



Australian Government
Department of Health
Therapeutic Goods Administration

TGA's Role in Clinical Trials Regulation and Administration

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ARCS Webinar

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TGA Health Safety
Regulation

Overview

- Supplying 'unapproved' therapeutic goods in clinical trials
- Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) Schemes
- TGA and Stakeholders Responsibilities
- Safety reporting and other regulatory requirements
- Clinical trials FAQs
- Australian Clinical Trials Handbook update



Supplying ‘unapproved’ therapeutic goods in clinical trials

- The therapeutic goods legislation requires that the use of therapeutic goods in a clinical trial conducted under the CTN/CTX schemes must be in accordance with:
 - ICH Guidelines for Good Clinical Practice (GCP).
 - National Statement on Ethical Conduct in Human Research (National Statement).
 - The procedural protocol as approved by the Human Research Ethics Committee (HREC) responsible for monitoring the conduct of the trial.



Guidance relevant to clinical trials conducted under the CTN and CTX schemes:

- [ICH Guideline for Good Clinical Practice](#)
 - Guideline for Good Clinical Practice (investigational medicines and biologicals)
 - ISO 14155 (investigational device)
- [National Statement on Ethical Conduct in Human Research \(National Statement\) issued by NHMRC](#)
- [Note for guidance on clinical safety data management: definitions and standards for expedited reporting](#)
- The NHMRC Guidance: [Safety monitoring and reporting in clinical trials involving therapeutic goods](#)

What are therapeutic goods?

Therapeutic goods are broadly defined as;

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury
- influencing inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment
- influencing, controlling or preventing conception
- testing for pregnancy

This includes things that are:

- used as an ingredient or component in the manufacture of therapeutic goods
- used to replace or modify of parts of the anatomy

Types of therapeutic goods

The trial sponsor needs to correctly identify the type(s) of therapeutic good(s) being supplied in a clinical trial as different regulatory requirements apply.



Medicine (prescription medicines, over-the-counter medicines and complementary medicines)



Biologicals (human cell and tissue-based therapeutic goods, or live animal cells, tissues and organs)



Medical devices (in vitro diagnostic medical devices (IVDs))



Other therapeutic goods (Sterilants, disinfectants and tampons)

What is an ‘unapproved’ therapeutic good?

- **‘Unapproved’ therapeutic goods include:**
 - Any medicine not entered in the ARTG.
 - Any medical device not entered in the ARTG.
 - Any biological not entered in the ARTG.
 - **A therapeutic good already in the ARTG that is used beyond the conditions of its marketing approval including labelling**



‘Unapproved’ products can also be:

- Placebos
- Comparators
- Products used as support medication for preventative, diagnostic or therapeutic reasons or needed to ensure that adequate medical care is provided for the participant

For example, an antiemetic supplied in a chemotherapy trial

- Imported products that are similar to the ARTG product
- Medical software and mobile medical ‘apps’
- Laboratory kits and procedure packs
- Genetically Modified Organisms (GMO)

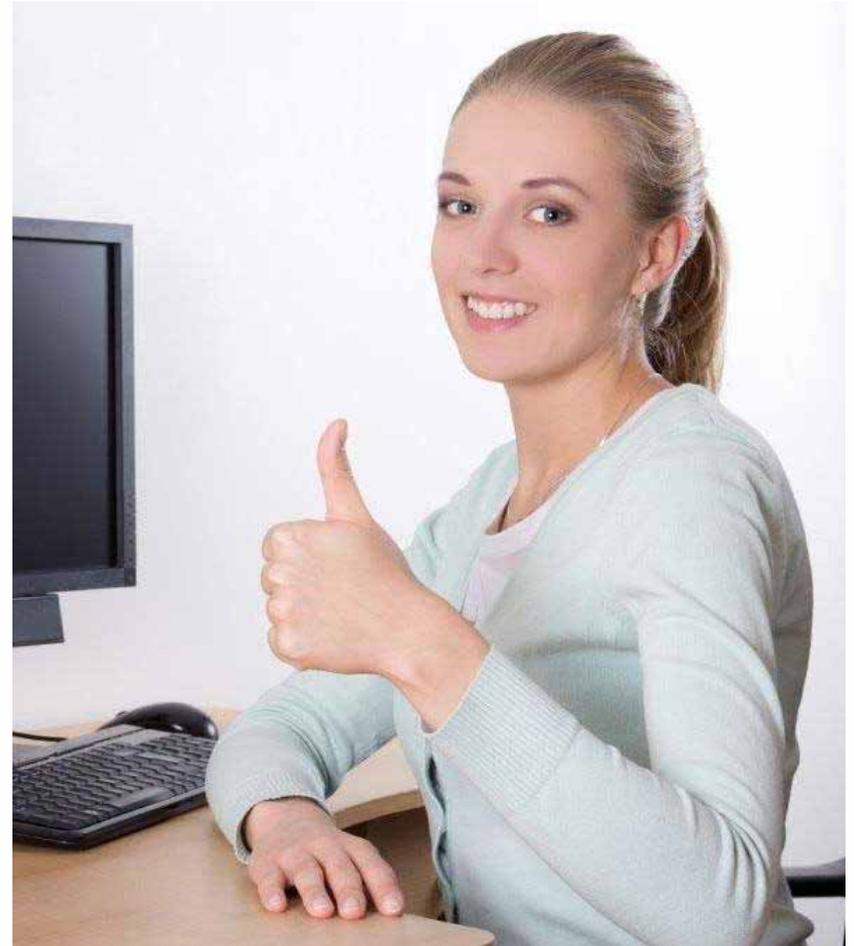
Pathways for accessing ‘unapproved’ therapeutic goods for experimental purposes in humans

- Clinical Trials Notification (CTN)
- Clinical Trials Exemption (CTX)



The CTN scheme

- Notification process
- TGA does not review/evaluate any data relating to clinical trials at the time of submission.
- All material relating to the proposed trial, including the trial protocol is submitted directly to the HREC for review and approval.
- Supply of goods cannot commence without valid notification and fee paid.
- Each additional trial site needs to be notified to us before commencing a trial at that site.



The CTX scheme

- Two step approval process – part 1 (approval) and part 2 (notification).
- Generally designed for complex therapies (required for certain class 4 biologicals).
- TGA evaluates the proposed Usage Guidelines.
- Supply of goods cannot commence without HREC and TGA approval.
 - Our primary responsibilities is to **review the safety of the product**
 - HREC is responsible for **considering the scientific and ethical issues** of the proposed trial protocol
- May conduct any number of clinical trials, provided use of the product falls within the original approved usage guidelines.
- Each trial must be notified to the TGA.

CTN or CTX?

Decision of whether a CTN or CTX is required lies with the sponsor in consultation with HREC (except for certain Class 4 biologicals, which must be approved under the CTX scheme)

- One of the determining factors for a HREC is whether the committee has access to appropriate scientific and technical expertise in order to assess the safety of the product.

Responsibilities of the Stakeholders under the CTN/CTX schemes

Sponsor

- Over all responsibility for trials conducted
- Submitting CTN/CTX
- Ensure the trial must be in accordance with the GCP, the National Statement and the protocol
- Safety reporting

Approving Authority

- The institution or organisation at which the trial will be conducted (trial sites)
- Gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

HREC

- Assess the scientific validity of the trial design, the safety and efficacy of the medicine or device, the ethical acceptability of the trial process
- Monitor the conduct of the trial
- Approve the trial protocol

Principal Investigator

- Personally supervises the trial at that site
- Must conduct the clinical trial in accordance with the clinical trial protocol.
- Must monitor safety
- Must comply with record management and reporting requirements for adverse events

Role of TGA

- Request certain information about therapeutic goods exempt under the CTN/CTX scheme.
- CTX scheme: inspect clinical trial sites.
- If the conditions of exemptions are not complied with:
 - a CTN exemption will automatically cease
 - a CTX approval can be revoked.
- Release information if required to the Commonwealth, a state or a territory as well as medical boards.

Safety reporting to TGA for CTN and CTX trials

What should be Reported?

- Suspected unexpected serious adverse reactions (SUSARs) from Australian site only
- Unanticipated serious adverse device effects (USADEs) from Australian site only
- Significant safety issues requiring urgent safety measures
- Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia)

Trial sponsors should refer to the NHMRC Guidance: [Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods \(NHMRC Guidance\)](#)

Safety reporting timeframe for CTN/CTX trials

1. Single case events from Australian sites: SUSARs and USADEs

Type of event	Type of good	Report format	Timeframe
<p>Suspected unexpected serious adverse reactions (SUSARs) from Australian sites only</p>	Medicines and biologicals	<ul style="list-style-type: none"> Electronic Data Interchange Please contact e2b.reports@tga.gov.au if you require assistance in connecting this service) <p>OR</p> <ul style="list-style-type: none"> Online reporting form <p>OR</p> <ul style="list-style-type: none"> Blue Card or CIOMS form emailed to adr.reports@health.gov.au 	<ul style="list-style-type: none"> For fatal or life threatening Australian SUSARs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days For all other Australian SUSARs, no later than 15 calendar days after being made aware of the case
<p>Unanticipated serious adverse device effects (USADEs from Australian sites only)</p>	Devices	<ul style="list-style-type: none"> Medical Device Incident Reporting System <p>OR</p> <ul style="list-style-type: none"> Users Medical Device Incident Report Form emailed to iris@health.gov.au 	<ul style="list-style-type: none"> For fatal or life threatening Australian USADEs, immediately, but no later than 7 calendar days after being made aware of the case, with any follow-up information within a further 8 calendar days For all other Australian USADEs, no later than 15 calendar days after being made aware of the case

2. Significant safety issues* and overseas regulatory action

Type of event	Type of good	Report format	Timeframe
Significant safety issues (SSIs) requiring implementation of urgent safety measures (USMs)	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Within 24 hours (where possible) and in any case, no later than 72 hours of the measure being taken
Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia)	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action
All other significant safety issues (SSIs): Notification of an amendment** Temporary halt of a trial for safety reasons Early termination of a trial for safety reasons	All therapeutic goods	In writing to the Pharmacovigilance and Special Access Branch via email to clinical.trials@health.gov.au	Without undue delay and no later than 15 calendar days of the trial sponsor becoming aware of the issue or temporary halt or early termination

*SSIs that arise from analysis of overseas reports (relating to a clinical trial in Australia) should be reported to us as per the timeframes above.

** We should receive notification that a SSI has occurred but the amendment revising trial documentation **should be submitted to the HREC only.**

Note: A SUSAR or USADE may also meet the definition of an SSI.

3. Other report types

Type of event	Type of good	Report format	Timeframe
Other single case adverse events (AEs)	All therapeutic goods	Up to date tabulations or line listings	On our request
Annual safety reports	All therapeutic goods	Development Safety Update Reports (DSURs) or other annual safety reports.	On our request

Other regulatory requirements relating to clinical trials

Advertising 'unapproved' therapeutic goods

- Sponsor can promote their trial but they cannot advertise any 'unapproved' therapeutic good.
- Advertisement for a clinical trial should be approved by the HREC reviewing the trial.

Clinical trial FAQs

Who can be the clinical trial sponsor under the CTN/CTX schemes?

- The sponsor of a trial can be an individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.
- If the investigator initiates and organises the trial, he or she is defined as the sponsor of the trial and will be responsible for the sponsor's functions.
- The sponsor of the trial must be a legal Australian entity.
- The Australian clinical trial sponsor is responsible for submitting the CTN or CTX.

Clinical trial FAQs

Can a clinical trial sponsor delegate responsibilities?

- A sponsor may transfer any or all of the sponsor's trial-related duties and functions, including adverse drug reaction reporting, to a Contract Research Organisation (CRO). **However, please note that the ultimate responsibility resides with the trial sponsor.**

Clinical trial FAQs

I have submitted a variation to a previously notified trial. Will this variation incur a fee?

- Certain variations to existing CTNs may incur a fee.
 - Addition of a new site(s).
 - Change that creates [separate and distinct goods](#).
 - Addition of a new therapeutic good.
- If you submit a CTN variation that incurs a fee, an invoice will be sent via email to the submitter of the CTN and to the billing contact of your organisation as provided to TGA Business Services.

Clinical trial FAQs

When do I advise the TGA of a completed clinical trial?

- The completion advice should be submitted to the TGA once the clinical trial related activity afforded by this exemption is complete and thus the exemption would no longer be required.
 - This would usually correspond with the last patient last visit (LPLV) however it is up to the sponsor to determine when the exemption is no longer required.
- It is not necessary to notify completion dates for individual trial sites.

Clinical trial FAQs

What are the labelling requirements for Investigational Medicinal Products (IMP) in clinical trials?

- The TGA has adopted the PIC/s Guide for Good Manufacturing Practice for Medicinal Products 2009, with Annex 13 of this guide referring to the manufacture of investigational medicinal products.
 - Labelling requirements under items 26-33.
 - This document is available on the TGA website:
<https://www.tga.gov.au/publication/manufacturing-principles-medicinal-products>.

Clinical trial FAQs

Do we need a license to manufacture investigational products?

Australian facilities participating in the manufacture of a medicine or biological for use in a clinical trial must hold a manufacturing license issued by us. However, certain persons or goods are exempt from this requirement.

- Goods prepared for the initial experimental studies in human volunteers.
- Pharmacists who manufacture goods in a pharmacy where the pharmacist practices and the pharmacy is open to the public and the goods are supplied from those premises (other than by wholesale). i.e. to individual patients.
- Pharmacists employed by a public hospital or public institution who manufacture goods for supply to patients in hospitals/public institutions in the same State or Territory.
- a person who applies supplementary labelling to a manufactured product, where the supplementary label contains only a name and address, the registration or listing number of goods, or the biological number of a biological.

Clinical trial FAQs?

Do I need a permit to import clinical trial material?

- The importer does not require approval from the TGA prior to importation of the clinical trial goods; however the trial must be notified to the TGA through the CTN scheme prior to supply of the goods to the trial sites.
- Sponsors are advised to contact other relevant agencies as there may be further [restrictions on importation](#) imposed through other legislation such as the [Customs \(Prohibited Imports\) Regulation 1956](#), the [Biosecurity Act 2015](#) and the [Environment Protection and Biodiversity Conservation Act 1999](#).

Clinical trial FAQs

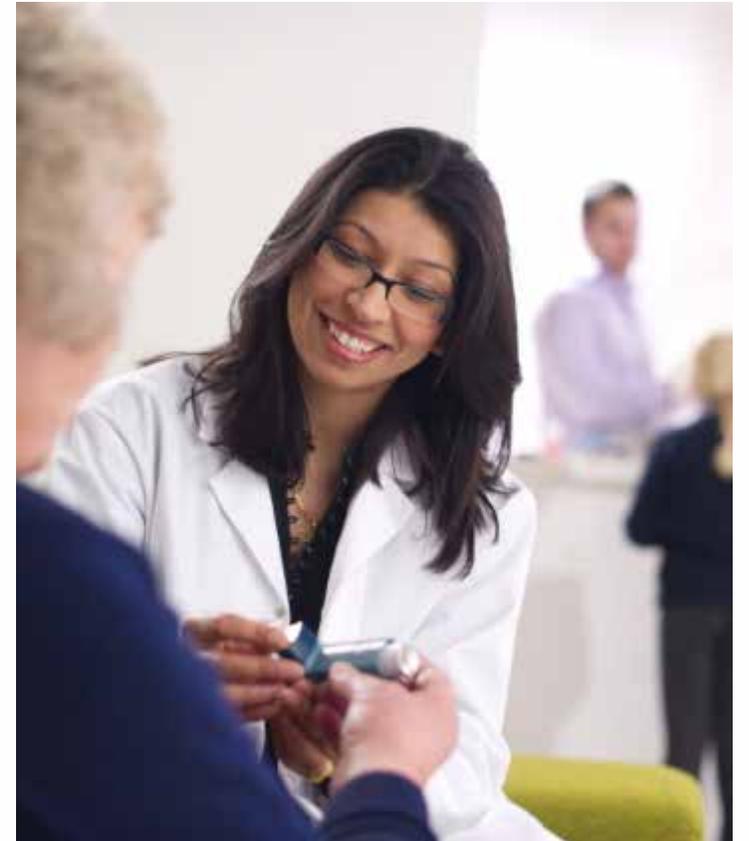
Are there special requirements for clinical trials involving medicinal cannabis products?

- The manufacturer of the medicinal cannabis product(s) is required to declare that their product conforms to the [Standard for Medicinal Cannabis \(TGO No. 93\)](#) by completing the [declaration form](#) available on the TGA website.
- This declaration form is provided by the manufacturer to the Australian clinical trial sponsor. The sponsor then completes the section at the end of the form, which includes the name of the medicinal cannabis product(s).
- The clinical trial sponsor should submit this form via email to clinical.trials@health.gov.au.

Update on Clinical trial handbook

March 2018:

- Restructured and brought up-to date to reflect current practices and meet government accessibility requirements. Replaces:
 - Access to unapproved therapeutic goods - Clinical Trials in Australia (October 2004)
 - Human Research Ethics Committees and the Therapeutic Goods Legislation (June 2001)
 - Australian Clinical Trials Handbook (March 2006).



Update on Clinical trial handbook

September 2018:

- Minor updates to text and links
- Updated the reporting methods for SUSARs and USADEs. Removed recommendation to submit IB&P and trial protocol with individual SUSARs and USADEs.
- Removed the information requiring importers to destroy or return unapproved goods if they are not used within 12 months of authorisation (legislative update).
- Further clarification provided on checking overseas legislative requirements for overseas trials, compliance with National statement, managing conflicts of interest, and transferring sponsorship



Any comments or questions?

Enquiries: clinical.trials@tga.gov.au



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