1. PURPOSE

This standard operating procedure (SOP) describes the process to manage investigational product (IP) for a clinical trial in accordance with the applicable regulatory requirements.

An IP is any investigational medicine, medical device, complementary medicine, comparator/s or placebo being tested or used as a reference in a clinical trial. This also includes all previously stated products if they have a marketing authorisation, when used or assembled in a way different from its approved form or different from the approved indication. or when used to gain further information about an approved use.

1. SCOPE

This SOP is applicable to all persons involved in conducting clinical trials.

1. REFERENCES

* Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)-Annotated with Australian Therapeutic Goods Administration (TGA) comments, Drug Evaluation and Safety Branch (DESB) July 2000.
* INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) Current Step 4 version dated 9 November 2016
* Therapeutic Goods Administration (TGA) Access to Unapproved Therapeutic Goods – Clinical Trials in Australia 1 Oct 2004

<https://www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia>

* TGA PIC/S Guide for Good Manufacturing Practice for Medicinal Products, PE009-13 2017 as of Jan 2018.

<https://www.tga.gov.au/publication/manufacturing-principles-medicinal-products>

1. DEFINITIONS

* **AQIS:** Australian Quarantine and Inspection Service.
* **Importer:** Party responsible for importing and shipping the IP.
* **Investigator:** A person responsible for the conduct of the clinical trial at a trial site. The principal investigator (PI) is the Investigator with overall responsibility for the conduct of a study at one or more sites.
* **Receiver:** Storage facility, approved by the sponsor to receive IP.
* **Sponsor:** An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.
* **Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical trial and under whose immediate direction the investigational product (IP) is administered to, dispensed, to or used by a subject. The term does not include any person other than an individual (e.g. it does not include a corporation or agency). The obligations of a sponsor-investigator include both those of a sponsor and of an investigator.

1. Appendices

* Appendix A – Investigational Product Labeling Checklist
* Appendix B – Investigational Product Dispensing and Accountability Template
* Appendix C- Subject Dispensation Template
* Appendix D- Investigational Product Relabelling Template
* Appendix E- Investigational Product Temperature Excursion at Site Template
* Appendix F- Transfer of Investigational Product Between Sites Template

1. procedure
   1. release of ip
      1. IP can be delivered to site once the following conditions have been met:

* Written acknowledgment of the receipt of the Clinical Trial Notification (CTN) by the Therapeutic Goods Administration (TGA).
* applicable certification stating the IP is manufactured according to Good Manufacturing Practice (GMP), or GMP-like in cases of phase I studies in Australia, and if required, any blinding is ensured through IP size, shape, colour, taste or packaging.
* A Certificate of Analysis is made available to document the identity, purity and strength of the IP to be used in the trial.
* Availability of the essential documents required before the start of a trial in accordance with GCP section 8.2 (refer SOP: Site Initiation and Activation).
  + 1. Once the sponsor has confirmed that the above documents are available, the sponsor may initiate distribution of the IP.
  1. Supply and Handling of IP
     1. The sponsor must provide written procedures for the handling and storage of the IP for the trial. The procedures will include receipt, handling, storage, dispensing, retrieval of unused product from subjects and return or destruction and the documentation thereof (refer SOP: Project Management).
  2. ip labelling
     1. The labelling of all IP, including inner and outer containers, must comply with the TGA requirements set out in TGA Access to Unapproved Therapeutic Goods – Clinical Trials in Australia.
     2. IP label review using the IP labelling checklist in Appendix A will be conducted prior to IP distribution to the sites.
  3. shipping and importation into australia
     1. If the sponsor is designated as the Importer they will in consultation with a shipper/ customs broker, ascertain the need for importation permits from AQIS and prepare necessary importation documents and contract a storage facility, if required.
     2. The sponsor should liaise closely with the shipper to ensure the shipping requirements are understood and appropriate plans made with respect to the shipping conditions and timelines required. In particular, temperature controlled shipments should be considered and validated processes implemented to ensure maintenance and documentation of the required conditions, e.g. temperature logger.
     3. Shipment of IP to Australia should not proceed until a receiver is contracted, notified of the date and time of expected receipt and confirms readiness to receive and store the IP under the correct conditions for the required duration.
     4. If the investigational site (site) is designated as receiver, the site must ensure that the IP is stored under appropriate conditions and quarantined until the appropriate documented regulatory approvals are available and the site is notified in writing that the trial can commence.
     5. Shipping records should accompany each shipment and include a description of the IP, relevant dates, method of shipment, name/ place of sender, batch number, amount and the applicable AQIS permit number (if required).
  4. randomisation Procedures and Unblinding
     1. For blinded trials, the investigator will follow the randomisation procedure as documented in the protocol and should ensure that, if unblinding be required, the code is only broken in accordance with the protocol.
     2. The location and access to randomisation/ emergency unblinding codes and any associated instructions should be controlled meaning that only certain site staff members may have access to the codes, but in sufficient numbers that a team member is always available to access the codes at any time of day including weekends and public holidays.
     3. The investigator must inform the sponsor of the premature unblinding of the IP.
     4. In the event of a randomisation code break, the sponsor will check that applicable procedures were followed, the reasons and events are fully documented and that the investigator is re-instructed if necessary.
  5. accountability of IP
     1. Accountability of the IP rests with the PI or responsible investigator at each trial site.
     2. Investigator responsibilities for the IP will be discussed at the site initiation (per SOP: Site Initiation and Activation) and will include:
* The investigator may assign the responsibility for accountability to a pharmacist or another appropriate individual who reports to the investigator. This must be documented
* Ensuring the site understands correct use and handling/temperature monitoring/secure storage/quarantine/return/destruction of the IP as outlined in the protocol.
* Ensuring the site understands what to explain to the subject (IP usage, storage at home and return to site where applicable).
* All appropriate records must be kept current and on site, preferably in a similar location to the IP (both used & unused).
  + 1. The person responsible for the IP accountability will develop and maintain suitable records and processes for the trial covering IP’s delivery to site, inventory at site, use by each subject, return or destruction of any unused IP.
    2. The overall accountability of IP into and out of the site may be tracked via the IP dispensing and accountability template (Appendix B). Individual subject accountability may be tracked via the subject dispensation template (Appendix C). These templates may be adapted to the differing requirements of each trial, filed in the trial master file (TMF) and may include:
* Protocol, site and investigator identification
* Date of receipt, amount (of kits; packs; bottles; etc.) received, batch number, expiry date, signature, by whom
* subject / randomisation /IP treatment number
* Treatment period (e.g. Visit 1 or Week 1, etc.)
* Initials of the person dispensing, the date, and details e.g. amount, # of bottles etc.
* Initials of the person to whom returned, the date, and details e.g. amount, # of bottles etc.
  1. re-labeling of ip
     1. Should the IP require relabelling for the extension of expiry dates relabelling forms used by the site should include:
* Protocol, site and PI reference,
* IP identification, affected batch and expiry date,
* Sample of new IP label to be used,
* Procedure for relabelling of IP,
* Reconciliation and checking of relabelling process.
  + 1. The study team will complete relabelling process without obscuring original batch/expiry details and document on IP relabelling form.
    2. The relabelling and reconciliation of labels should be performed by one member of the study team and verified by another.
    3. Appendix D provides a template which may be used for IP relabelling and can be altered for trial specific use.
  1. ip temperature deviations
     1. In the event of a temperature deviation with IP, the affected IP is to be clearly labelled and quarantined.
     2. Details of the temperature deviation should be reported to the sponsor immediately (or as soon as practically possible).
* The Appendix E provides a temperature excursion at site template which may be used for reporting and can be altered for trial specific use.
  + 1. Once the report has been reviewed, the sponsor will communicate to the site what should be done with the IP.
  1. transfer of ip between sites
     1. IP transfer will only occur upon documented approval from the sponsor.
     2. IP should be packaged in a manner similar to how it was initially sent to site (e.g. in a cooler box surrounded with ice bricks) to maintain cold chain / storage temperature requirements.
     3. Temperature monitoring and the equipment used should be similar to the initial shipment of IP to site (e.g. use of a temp-tale device).
     4. IP transfer should be documented.
* Appendix F provides a transfer of IP between sites template which can be altered for trial specific use.
  1. return and/or destruction
     1. The procedure and requirements for return and /or destruction of IP should be documented in the project management plan (refer to SOP: Project Management)
     2. Where IP is to be destroyed locally any country, federal, state and council by-laws, including Environmental Protection Agency (EPA) laws or similar must be complied with at all times.
  2. Filing

All documentation and correspondence will be filed as required by GCP Section 8, Essential Documents (refer to SOP: Essential Documents and Trial Master File).

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| Study: |  | | | | |
| IP Identification: |  | | | | |
| IP Label Version: |  | | | | |
| Requirement | Are Items included on all Labels? | | If No, is item a permissible exclusion? | | Comment |
| Yes | No | Explain | |
| Local Sponsor Name  Contact Details |  |  | N/A, required on all containers | |  |
| Batch/code number to identify contents and packaging operation |  |  | N/A, required on all containers | |  |
| Trial subject identification number |  |  | N/A, required on all containers.  Not required for bulk IP | |  |
| Storage conditions |  |  |  | |  |
| Expiry or Re-test date (month/year) |  |  |  | |  |
| Dosage form |  |  |  | |  |
| Trial reference code (may include Site ID and/or PI) |  |  |  | | Site/PI details can be on external packaging only |
| Route of administration |  |  |  | |  |
| Quantity of dosage units |  |  |  | |  |
| Directions for use |  |  |  | |  |
| “For clinical trial use only” |  |  |  | |  |
| “Keep out of reach of children” Except where product is not taken home by the subject |  |  | Not required for Bulk IP | |  |
| Drug name/identity and strength/potency |  |  | Open Trials Only | |  |
| **Comments:** | | | | | |
| **Checklist Completed by:**  **Name, Position, Signature & Date** | | | | **Checklist Approved by:**  **Name, Position, Signature & Date** | |

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| Protocol No.: |  | Investigator: |  | Site Name & No.: |  |
| IP Name: |  | Form & Strength: |  | Batch No.: |  |

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| RECEIVED | | | DISPENSED | | | RETURNED TO SITE | | | RETURNED TO SPONSOR/DESTROYED | |
| Quantity received | Kit No.: | Date received & initials | Disp’d to Subject No.: | Quantity dispensed | Date disp’d & initials | Quantity returned | Date returned & initials | Verification (initials & date) | Quantity | Verification (initials & date) |
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| TOTAL RECEIVED: | | | TOTAL DISPENSED: | | | TOTAL RETURNED TO SITE: | | | TOTAL RET/DES: | |
| COMMENTS:  Site Signature & Date: | | | | | | | | | | |

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| Protocol No.: |  | Investigator: |  | Site Name & No.: |  |
| Subject No.: |  | Subject Initials: |  |  |  |

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| DISPENSATION | | | | | | | RETURNED TO SITE | | | VERIFICATION |
| Date Disp’d | Kit No. | Quantity | Batch No. | Expiry Date | Dispensed By | Checked By | Date Returned | Quantity Returned | Checked By | CRA (initials & date) |
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| COMMENTS:  Site Signature & Date: | | | | | | | | | | |

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| --- | --- | --- | --- | --- |
| ***PROTOCOL:*** |  | | | |
| ***Investigator & Site:*** |  | | | |
| ***IP Identification (form, strength):*** |  | | | |
| ***Affected batch and expiry:*** |  | | | |
| ***IP Label Version:*** |  | | | |
| ***Sample of label*** | ***STICK ONE***  ***LABEL HERE*** | | | |
| ***Directions:*** | 1. *Assemble all IP with affected batch in one area* 2. *Re-label affected IP without obscuring batch number and original expiry date.* 3. *Document label reconciliation and verification* 4. *Send copy to sponsor and file original in Pharmacy file* | | | |
| ***(A) Number of labels received:*** |  | ***LABEL RECONCILIATION***   1. ***– (B) – (C) – 1 sample label =*** | | |
| ***(B) Number of labels used:*** |  |
| ***(C) Number of labels destroyed:*** |  |
| ***Relabeling performed by:*** | | | | |
| ***Print Name:*** | | | ***Title:*** | |
| ***Signed:*** | | | ***Date:*** | |
| ***Relabeling verified by:*** | | | | |
| ***Print Name:*** | | | | ***Title:*** |
| ***Signed:*** | | | | ***Date:*** |

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| --- | --- | --- | --- |
| Protocol: |  | Investigator: |  |
| Site Name: |  | Date: |  |
| IP Name: |  | Acceptable Storage Conditions: | □ Frozen (-20°C)  □ Refrigerated (2-8°C)  □ Ambient 25°C (15-30°C)  □ Other\_\_\_\_\_\_ |
| IP Form & Strength: |  |

**Section A (to be completed by Clinical Trial Pharmacy Staff)**

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| --- | --- | --- | --- | --- |
| IP affected | Kit number (if applicable) | Batch | Expiry | Quantity |
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| --- | --- | --- | --- | --- |
| Date of excursion  (DD/MMM/YYYY)) | Max temp reached | Start time | End time | Elapsed time |
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Cause & Description of Event:

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Clinical Trial Pharmacy Staff Name, Position, Signature and Date

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| --- |
| **Send to: + XXXX XXXX**  **QUARANTINE AFFECTED STOCK UNTIL EXCURSION DATA REVIEWED** |

**Section B: To be completed by sponsor**

The affected IP has been reviewed by QC / QA on the suitability for further use.

IP name:

□ The IP material is usable – remove from quarantine and proceed to use

□ The IP material IS NOT usable – remove from stock and store separately until destruction / return can be arranged.

Does a Corrective and/or Preventative Action(CAPA)to be raised? YES□ NO□

Comments:

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Evaluated by:

Name, Position, Signature and Date

Date and time reported to Site & Sponsor:

ENSURE THIS PAPERWORK IS FILED IN THE PHARMACY FOLDER

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| --- | --- | --- | --- |
| Protocol: |  | Sponsor: |  |
| IP Name: |  | IP Form & Strength: |  |
| Transfer from: |  | Transfer to: |  |

**SECTION 1: To be completed by Clinical Trial Pharmacy Dispatching IP**

I confirm that the following IP material has been removed from site inventory and shipped in good condition and at the appropriate storage temperature.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| IP Name | Batch | Expiry | Quantity | Storage Temperature:  □ Ambient  □ Fridge  □ Freezer  □ Other: | Temp recorder included?  □ Yes  □ No |
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Date and time IP dispatched:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Clinical Trial Pharmacy Staff Name, Position, Signature and Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**SECTION 2 To be completed by clinical trial pharmacy receiving IP**

I confirm that the above listed IP material has been received:

□ In good condition and within the appropriate storage temperature range

□ In good condition **BUT NOT WITHIN** the appropriate temperature

**IF NOT WITHIN TEMPERATURE RANGE, COMPLETE AN IP TEMPERATURE EXCURSION REPORT AND NOTIFY SPONSOR IMMEDIATELY**

**Comments:**

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Date and time IP received:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_