). Investigators should continue conducting trials in line with GCP and maintain an awareness that the TGA can conduct an inspection of the clinical trial site and investigate any breaches of requirements as appropriate. Further detailed information about the GCPIP Inspection Program is available in the TGA's '*Guidance for GCP inspection of clinical trial sites for investigational biologicals and medicinal products*'.[7]

Inclusion of medical devices in the existing GCPIP will assure the public that the Guideline is adhered to and that the rights, safety, and well-being of clinical trial participants are protected and that the trial data generated are credible.

Benefits of the proposed changes

The proposed changes will strengthen clinical trials of high-risk medical devices in Australia. The TGA would have better oversight of high-risk devices commensurate with the potential for patient harm. This approach is consistent with TGA's broad 'risk-based' approach to regulating therapeutic goods.

Inclusion of **all** medical devices in the existing GCP Inspection Program would enhance protection of Australian patients and improve data quality, reliability, and acceptability. This would in turn raise the standard of conduct and quality of clinical trials conducted in Australia and strengthen Australia's competitive position in clinical trials globally.

[7] www.tga.gov.au/sites/default/files/good-clinical-practice-inspection-program-22-04-26.pdf

Your input is valuable to us

We invite you to review the consultation paper and provide a response using our online survey, both of which are accessible through our consultation hub. We appreciate all views, so if you would prefer to respond by email or written document, you can find further details on the hub.

Questions

1. Do you think the TGA should have more oversight of clinical trials involving high-risk medical devices (i.e. invasive or implantable medical devices that have not previously been approved for use in people)?
2. Do you think clinical trials of medical devices should be included in the existing GCP Inspection Program?

How to submit

Complete the online consultation submission form to upload your submission in either pdf or word format.

You can also submit your feedback directly to the TGA by email at: devicereforms@tga.gov.au. If you do so, **please ensure your submission is accompanied by a cover sheet**.

This consultation closes on 28 September 2022.

Enquiries

If you have any questions relating to submissions, please direct them to: devicereforms@tga.gov.au.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Authorisation Branch, Therapeutic Goods Administration	August 2022

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