

**MODULE TWO:  
PROJECTS INVOLVING DRUGS & THERAPEUTIC  
DEVICES – GUIDELINES**

**GUIDELINES**

These guidelines provide information and instructions on how to best answer the questions in the **Module Two: Projects Involving Drugs & Therapeutic Devices Form**. Refer to these guidelines when answering each of the questions in the form.

The application forms and guidelines are modified and updated from time to time. Please go back to the website each time you make a new application, to ensure that you have the latest version of this Module.

It is important to include all relevant information so that your application can be assessed for approval without delay. It is also important to write in clear, everyday English so that the members of the Human Research Ethics Committee (HREC) who do not have a science or health industry background can easily understand your answers. Clearly define all terminology and abbreviations. **All pages must be clearly numbered.**

With the Form, you must also include:

- One copy of the Module Two Checklist (last page of the Form);
- Full Clinical Protocol and Investigator's Brochure (if applicable);

Important Notes:

- Sections may be marked "N/A" (for not applicable) if this is the most appropriate response.

**2.1 Full Project Title**

Please provide the same title as given at question 1.2 in Module One.

**2.2 Detailed Project Protocol**

**(a)** Use the checklist to indicate where in the attached full clinical protocol (page and/or section numbers) the information is to be found. If a particular item is not in the protocol because it is not relevant to the project, tick the box for 'Not Applicable' in the right-hand column.

**(b)** Attach the full clinical protocol to the end of the application form (see *National Statement* 12.2(d)). Also attach any Investigator's Brochure or product information brochure.

The clinical protocol needs to include:

- Summary of previous literature that clearly shows the reason why the project is being undertaken and the potential benefits of its results;
- Primary hypothesis, if appropriate;
- Design of the project, method of randomisation (if appropriate) and sequence of procedures;
- Source of participants, inclusion and exclusion criteria, and method of screening before inclusion;
- Details of statistical analyses and sample size calculations to ensure that the project contains the appropriate number of participants;

- Response variables to be measured and methods used to measure them;
- Major anticipated sources of bias and details of dealing with these;
- Details of contingencies and management of these (for example, the need for code breaking and the need to contact patients if found incidentally to have disease);
- Details of handling of any adverse events should they occur; and
- Details for ensuring confidential handling of records relating to the project and storage arrangements of records for 15 years for adults and 23 years for children.

### 2.3 Type of Trial

If the trial involves a drug, indicate which phase the trial will involve. There are four phases of drug trials:

<p><b>Phase I trials: The first administration of the drug to humans</b></p>	<p>Data from these trials is used to identify the preferred routes of administration for subsequent trials.</p> <p>The drug is administered to small numbers of volunteers, to determine pharmacological activity, tolerance absorption, distribution, metabolism and excretion. The volunteers are usually healthy but may be patients. These projects must be carried out in a closely supervised setting with a laboratory appropriately equipped for specialised monitoring and high degree of surveillance.</p> <p>Approval by recognised regulatory authorities should generally be provided before an HREC can consider a Phase I project as a CTN application. Otherwise, Phase I projects should generally be submitted via the CTX scheme. Please refer to the TGA Guidelines for clarification of the requirements for these schemes.</p>
<p><b>Phase II trials: The first trials of the drug in people with the disorder for which the drug is intended</b></p>	<p>The purpose is to determine efficacy and safety in a small number of patients who are closely supervised.</p> <p>These trials are usually conducted by researchers who are specialists in the disorder and its treatment. By using several doses of the drug, they can establish the therapeutic range and maximum tolerated dose. These principles also generally apply to evaluation of vaccines.</p> <p>Before an HREC can consider the application as a CTN application, the following steps apply:</p> <ul style="list-style-type: none"> <li>• An accepted regulatory authority must have reviewed the data from Phase I trials.</li> <li>• The results must have been documented and available for review by HREC; and</li> <li>• Data must show that the project has a potential benefit that outweighs the possible hazard.</li> </ul> <p>Before an HREC can grant final approval, all Phase I and II project applications need to be considered by and approved by the Institution's insurers.</p>
<p><b>Phase III: Extended clinical trials</b></p>	<p>The purpose is to find out whether the drug confers clinical benefit in the disease states for which effectiveness is to be claimed, with an acceptable</p>

	<p>incidence and nature of adverse events.</p> <p>These projects involve numerous patients and are undertaken by experienced clinical researchers.</p> <p>Phase III projects under the CTN scheme must satisfy the following:</p> <ul style="list-style-type: none"> <li>• An accepted regulatory authority must have approved the drug for marketing or clinical trial for the use, dose, duration of treatment and broad patient groups proposed for the clinical trial. Evidence of this <b>must</b> be provided to the HREC.</li> <li>• The clinical trial must be in Phase III of the accepted clinical project classification, i.e. dates from Phase II projects indicate that the potential benefits of the project outweigh possible hazards, and projects must have been completed, the results documented and available for review by the HREC.</li> </ul>
<b>Phase IV: Post Marketing Projects</b>	<p>These projects involve the use of a drug with an approved indication, formulation and route of administration. They are designed to extend the information developed in pre-marketing projects.</p>

If the trial involves a therapeutic device, indicate whether this is the first use of the device in humans.

The TGA defines a therapeutic device as

*"An instrument, apparatus, appliance, material or other article (whether for use alone or in combination), together with any accessories or software required for its proper functioning, which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means though it may be assisted in its function by such means."*

Projects involving therapeutic devices must be considered by the Institution's insurers before final approval can be given.

Please check with the TGA ([www.health.gov.au/tga](http://www.health.gov.au/tga)) for their requirements for clinical trials of therapeutic devices in Australia.

## **2.4 Registration Status of Drugs**

*Only answer this question if the trial involves a drug.*

**(a)** Indicate whether the drug is registered in Australia by the TGA and, if so, under what name.

**(b)** If the drug is registered in Australia, the TGA may have approved dosage, administration, age group of participants or indications for use of the marketed drug. If this is the case, does the use of the drug in this project differ from the Australian approved product information? If so, justify the unapproved use in this project, including provision of the latest information.

### **Note: Current Regulations versus Grandfather Drugs**

Current government regulations require that a new drug's pharmacological properties and appropriate toxicological studies in animals be demonstrated before administration to humans. They also require extensive clinical studies to evaluate the drug's efficacy

and relative safety before approval for marketing. "Grandfather drugs" refers to drugs that came into clinical use before these government regulations were introduced.

**(c)** Indicate whether the drug has been **registered/licensed/approved for marketing** for the indication proposed in this project by an accepted international regulatory authority. If so, identify the country and/or the regulatory authority that has registered, licensed or approved the drug for this indication.

The following international regulatory authorities are acceptable reviewers of drugs. *Note:* Check that the authorities are also acceptable to the Institution's insurers.

• United States	Food and Drug Administration (FDA) <a href="http://www.fda.gov">www.fda.gov</a>
• United Kingdom	Medicines Control Agency (MCA) <a href="http://www.open.gov.uk/mca">www.open.gov.uk/mca</a>
• Canada	Health Canada's Therapeutic Products Programme_____ <a href="http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/index.html">www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/index.html</a>
• Sweden	Medical Products Agency <a href="http://www3.mpa.se/ie_engindex.html">www3.mpa.se/ie_engindex.html</a>
• New Zealand	New Zealand Medicines and Medical Devices Safety Authority <a href="http://www.medsafe.govt.nz">www.medsafe.govt.nz</a>

**(d)** Indicate whether the drug has been **registered/licensed/approved for marketing** for an indication other than that proposed in this project by an accepted international regulatory authority. If so, identify the country and/or the regulatory authority that has registered, licensed or approved the drug for this indication and provide details of the other indication(s) for which the drug has been registered, licensed or approved.

**(e)** Indicate whether the drug has been **reviewed for investigational or research purposes** by an accepted international regulatory authority. If not, do not answer any further parts of this question, but move directly to question 2.5 (if applicable) or 2.6. If "yes" give details of the investigational or research purposes for which the drug has been reviewed.

**(f)** In its review of the drug, did the international regulatory authority raise any objections to any aspect of the drug? Provide details.

**(g)** Have all issues raised by the international regulatory authority been addressed? If no issues were raised, write "not applicable". Indicate whether the drug was approved.

## 2.4 Registration Status of Devices

*Only answer this question if the trial involves a therapeutic device.*

**(a)** Indicate whether the device is included on the Australian Register of Therapeutic Goods. If "no", move directly to question 2.5(c). If "yes", give the name under which the device is included on the register.

**(b)** If the device is included on the ARTG, the TGA may have approved particular applications for the device. If this is the case, does the use of the device in this project differ from the Australian approved product information? If so, justify the unapproved use in this project, including provision of the latest information.

(c) Indicate whether the device has been **registered/licensed/approved for marketing** for the application proposed in this project by an accepted international regulatory authority. If so, identify the country and/or the regulatory authority that has registered, licensed or approved the device for this application.

The following international regulatory authorities are acceptable reviewers of devices. *Note:* Check that the authorities are also acceptable to the Institution's insurers.

• United States	Food and Drug Administration (FDA) <a href="http://www.fda.gov">www.fda.gov</a>
• United Kingdom	Medicines Control Agency (MCA) <a href="http://www.open.gov.uk/mca">www.open.gov.uk/mca</a>
• Canada	Health Canada's Therapeutic Products Programme_____ <a href="http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/index.html">www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/index.html</a>
• Sweden	Medical Products Agency <a href="http://www3.mpa.se/ie_engindex.html">www3.mpa.se/ie_engindex.html</a>
• New Zealand	New Zealand Medicines and Medical Devices Safety Authority <a href="http://www.medsafe.govt.nz">www.medsafe.govt.nz</a>

(d) Indicate whether the device has been **registered/licensed/approved for marketing** for an application other than that proposed in this project by an accepted international regulatory authority. If so, identify the country and/or the regulatory authority that has registered, licensed or approved the device for this application and provide details of the other application(s) for which the device has been registered, licensed or approved.

(e) Indicate whether the device has been **reviewed for investigational or research purposes** by an accepted international regulatory authority. If not, do not answer any further parts of this question, but move directly to question 2.6. If "yes" give details of the investigational or research purposes for which the device has been reviewed.

(f) In its review of the device, did the international regulatory authority raise any objections to any aspect of the device? Provide details.

(g) Have all issues raised by the international regulatory authority been addressed? If no issues were raised, write "not applicable". Indicate whether the device was approved.

## 2.6 Drug/Device Details

The following information is required for each investigational drug or device involved in the project:

- Approved name
- Trade name (if any)
- Manufacturer
- Supplier of drug (eg manufacturer/pharmacy)
- Approved therapeutic indication, dosage/duration in Australia
- Outline of pharmacology
  - Believed mode of action
  - Dosage regimen
  - Mode of excretion
  - Known adverse effects
  - Known contra-indications/warnings

- Concurrent medication which should be avoided
- How long the participants will be monitored for adverse events

## **2.7 Use of Placebo**

Use of a placebo alone or a non-treatment control group is ethically unacceptable in a controlled trial where:

- Other available treatment has already been clearly shown to be effective. Refer to *National Statement* 12.4(a); or
- There is a risk of significant harm in the absence of treatment. Refer to *National Statement* 12.4(b).

If there is genuine uncertainty about the net clinical benefit of treatment, a placebo controlled trial or a trial with a no-treatment arm may be considered. This must be justified in your application.

If a placebo is to be used, provide details of any other effective treatments available for this disease or condition. Indicate whether participants receiving the placebo will also receive any other treatment and indicate whether there is any risk of harm in the absence of treatment.

## **2.8 External Sponsor**

Projects are often initiated by a commercial company or other organisation, for example the company manufacturing the drug or device or another agent conducting the project on behalf of the drug or device manufacturer. These organisations therefore become the "external sponsor" of the project. If no organisation external to the institution is involved, that institution is named as the "sponsor".

## **2.9 Independent Safety and Monitoring Committee**

External sponsors are sometimes expected to establish a safety and monitoring committee of members to oversee the project. The committee oversees analysis of serious adverse events, conduct of interim analyses, and advises on safety, efficacy and other aspects of the project that may have an impact on the wellbeing of research participants. Provide details of any such committees. Indicate whether the committee will be independent of the sponsor.

## **2.10 External Monitors**

Some sponsors provide an external monitor to coordinate the project. Ensure that the Institution's records accessed by these monitors remain confidential.

## **2.11 Supply of Drugs or Devices**

How are the drugs or devices required for this project to be supplied? Has the sponsor or manufacturer agreed to supply these at no charge to the Institution?

## **2.12 Safe Packaging of Drugs**

Ensure safe and secure packaging of trial drugs. *Note:* It is best to use childproof containers. The sponsor is responsible for covering costs of packaging.

## **2.13 Post-Project Use of Drugs**

If it is advisable for participants to continue to use the drug after the project is completed:

- Provide evidence of the benefits and possible harm; and

- Justify the use of the new medication and its advantages over existing therapies.

#### **2.14 Post-Project Cost of Drugs**

If it is advisable for participants to continue to use the drug after the project is completed, has the sponsor agreed to supply the drug to such participants post-project free of charge? If not, what arrangements have been made with the Institution to fund the drugs?

#### **2.15 Post-Project Follow-up for Implantable Devices**

For implantable devices, confirm the existence of or establish a system for:

- Tracking the participant, with consent, for the lifetime of the device; and
- Reporting any device incidents to the TGA. See *National Statement* 12.8(g)

#### **2.16 Clinical Trial Information**

The sub-parts of this question request administrative information in relation to clinical trials.

**(a)** The researcher must determine whether the Institution requires its Pharmacy Department to receive or dispense the drugs involved in the project. If arrangements have not been made with the Pharmacy Department, explain what processes have been put in place to deal with receipt and dispensing of drugs.

**(b)** For all externally sponsored projects, a written Clinical Trial Agreement between the parties involved is required. This Agreement must clearly set out the responsibilities of the sponsor, researcher and the institution, including responsibilities for compensation or treatment of injury or death, and any insurance indemnity to cover the liability of each of the parties. **Check with the HREC about the number of original copies required.** If the Agreement is not attached, please state the reasons.

*The Guidelines for Institutions Participating in the Clinical Trial Notification (CTN) Scheme*, which are a stand-alone section of the *Insurance Manual and Register for Department of Human Services Public Hospitals*, provide further guidance about the information that should be included in a Clinical Trial Agreement. These *Guidelines* will be available on the website of the Victorian Managed Insurance Authority (VMIA). All Clinical Trial Agreements should include reference to the following:

- The commercial sponsor must clearly identify a person ("the Monitor") to be its principal link with the Investigator.
- The commercial sponsor must provide the Investigator and the HREC with accurate, current information about the drug/device prior to the agreement being made.
- The commercial sponsor must monitor the application of the drug/device in other places (elsewhere in or outside Victoria or in other countries) and advise the Investigator, HREC and TGA of the cessation elsewhere of any relevant trial or the withdrawal of the drug/device from any other market for safety reasons.
- The commercial sponsor shall provide a standard form indemnity no less favourable to the recipient than the sample provided in Appendix 1 of these Module Two Guidelines.
- The proper law of any clinical trial agreement is to be that of the State of Victoria.
- The responsibility of the Investigator with respect to reporting adverse events and the maintenance of records.

(c) Applications for projects involving an external sponsor also require an Indemnity Statement signed by the sponsor (see *National Statement 12.7*). An Australian company or an Australian subsidiary or equivalent must provide the indemnity for an international company **Check with the HREC about the number of original copies required**. If the Indemnity Statement is not attached, please state the reasons.

Medicines Australia has produced a standard indemnity form that has been approved by the VMIA. A sample of this form is included in Appendix 1 of these Guidelines.

In the interests of expeditious clinical trial approval, it is strongly recommended that Hospitals require sponsors to use this standard Medicines Australia indemnity, if it is acceptable to the individual institution's insurers and solicitors. Individual institutions or sponsors may wish to use their own indemnity forms. If an indemnity other than the standard form is submitted, it should be in a form no less favourable to the recipient than the wording set out in the sample form and should be sent to the institution's solicitors for approval, at the sponsor's expense.

Further information on Indemnity can be found in *The Guidelines for Institutions Participating in the Clinical Trial Notification (CTN) Scheme*, as described above in part (b).

(d) Provide a copy of the sponsor's Certificate of Insurance. The Institution must be satisfied that sufficient cover is available for both individual and group actions (see *National Statement 12.7*). Specific minimum coverage and other requirements concerning insurance are set out in *The Guidelines for Institutions Participating in the Clinical Trial Notification (CTN) Scheme*. Researchers are strongly advised to consult these *Guidelines*.

(e) For the Clinical Trial Notification (CTN) scheme, only the technical reviewers and the Institution's HREC review the data. The TGA does not review data before allowing the project to proceed. After the HREC has given approval, the sponsor or researcher notifies the TGA that a clinical trial is to be conducted. The blue CTN form is used for this notification. The Chair of the HREC must sign the form before it can be sent to the TGA.

(f) For the CTX scheme, the TGA evaluates the data to assess safety and decides whether the usage guidelines for the product are acceptable. In doing this, the TGA reviews:

- Pharmaceutical chemistry checklist or full pharmaceutical data for biological materials;
- Product information;
- Preclinical data;
- Clinical safety data; and
- Summary documents provided to the HREC, including the usage guidelines.

**Note: Fees payable to the TGA for Clinical Trials**

CTN	\$200 for both single and multi-centre trials
CTX	\$1,100 for assessment of applications when the supporting data relates only to chemical, pharmaceutical and biological issues (requires 30 working days)
	\$13,500 for assessment of applications when the supporting data relates to chemical, pharmaceutical and biological, pharmacotoxicological and clinical issues (requires 50 working days)

The sponsor or researcher is responsible for payment of all legal and regulatory costs for clinical trials. This includes any fee increases.

## APPENDIX 1

### MEDICINES AUSTRALIA FORM OF INDEMNITY FOR CLINICAL TRIALS STANDARD

(For use where the Indemnified Party is providing premises for the conduct of the Study and HREC Review, **or** is providing premises only. NOTE there is a separate Form of Indemnity for use where the Indemnified Party is providing HREC review ONLY of the study)

*This Form has been developed by Medicines Australia and is an adaptation of the form used by The Association of the British Pharmaceutical Industry (ABPI), for use in Australia. It is to be regarded as the basis for agreements between pharmaceutical companies sponsoring clinical studies and the institution that hosts the study to be conducted. Non-members of Medicines Australia are encouraged to use this Form of Indemnity.*

**To: [Name and address of the legal entity (hospital, institution or authority) in which the Study is to be conducted ("the Indemnified Party")  
Only a single legal entity should be named. Where more than one legal entity is to be indemnified, separate Forms of Indemnity should be used for each legal entity to be indemnified.**

**From: [Name, registered address and Australian Business Number of sponsoring company] ("the Sponsor")**

**Re: Clinical Study No. [ ], [protocol title including name of product]**

- 1 The Indemnified Party agrees to participate in the above sponsored study ("the Study") involving [{patients of the Indemnified Party} {non-patient volunteers}] ("the Subjects") to be conducted by [name of investigator(s)] ("the Investigator") in accordance with the protocol annexed, as amended in writing from time to time with the agreement of the Sponsor and the Indemnified Party ("the Protocol"). The Sponsor confirms that it is a term of its agreement with the Investigator that the Investigator shall obtain all necessary approvals from the applicable Human Research Ethics Committee ("HREC") and the Indemnified Party, where appropriate.
- 2 The Indemnified Party agrees to participate by allowing the Study to be undertaken on its premises or as otherwise agreed, utilising such facilities, personnel and equipment as may reasonably be required for the Study.
- 3 In consideration of such participation by the Indemnified Party, subject to paragraph 4 below, the Sponsor indemnifies and holds harmless the Indemnified Party and its employees, agents, and members of and advisors to its HREC in respect of and against all claims and proceedings (including any settlements or ex gratia payments made with the consent of the parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise) by or on behalf of Subjects (including their dependants and children injured *in utero* through the participation of the child's mother in the Study) against the Indemnified Party or any of its employees, agents or members of and advisors to its HREC for personal injury (including death) to Subjects (and children injured *in utero* through the participation of the child's mother in the Study) arising out of or relating to the administration and/or use of the product(s) under investigation or any clinical intervention or procedure provided for or required by the Protocol to which the Subjects would not have been exposed but for the participation of the Subjects in the Study.
- 4 The above indemnity by the Sponsor will not apply to any such claim or proceeding referred to in paragraph 3 above:

- (1) to the extent that such personal injury (including death) is caused by the negligent or wrongful acts or omissions or breach of statutory duty of the Indemnified Party or any of its employees, agents or members of and advisors to its HREC.
  - (2) to the extent that such personal injury (including death) is caused by the failure of the Indemnified Party, its employees, or agents to conduct the Study strictly in accordance with the Protocol.
  - (3) unless as soon as reasonably practicable following receipt of notice of such claim or proceeding, the Indemnified Party notifies it to the Sponsor in writing and at the Sponsor's request, and cost, has permitted the Sponsor to have full care and control of the claim or proceeding using legal representation of its own choosing.
  - (4) if the Indemnified Party, its employees, agents, or members of and advisors to its HREC have made any admission in respect of any such claim or proceeding or taken any action relating to any such claim or proceeding prejudicial to the defence of any such claim or proceeding without the written consent of the Sponsor. Such consent will not be unreasonably withheld. This condition will not be treated as breached by any statement properly made by the Indemnified Party, its employees, agents, or members of and advisors to the HREC in connection with the operation of the Indemnified Party's internal complaint procedures, accident reporting and quality assurance procedures or disciplinary procedures or where such statement is required by law.
- 5 The Sponsor will keep the Indemnified Party and its legal advisers fully informed of the progress of any such claim or proceeding, consult fully with the Indemnified Party on the nature of any defence to be advanced and not settle any such claim or proceeding without the written approval of the Indemnified Party which approval is not to be unreasonably withheld.
  - 6 Without prejudice to the provisions of paragraph 4(3) and 4(4) above, the Indemnified Party will use reasonable endeavors to inform the Sponsor promptly of any circumstances of which it has knowledge and which may reasonably be thought likely to give rise to any such claim or proceeding and will keep the Sponsor informed of developments in relation to any such circumstances even where the Indemnified Party decides not to claim indemnity from the Sponsor. Likewise, the Sponsor will use reasonable endeavors to inform the Indemnified Party of any such circumstances and will keep the Indemnified Party informed of developments in relation to any such claim or proceeding made or brought against the Sponsor alone.
  - 7 The Sponsor and the Indemnified Party will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding by or on behalf of Subjects (including their dependants and children injured in utero through the participation of the child's mother in the Study).
  - 8 Without prejudice to the foregoing, if injury is suffered by a Subject while participating in the Study, the Sponsor agrees to adhere to the "Guidelines for Compensation for Injury Resulting From Participation in a Company-sponsored Clinical Trial" published by Medicines Australia and will request the Investigator to make clear to the Subjects that the Study is being conducted subject to those Guidelines.
  - 9 For the purpose of this indemnity, the expression "agents" is deemed to include, but is not limited to:

- (1) any person carrying out activities for the Indemnified Party under a contract connected with such of the Indemnified Party's facilities and equipment as are made available for the Study under paragraph 2 above; and
- (2) any health professional providing services to the Indemnified Party under a contract for services or otherwise.

10 This indemnity will be governed by and construed in accordance with the laws applicable in the State or Territory in which the Indemnified Party is established.

DATED the        day of        in the year        .

SIGNED by a duly authorised representative of the Sponsor

.....  
(Signature)

.....  
(Position)

SIGNED by the Chief Executive or a duly authorised representative of the Indemnified Party

.....  
(Signature)

.....  
(Position)