



Australian Government

Department of Health

Therapeutic Goods Administration

Clinical Trials – TGA Role

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TGA Health Safety
Regulation



Overview

- TGA role
- Unapproved therapeutic goods
- Clinical trials



TGA Role

- The *Therapeutic Goods Act, 1989* (the Act) and associated Regulations establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of therapeutic goods for human use.
- Responsibility for the regulatory controls lies with the Therapeutic Goods Administration (TGA) as the national regulatory authority for therapeutic goods.

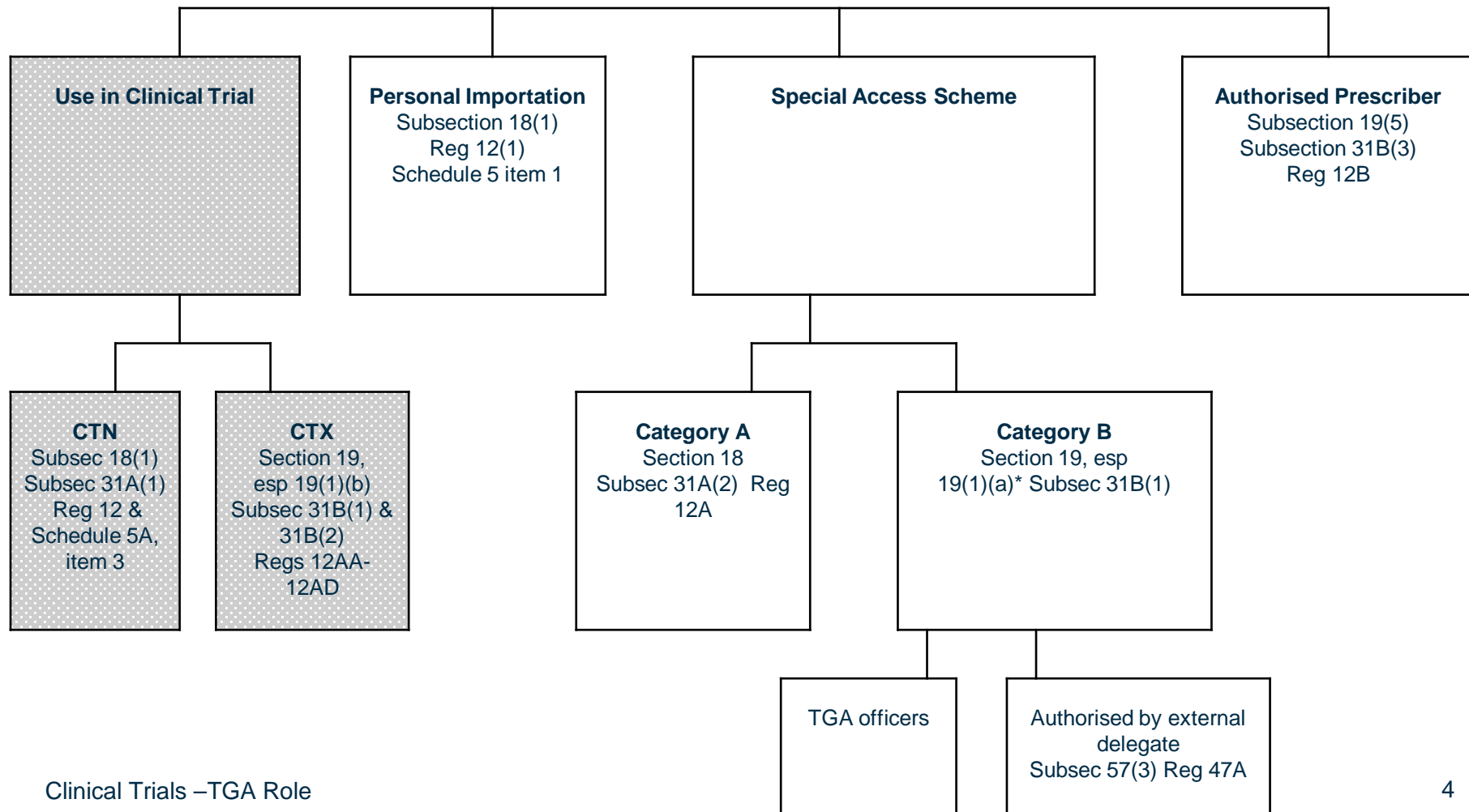


What is an Unapproved Therapeutic Good?

- Therapeutic goods must be entered in the Australian Register of Therapeutic Goods (ARTG) before they can be lawfully supplied in or exported from Australia unless exempt from being entered in the ARTG, or otherwise authorised by the TGA.
- Generally, unapproved goods are goods which are not on the ARTG or ARTG goods which are being used outside of TGA approved indications.
- Unapproved goods have not been evaluated by the TGA for quality, safety or efficacy and are therefore considered ‘experimental’ products

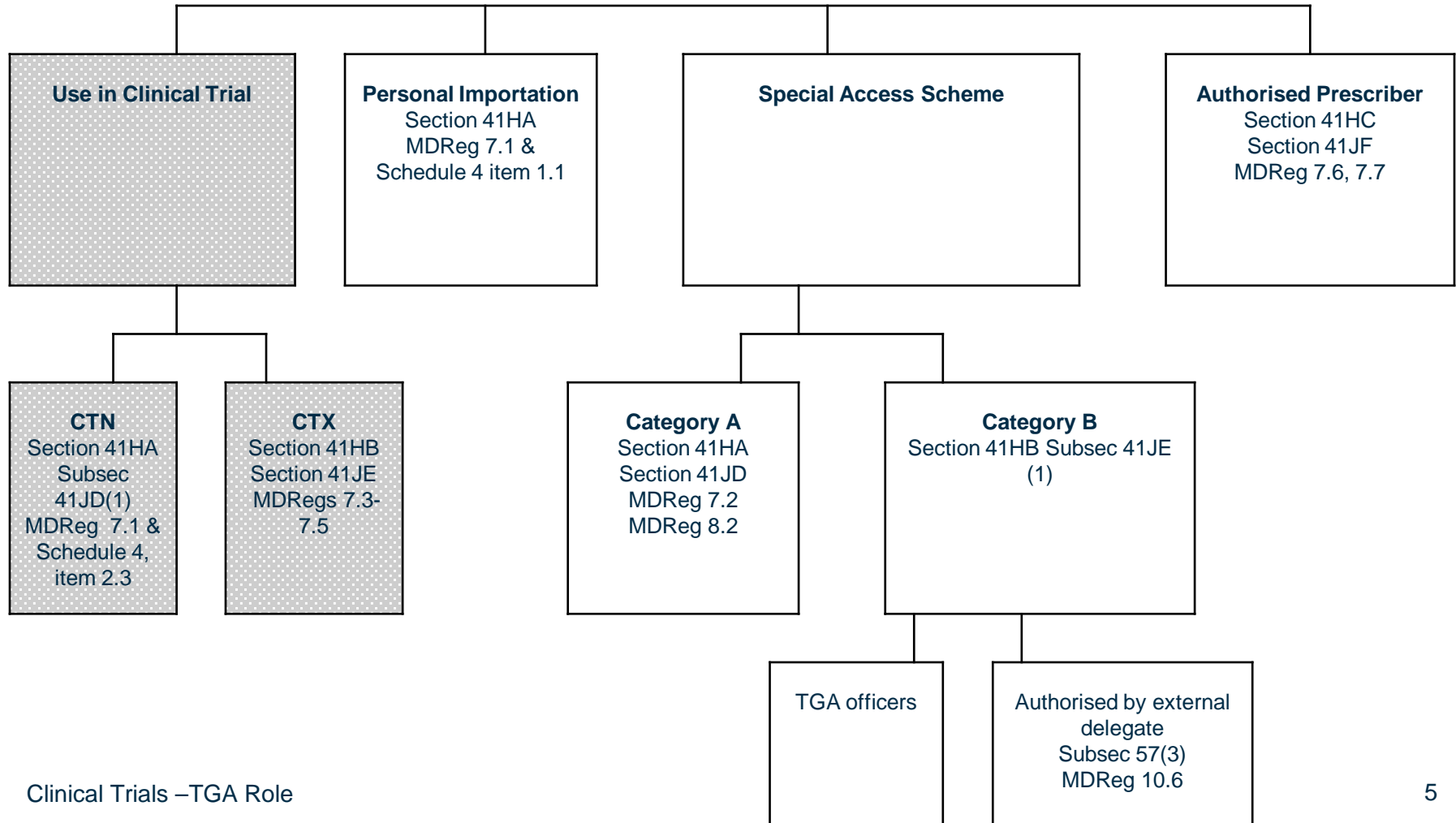


Access to unapproved medicines





Access to unapproved medical devices





Special Access Schemes

Category A

- Defined in the Regulations and Medical Device Regulations as **“persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment”**
- Notification by doctor of use of unapproved therapeutic goods on an individual patient

Category B

- Category B all other patients
- Application for a nominated doctor to prescribe an unapproved therapeutic good to a nominated patient for a specific condition



Authorised Prescriber Scheme

Application for a nominated doctor to prescribe an unapproved therapeutic good for a specific condition to any patients with that condition

- Requires ethics approval
- Requires a protocol
- Requires informed consent

To be an Authorised Prescriber the medical practitioner must:

- Have the training and expertise appropriate for the condition being treated and the proposed use of the product;
- must be able to best determine the needs of the patient; and
- to monitor the outcome of therapy.

An Authorised Prescriber is allowed to supply the product directly to specified patients under their immediate care and not to other practitioners who prescribe/administer the product. Use of the product under an authorisation must be at all times in line with the conditions specified in the authorisation.

Once a medical practitioner becomes an 'Authorised Prescriber' they do not need to notify the TGA when they are prescribing the unapproved product, however they must report to the TGA the number of patients treated on a six monthly basis.

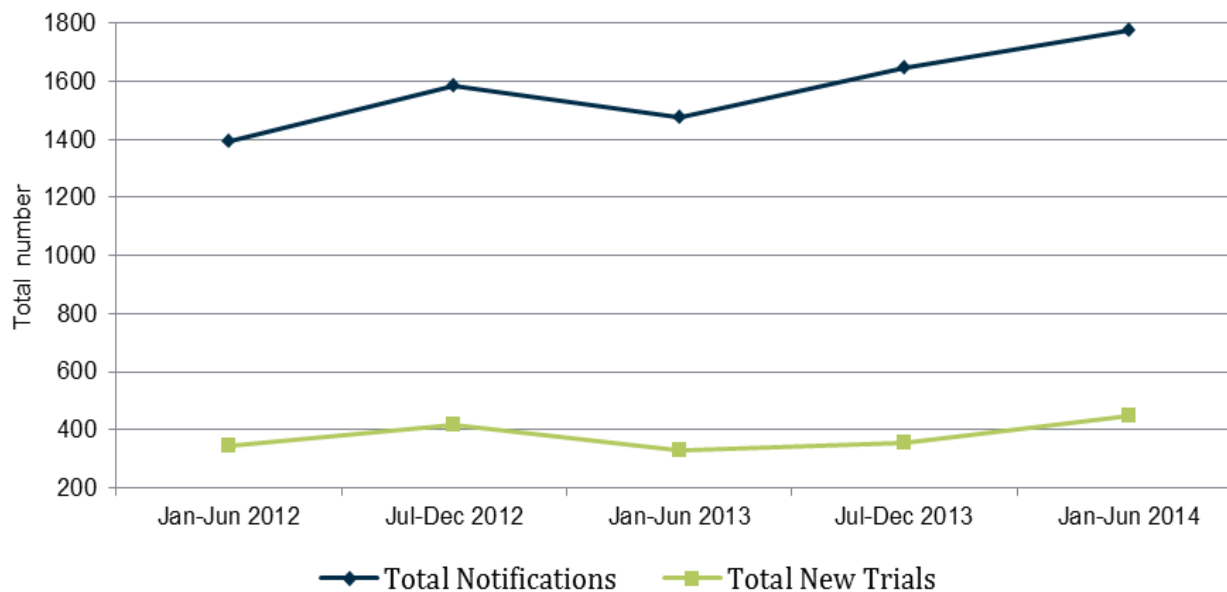


CLINICAL TRIALS



New trial notifications that include a medicine or biological (single & multi-site trials)

	2012		2013		2014
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun
Total	343	416	326	355	449





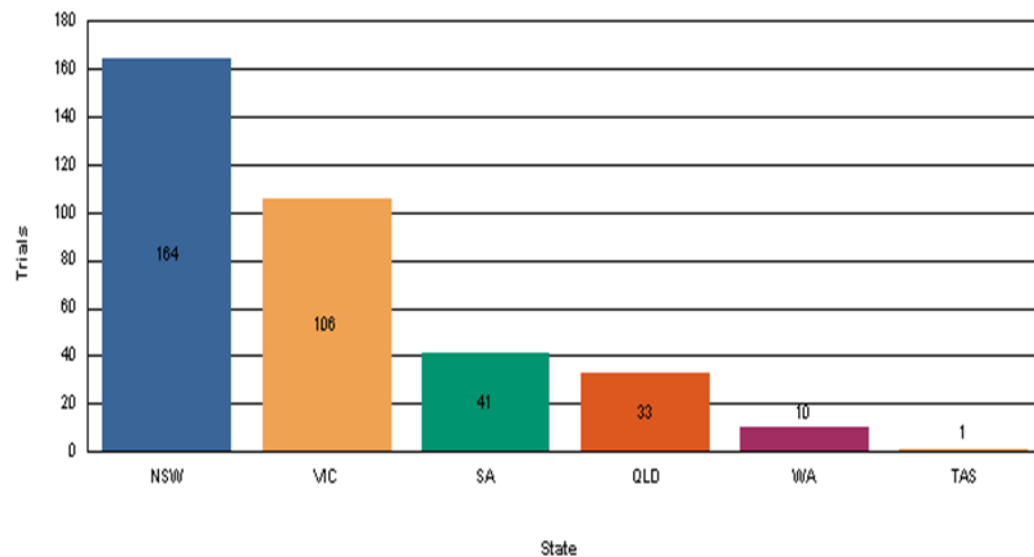
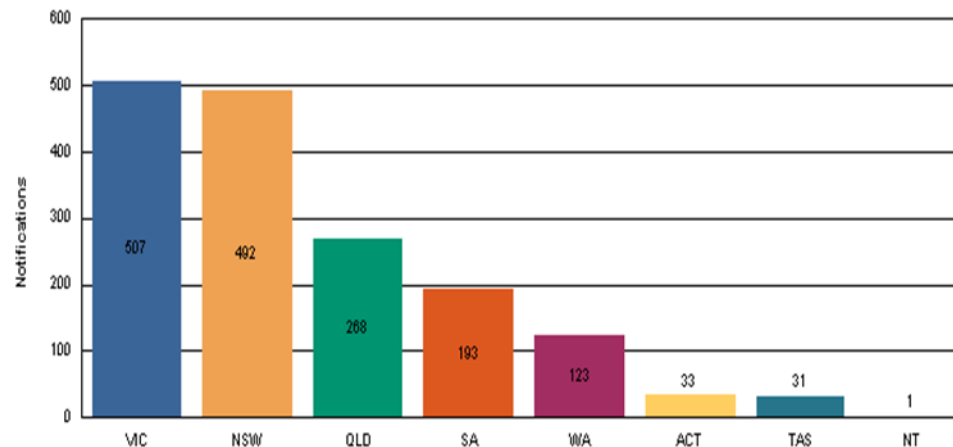
New trial notifications received that include a medical device or biological

	2012		2013		2014
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun
Number of notifications received – medical devices	130	165	168	199	153
Number of notifications received - biologicals	4	9	4	6	6



Clinical Trial Statistics 1 July 2013 – 31 December 2013

Total Notifications – 1,648
Total New Trials - 355





New trial notifications that include a medicine or biological received by phase (single & multi-site trials)

	2012		2013	
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec
Phase 1	55	85	65	132
Phase 2	84	128	86	102
Phase 3	143	155	131	70
Phase 4	43	34	28	32
Bioavailability/equivalence	3	5	4	5
None specified	15	9	12	14
Total	343	416	326	355



Clinical Trial Regulation in Australia

- Access to unapproved therapeutic goods in Australia is regulated under:
 - Therapeutic Goods Act 1989
 - Therapeutic Goods Regulations 1990
 - Therapeutic Goods (Medical Devices) Regulations 2002
- 2 Schemes:
 - Clinical Trial Notification (CTN) Scheme – trial sponsor notifies the TGA of their intention to conduct a clinical trial using an unapproved therapeutic good.
 - Clinical Trial Exemption (CTX) Scheme – TGA reviews information about the product and decides whether or not to approve the proposed Usage Guidelines of the product.



TGA's role in clinical trials differs from some regulators

- Our main focus is on **access to (as yet) unapproved medicines and devices** for trials rather than end-to-end regulation of trials e.g. FDA
- **CTX/CTN schemes** for any product not entered on the ARTG or use of a product in a clinical trial beyond the conditions of its marketing approval
- **TGA is a "user" of clinical trial information in the market authorisation** processes for devices and medicines and biologicals
- **Key references** on TGA website:
 - *Access to unapproved therapeutic goods: clinical trials in Australia, Oct 2004*
 - *Note for guidance on Good Clinical Practice, July 2000 (adaptation of ICH guideline)*



Clinical Trial Regulation in Australia

Notification under CTN Scheme or application under CTX Scheme required where investigational use of a product involves:

- Any product not entered on the ARTG, including:
 - any new formulation of an existing product
 - any new route of administration,
 - in the case of an existing medical device, new technology, new material or a new treatment modality
- Use of a product beyond the conditions of its marketing approval, including:
 - new indications extending the use of a medicine to a new population group
 - extension of doses or duration of treatments outside the approved range.



Clinical Trial Regulation in Australia Standards

- Therapeutic Goods Regulations 1990 – Regulation 12AD
- Therapeutic Goods (Medical Devices) Regulations 2002 – Regulation 7
- Medical Device Standards Order (Standard for Clinical Evidence) 2008

Requires that use of unapproved therapeutic goods for experimental purposes in human be in accordance with:

- National Statement on Ethical Conduct in Human Research, NHMRC, 2007
- The Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95),
- AS ISO 14155 – 2004 Clinical Investigation of Medical Devices for Human Subjects



Clinical Trials Exemption (CTX) and Notification (CTN)

CTX Scheme is an approval process

- Sponsor submits an application to TGA for evaluation of the usage guidelines of the investigational product
- HRECs can require an application to go through the CTX route

CTN Scheme is a notification scheme

- HREC responsible for assessing the validity of the trial design, the safety and efficacy of the product and the ethical acceptability of the trial and for approval of the protocol
- TGA Clinicians informally review protocols, particularly for first in human studies



CTX Mandated in certain circumstances

The CTX Scheme is mandatory for a trial of any Class 4 biological unless:

- Use of the biological is supported by evidence from previous clinical use; or
- Has received clinical trial approval for an equivalent indication from a national regulatory body with comparable regulatory requirements.
- The sponsor is responsible for initially deciding whether a trial should be run under a CTN or CTX scheme. They forward their application to the relevant human research ethics committee (HREC) who reviews the protocol, including the suggested scheme classification. If the HREC supports the current protocol and classification, the HREC provides advice to the 'approving authority', which decides whether the trial should be run. Alternatively, the HREC may recommend the trial be run under the alternative scheme.



Biologicals Classification (Regulation 2)

- *Class 4 biological* means a biological that is:
- (a) processed:
 - (i) using a method in addition to any of the actions of minimal manipulation; and
 - (ii) in a way that changes an inherent biochemical, physiological or immunological property; or
- (b) mentioned in Schedule 16 as a Class 4 biological.
- e.g. Stem cells for cardiac muscular repair (cells isolated from bone marrow); dermal fibroblasts for skeletal muscle repair in primary myopathy (e.g. Duchenne muscular dystrophy)



Schedule 5A Therapeutic goods exempt from the operation of Parts 3-2 and 3-2A of the Act subject to conditions – Biologicals

Item 3 Therapeutic goods used solely for experimental purposes in humans
Conditions

(h) the goods are not any of the following:

- (i) a Class 4 biological that has not received clinical trial approval for an equivalent indication from a national regulatory agency with comparable regulatory requirements;
- (ii) a Class 4 biological that does not have a history of previous usage that is supported by clinical evidence received by the TGA



CTN vs CTX Schemes - Overview

CTN

- Notification process
- One step process to notify
- Can be used for medicines, devices or biologicals
- No TGA review of data prior to trial
- Trial cannot commence without valid notification and fee paid
- Assurances pertaining to the trial conduct and protocol are provided by the sponsor, HREC, PI and AA
- Each additional trial site must be notified before commencing trial at that site

CTX

- Approval Process
- Two step process – Part 1 (approval) Part 2 (notification)
- Can be used for medicines, devices or biologicals but REQUIRED for class 4 biologicals
- TGA must evaluate and approve
- Trial cannot commence without Part 1 being approved
- Assurances pertaining to the trial conduct and protocol are provided by the sponsor, HREC PI and AA
- May conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines.
- Each trial conducted must be notified to the TGA



GCP and GMP requirements for Clinical Trials

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

GCP compliance provides:

- “public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible.”

Requirement for GMP under GCP notes:

- “2.12 Investigational products should be manufactured, handled and stored in accordance with applicable good manufacturing practice (GMP).”



PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-8 Annex 13 Manufacture of Investigational Medicinal Products

“The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.”



GMP issues

Requirement for GMP under GCP:

- Schedule 7 Therapeutic goods exempt from the operation of Part 3-3 of the Act unless supplied as pharmaceutical benefits
 - Item 1 - goods prepared for the **initial** experimental studies in human volunteers
- Generally refers to Phase 1 studies which better suits medicines than biologicals
- In the end sponsor requirement to be assured that they have appropriate GMP for investigational product



Legal Responsibilities

- **All trials under TGA regulation must have an Australian sponsor** - initiates, organises and supports a clinical study and carries the medico-legal responsibility
- If there is a **major protocol change** to the protocol such that the ethics committees require a change to the conditions of their approval a new notification to the TGA may be required
- **TGA has the authority to audit clinical trials** on safety grounds and investigate non-compliance with either Good Clinical Practice guidelines or legislative requirements
- **Sponsor responsible** for reporting serious and unexpected adverse events during trials directly to TGA
 - Clinical Investigators to report adverse events to both HREC and Sponsor



Adverse Event Reporting

Reporter	→ Reports what?	→ To whom?	→ In what timeframe?
Sponsor of trial	Serious and unexpected adverse drug reactions	TGA	<p>For fatal or life-threatening ADRs, send initial report within 7 calendar days of first knowledge. Follow up with complete report within 8 additional calendar days.</p> <p>For all other serious and unexpected ADRs, full report no later than 15 calendar days of first knowledge by the sponsor.</p>
	Other reactions and adverse events	TGA	On request by TGA.
Clinical investigator(s)	Adverse reactions/events	HREC	As required by HREC
		Sponsor of trial	As per study protocol



Guidelines for Clinical Trials

- Before commencement of a clinical trial, all regulatory stakeholders must be satisfied that the conduct of the proposed trial is in accordance with:
 - the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007);
 - the current World Medical Association Declaration of Helsinki;
 - the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) or the ISO 14155 Clinical Investigation of Medical Devices, whichever is applicable;
 - the requirements of the Therapeutic Goods Administration as outlined earlier and
 - any requirements of relevant Commonwealth and/or State/Territory laws.
- In addition, generally, a facility manufacturing therapeutic goods, including Investigational Medicinal Products (IMP) and placebo, for supply in Australia must comply with appropriate GMP standards and must be licensed accordingly. 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 IMP.



Roles of the Stakeholders in CTN/CTX

TGA Role

- Process CTN Submission and provide acknowledgement as submitted by Sponsor (or review/approve CTX)
- Request IB & P documents for review
- Audit and investigate non-compliance with GCP
- Stop clinical trials
- Collate ADR submissions

HREC Role

- Review all material relating to the proposed trial as supplied by trial sponsor
- Assess the scientific validity of the trial design, the safety and efficacy of the medicine or device, the ethical acceptability of the trial process
- Approve the trial protocol (CTN)

Approving Authority Role

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

Principal Investigator Role

- Personally supervises the trial at that site
- Only makes change to protocol with approval by sponsor/HREC
- Must monitor safety
- Must comply with record management and reporting requirements for adverse events



Roles of the Stakeholders

Sponsor Role

- Must be an Australian entity
- Take overall responsibility for conduct of trial
- Meets or agrees to meet HREC conditions
- Ensures persons conducting trial have appropriate training and experience
- Ensures adequate resources for proper conduct
- Agrees to report all serious and unexpected adverse reactions to the TGA
- Generally submits the CTN or CTX to the TGA and provides payment ('client')

Consumer/Participant Role

- Have an in-depth, informed discussion with their primary health care provider and the researchers regarding the risk/benefit of participation
- Provide informed consent
- Payment may be required
- Ask questions and be informed!



Common issues re developmental drugs/devices

- Lack of understanding on regulatory issues/requirements
- Collecting right data for TGA approval
- Running clinical trials
- Manufacturing licence
- Conformity Assessments for medical devices





TGA does not develop its own clinical guidelines on trial requirements for medicines

- US FDA and European Medicines Agency develop various guidelines on good clinical practice
- To assist sponsors and clinical researchers, TGA does endorse a number of the European guidelines for clinical development of different groups of medicines (although references to EU legislation in those guidelines do not apply)
- TGA is planning to develop clinical guidelines for different types of devices but these will reference international approaches where possible and will not be prescriptive
- Conduct of clinical trials to International standards of Good Clinical Practice is able to be monitored by TGA - see www.tga.gov.au/pdf/clinical-trials-handbook.pdf



Collecting data

- Ensuring right information is collected that will allow submission to TGA/FDA/EMA
- Requires consideration when designing trial
- Different data to PBAC/MSAC requirements but pre-requisite



Online submission of CTN / CTX

- Currently paper driven
- Re-entered into a database
- Online process through TGA E-Business portal
- Will be after sponsors to trial it in early 2015



Questions?



Australian Government

Department of Health
Therapeutic Goods Administration