A Framework for Developing Standard Operating Procedures for Pre-licensure Vaccine Trials in the Northern Territory

Kerry-Ann O’Grady, Fiona Russell & Patricia Hurley

Cooperative Research Centre for Aboriginal & Tropical Health

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# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgements</td>
<td>iv</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Recruitment</td>
<td>3</td>
</tr>
<tr>
<td>Study Visit One – Enrolment</td>
<td>7</td>
</tr>
<tr>
<td>Subsequent Study Visits</td>
<td>11</td>
</tr>
<tr>
<td>Medical/Physical Assessments</td>
<td>13</td>
</tr>
<tr>
<td>Adverse Event Monitoring</td>
<td>17</td>
</tr>
<tr>
<td>Data Management</td>
<td>23</td>
</tr>
<tr>
<td>Vaccine Accountability</td>
<td>27</td>
</tr>
<tr>
<td>Ethics</td>
<td>31</td>
</tr>
<tr>
<td>Administrative procedures</td>
<td>33</td>
</tr>
<tr>
<td>References</td>
<td>36</td>
</tr>
<tr>
<td>Appendices</td>
<td>37</td>
</tr>
</tbody>
</table>
Acknowledgements

This document was prepared at the conclusion of a Feasibility Study for a proposed vaccine trial in the NT and arose from the lessons learned during that process. Many individuals were involved in the Feasibility Study. Particular thanks for assistance with this document are extended to Maryanne Skeljo, Serge De Bartolo and Joanne Wolter at SmithKline Beecham Biologicals, Australia. The Feasibility Study was funded by SmithKline Beecham International (now GlaxoSmithKline).
Introduction

This manual has been designed to assist investigators and study coordinators in the Northern Territory (NT) in preparing implementation plans for industry sponsored vaccine trials, particularly those in pre-licensure phases. It provides the framework for the preparation of study site Standard Operating Procedures (SOPs) which dictate how study procedures are to be performed and study quality is maintained. While aspects of the manual are specific to planning for paediatric vaccine trials in the NT, much of the information can be applied to studies elsewhere for adult populations or even for non-vaccine pharmaceutical trials.

The manual draws heavily on the requirements of sponsors (as stated in study protocols), the International Conference on Harmonisation Good Clinical Practice guidelines (ICH GCP), the National Health & Medical Research Council (NH&MRC) guidelines for the conduct of clinical trials in Australia, and the requirements of the Australian Therapeutic Goods Administration (TGA). These documents are essential reading for all staff involved in the planning and conduct of vaccine or other clinical trials. Similarly, all staff involved in vaccine trials should have access to, and be conversant with, immunisation principles and practices as described by the NH&MRC, and clinical staff should undertake an accredited immunisation training course.

The scientific design, the target population and the environment in which the trials are conducted will to some extent dictate a study’s SOPs. However the framework provided in this document outlines the core requirements of vaccine trials and the essential steps that must be taken. It also provides examples of the detail required in field manuals. Study coordinators are responsible for preparing these manuals, which explicitly state each requirement and/or step to be taken for each aspect of the study. This ensures standardisation of study procedures and provides recourse for action and decision making when difficulties arise.

A glossary of terms has not been included in this document. An excellent glossary is provided in ICH GCP guidelines.
A Framework for Developing Standard Operating Procedures for Pre-licensure Vaccine Trials in the Northern Territory
Recruitment

Aim
To ensure maximum recruitment of eligible subjects into the study

Objectives
- All children in the target population are identified.
- All children in the target population are screened for eligibility to participate.
- Parents/guardians are provided with the appropriate information in an acceptable manner to enable an informed choice about participating in the study.
- All eligible children with appropriate consent are enrolled in the study.
- Accurate screening and recruitment logs are maintained by the investigators and those without personal identifiers are forwarded to study sponsors as required.

Identification of the target population
There are five avenues for identification of children in the NT.

1. Daily visits/telephone calls to maternity units to identify new births.
2. Obtain daily hospital admission reports from the medical records department.
3. Fortnightly data from the NT births, deaths and marriages register can be downloaded from the Business Information Management Unit of THS.
4. The NT Childhood Immunisation Register - NTCIR (children aged 0 - 6 years).
5. Community population registers - usually maintained by local clinics.

If the study is to involve infants, a brief visit to the postnatal ward to give preliminary information to parents is recommended. This allows staff to leave some details about the study, and to inform parents that they will be contacted in the coming weeks to discuss enrolling their child in the study. Similarly antenatal classes are conducted in all urban settings in the NT and they provide a good avenue for raising awareness of the study.

The most appropriate method is dependent on the age range required for the study and how frequently the information is required. Each method has varying degrees of administrative complexity. Option three requires the consent of the mother at the time of birth for the information to be provided to the study. Option four requires approval from the Centre for Disease Control, NT. This information will not include children not born in a DHCS hospital. Children born elsewhere are only included if they have received a vaccination in the NT. Health Insurance Commission data are not recommended due to inaccuracies with Medicare data.

These data form the basis of the study-screening log. The screening log is a record of the target population who are approached and screened for participation in the study. The log forms the basis of a recruitment tracking system and plan which is maintained by the investigators. There are some mandatory fields required by the sponsor that should be determined prior to database development. The sponsor can provide examples.
The screening log should be linked by a unique identifier to the recruitment log, which is a record of all subjects enrolled in the study. Screening and recruitment logs are required to be forwarded to the sponsor on a regular basis and will be audited by their study monitors.

**Screening and recruitment of participants**

Prospective subjects and/or their parents/guardians should have at least one to two information visits from study personnel prior to being enrolled in the study. This allows a cooling off period and time to think about the study in more detail prior to formal written consent being obtained. The consent form should be signed at study visit one. A staged consent process is particularly important in Aboriginal communities.

A typical task list for screening would be:

1. Obtain list of children to be screened from the database
2. Contact parents/guardians - letter followed by phone call. If no phone, arrange home visit.
3. Arrange appointment for screening/information visit
4. If refuse further contact, record date and reason for non-participation on screening log
5. On the day before the visit, confirm appointment
6. Deliver the information package to parents/guardians and obtain consent for screening.
7. Check eligibility criteria.
8. Arrange location, time and date for first study visit if parents indicate willingness to participate and there are no immediately applicable exclusion criteria.
9. Complete appointment card for parents.
10. Arrange review of medical records/vaccination records if required to confirm eligibility.
11. Complete screening log.

**Notes for remote communities**

- Medical records should be reviewed to confirm the absence of any exclusion criteria. This is likely to be more reliable than participant recall. A suitable time and place is to be negotiated with clinic staff. Study staff are responsible for accessing records and returning them to their filing location when reviews are complete.
- Information packages are best delivered in a staged process, and an interpreter and/or community liaison officer should be present at all times.

**Sample recruitment process in remote communities**

*Step 1* - Arrange for groups of parents/guardians to view consent materials (e.g. video and flip charts) in a suitable location. These may include the women's centre, school or council buildings. Inform them that they will be contacted individually in the next few days to go through the patient information sheets. Record attendees on screening logs at each session.
Step 2 - visit parents/guardians who have viewed the consent materials at home to deliver the patient information booklet. Often visits with parents/guardians will occur opportunistically. Recruitment staff should work closely with Community Liaison Officers (CLOs) and be prepared for the recruitment process to take extended periods of time. Staff must be flexible and interviews should be held in locations convenient to the interviewees. Allow at least one hour per interview to deliver the patient information booklets. These booklets remain with parents for their future reference.

![Flowchart](image)

**Figure 1. Overview of recruitment process**

**Consent materials**

Sponsors will probably provide standard formats for patient information sheets and consent forms. Deviations from these will need to be approved by them, as they need to ensure the forms meet ICH standards and internal SOPs. It is mandatory that patient information sheets address the 21 elements of consent as outlined in the World Medical Association’s Declaration of Helsinki. These elements are found in ICH GCP guidelines. The sponsor must also approve videos and/or other visual aids used as well as any translated material.

Patient information sheets are to be read out to the study subject (or their parent/guardian) by study staff prior to written consent being obtained. Information sheets are to be retained by the study subject, together with a copy of their signed consent form.
Study visit one - enrolment

Specific procedures

The following outlines specific steps that would usually occur at visit one:

1. Prepare list of children to be enrolled that day from the screening log.
2. Obtain clinic notes/medical records for the participant.
3. In remote communities, arrange for CLO to collect participants and their medical records.
4. On arrival at clinic, confirm participant details against screening log.
5. Explain sequence of events at study visit.
6. Obtain written informed consent.
7. Check inclusion/exclusion criteria and contraindications and record in study workbook or clinical record (whatever constitutes source documentation) if child to be excluded or inclusion postponed until a later date.
8. Record demographics.
9. Complete medical/physical exam, including body temperature.
10. Liaise with study medical officer if required.
11. Allocate study number - the sponsor will provide blocks of study ID numbers which are used in consecutive order. These may be developed with the sponsor to correspond to specific study groups (e.g. by community, age-group etc).
12. Perform any procedures relevant to baseline or outcome measures.
13. Prepare vaccine as per protocol.
14. Administer study vaccine as per protocol.
15. Record subject details on vaccine packaging and store package.
16. Observe child for 30 minutes and record any adverse reactions.
18. Complete recruitment log proforma.
19. Discuss with parents details of subsequent study visits and record appointments.
20. Give parents the child's study identification card.
21. Apply study identification and Adverse Event (AE) reporting requirements label in child's medical record.
22. Record details of study visit and findings of medical/physical history in clinic or medical record if applicable.
23. Record details of study visit vaccinations on NTCIR Immunisation report form.
General considerations

- The flow of children through a study centre will be dependent on the location in which study procedures are being performed, the type of procedures and available space. In many remote communities it will not be possible to use clinic space and alternative venues such as schools, women’s centres or council buildings will need to be identified. An example is outlined in Figure 2.

- It is preferable to have consent procedures and physical exams performed separately to where injections are being given to avoid child and parental distress.

- In remote communities a CLO should be available at all times to assist with communication, crowd control and observation of children post-study procedures. This may be facilitated by the provision of food and drinks, toys, magazines, videos or other entertainment. It will be important to keep parents/guardians regularly informed of waiting times and anticipated delays.

- At the end of each clinic session, study staff should liaise with local clinic personnel/local medical officer regarding any findings of the physical examination that require follow-up, particularly if minor conditions have been treated. All medical records should be returned to the clinic and filed by study personnel.

Allocating vaccine doses to study participants

Vaccine doses are usually provided in individually numbered packs that contain a single dose of the study vaccine for individual study subjects. The pack numbers will correspond to the unique study IDs given to each participant on enrolment. Staff should ensure that the two numbers correlate.

Depending on the size and design of the study this may not be possible in the NT, particularly given population mobility. An alternative is to create barcode stickers with numbers unique to the particular vaccine dose. These are then inserted in the subject’s workbook and CRF after administration. Liaise with the sponsor’s study monitor to determine the best approach.

Injection technique

Study vaccines should always be given in a separate limb to other concomitantly administered vaccines. This ensures accurate assessment of reactogenicity. If the vaccine is to be given intramuscularly, a 23 or 25 gauge needle, long enough to reach the substance of the muscle should be used (25mm long). The following injection technique is recommended:

**Anterolateral thigh injections**

The needle should be inserted in the upper lateral quadrant of the thigh, directly inferiorly at an angle of 45 degrees with the long axis of the leg, and posteriorly at an angle to the tabletop, with the subject supine. During the injection, the tissues of the injection site are compressed with the free hand, increasing the penetrable muscle mass and stabilizing the extremity. If two injections are to be given in the upper left thigh, they should be separated by several centimetres.

**Deltoid injections**

The best site is the middle of the muscle, which is half way between the shoulder tip and the muscle insertion at the middle of the humerus. The 25mm long needle should be introduced at a 45-60 degree angle pointing towards the shoulder.
**Intradermal**

An intradermal injection deposits the vaccine into the dermal (top) layer of the skin. The usual place is the upper part of the arm at the insertion of the deltoid muscle. To give an intradermal injection, you should stretch the skin tight and keep the needle almost flat along the skin at all times, with the bevel facing upwards. Only the tip of the needle, just past the bevel, should be inserted.

**Subcutaneous**

Subcutaneous injections can be given in the arm or the leg. Hold the syringe in your dominant hand and with the thumb and forefinger of the other hand on the outer edges of the injection area, pinch up the skin. Insert the needle at a 45° angle with the bevel facing upwards into the subcutaneous layers.

**General considerations**

- At any visit when scheduled vaccines are to be administered as well as the study vaccine, the scheduled vaccines must be given first in case consent is withdrawn following the first vaccination.
- The vaccinees should be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines. For guidelines on the treatment of anaphylaxis, refer to the Australian Immunisation Handbook 7th Edition. These guidelines should be clearly visible in all locations where vaccinations are performed.

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![Diagram](image-url)

**Figure 2. Example of procedures in remote communities**
Subsequent study visits

Timing of subsequent study visits is crucial to ensuring that a subject enrolled in the study remains evaluable as per study protocol. Minimum and maximum time periods between visits specified in the protocol must be adhered to.

Urban subjects in households with telephones should be sent reminder letters at least one week before the scheduled visit, followed by a telephone call one or two days prior to confirm the time and location.

In remote communities, subjects should ideally be followed up in the order in which they were recruited. If study staff are not based permanently in the community, the CLO or community clinic should be contacted in the week prior to scheduled visits to ascertain the current location of children due for study visits when the team arrives. Clinics and CLOs should be forwarded subject recruitment logs for children in their community/region following each study visit and on a regular basis (e.g. fortnightly) if there are significant time periods between scheduled team visits, and if recruitment has been occurring in other communities in the region.

If a participant is not in the community in which they were recruited at the time of subsequent visits, the CLO should be engaged to determine where they are. Follow-up for that child should be organised with the relevant community clinic and/or other study staff. A repeat visit to the community may be necessary. If a child is located at another site, study staff should contact head office to obtain the subject’s study ID number and confirm their study status prior to undertaking any study procedures.

Specific procedures - subsequent study visits

The following outlines specific steps that would usually occur at subsequent study visits:

1. Prepare list of children to be accessed that day from the recruitment log
2. Obtain clinic notes/medical records for the participant
3. In remote communities, arrange for CLO to collect participants and their medical records
4. On arrival at clinic, confirm participant details against recruitment log
5. Explain sequence of events at study visit
6. Confirm consent to continue in the study
7. Check elimination criteria and contraindications and record on recruitment log if child to be eliminated or postponed until a later date
8. Record adverse events (Serious Adverse Events and unsolicited Adverse Events)
9. Liaise with study medical officer if required
10. Perform any procedures relevant to baseline or outcome measures
11. Prepare vaccine as per protocol
12. Administer study vaccine as per protocol
13. Record subject details on vaccine packaging and store package
14. Observe child for 30 minutes and record any adverse reactions
15. Complete required details in workbook, CRF and file
16. Complete recruitment log proforma

17. Discuss with parents details of subsequent study visits and record appointments

18. Record details of study visit and findings of medical/physical history in clinic or medical record if applicable

19. Record details of study visit on NT CID Immunisation report form
Medical/physical assessments

Medical histories and physical assessments are required prior to enrolment in the study to ensure that a subject is fit to participate in a vaccine trial. The detail required is usually outlined in the CRF and assessments are usually conducted by medical officers. All conditions which meet the exclusion or elimination criteria stated in the scientific protocol should be highlighted in operating procedures and in CRFs and workbooks.

In the NT, registered nurses may potentially be given the responsibility for undertaking medical histories and examinations. This will be dependent on the size and location of the study, and the skills of staff employed. If this strategy is employed, a “note to file” to the sponsor will be required from the investigator delegating this responsibility. As a minimum, staff should be experienced in paediatric nursing and preferably have remote clinic experience.

The general health status of Aboriginal children in the NT means that many potential study subjects will not be physically well at the time of enrolment. They may have one or more existing illnesses for which they may or may not be receiving treatment. A decision on enrolling these children or excluding will have significant implications for recruitment rates and safety monitoring. Therefore detailed SOPs for the assessment and care of children will be required. These should include the steps to be taken if illness is detected. These steps should be discussed with community clinics and formal agreements reached between clinic staff and the Principal Investigator. Clinical pathways need to be consistent with standard treatment manuals used in the NT such as the CARPA Standard Treatment Manual.

Minor illnesses will generally not be a reason to exclude children from the study. Whether and how these are documented and treated by study staff will impact on the assessment of safety data. Any condition that is identified during the study that was not documented at baseline will potentially be considered an adverse event. Similarly an accurate assessment of the severity of pre-existing conditions at baseline is essential for the detection and reporting of exacerbations of the condition during the study.

Medical and physical assessments should include medical record review to validate or confirm the participant’s history and findings of the physical exam. This will be particularly important for documentation of vaccination history and concurrent medications.

Medical history

1. Review the subject's medical record and document any significant past or current conditions which have been diagnosed by a doctor
2. Record any current medications
3. Record any previous vaccinations

System Review

A systematic approach to medical history taking should be applied while both interviewing parents and reviewing the medical record. The following definitions apply:

- Allergies: any reaction that results in immediate swelling, wheezing or anaphylaxis
- Cardiovascular: any condition involving the heart or circulatory system, e.g. congenital heart defects, enlarged heart, rheumatic fever
- Cutaneous: any condition involving the skin, e.g. scabies, fungal infections, sores, cellulitis
- Endocrine: any endocrine disorder, e.g. diabetes
• ENT: any condition involving the ears, nose or throat, e.g. deafness, otitis media (acute or chronic), tympanic membrane perforation, grommets, congenital defects, dental caries, abstractions or abscesses

• Eyes: any condition involving the eyes, e.g. trachoma, cataract, squint, congenital defects, infections

• Gastrointestinal: any condition involving the GIT and/or nutritional status, e.g. FTT, stunting, gastroenteritis of any cause, surgery, hepatitis

• Genitourinary: any condition involving the kidneys and genitalia, e.g. congenital conditions, UTI, poststreptococcal glomerulonephritis

• Haematological: any condition involving the blood, e.g. anaemia

• Infectious diseases: other infectious diseases not included in any other category, e.g. chickenpox, glandular fever, rubella, measles, mumps, pertussis

• Musculoskeletal: any condition involving bones and muscle, e.g. fractures, congenital defects, osteomyelitis

• Neurological: any condition involving the nervous system, e.g. cerebral palsy, meningitis, plegias, seizures, febrile convulsions, microcephaly

• Respiratory: any condition involving the respiratory system e.g. asthma, pneumonia, chronic lung diseases, bronchiolitis

Conditions should be documented as past, current or normal. A past condition is one that is completely resolved at the time of enrolment or one for which medication has been taken in the seven days preceding vaccination.

Assessment of current health

It is difficult to obtain detailed medical histories and assessing current health status in cross-cultural settings where English is predominantly a second language. General symptoms relating to irritability, fussiness, drowsiness, and loss of appetite prior to vaccination need to be documented and graded in terms of severity. General danger signs and contraindications to vaccination include a current illness involving convulsions, lethargy, unconsciousness, inability to drink or breastfeed, and excessive vomiting. To standardise measurements it is suggested a question like the following is used.

“Has your baby been the same as other babies, better than other babies or worse than other babies?”

Other symptoms that need to be documented include fever, vomiting, diarrhoea, cough, difficulty breathing, ear problems and runny nose. Severity should be assessed through physical examination and repeating the above question with the parent.

Medical examination

A medical examination needs to be performed on all children prior to vaccination. Normal ranges are listed below. Any child outside the normal range needs to be referred to the study medical officer to determine inclusion/continuation in the study and possibly referral to the clinic for review. Vaccinations can be administered to children with minor illnesses such as diarrhoea and upper respiratory tract infections. All liaison with the study medical officer should occur through the site coordinators in each community/clinic.
Normal ranges

1. Temperature:  
   - axillary < 38.0°C  
   - oral < 38.0°C  
   - rectal < 38.5°C  
   - tympanic on oral setting < 38.0°C  
   - tympanic on rectal setting < 38.5°C

2. Heart rate/min:  
   - 3 - 11 months of age: 100-170  
   - 12 - 24 months of age: 100 - 160  
   - 24 - 47 months of age: 80-130  
   - 4yrs - 6 yrs of age: 70-115

3. Respiratory rate/min:  
   - 2 - 11 months of age: = or < 50  
   - 12 - 60 months of age: = or < 40

4. Ears: the canal should not be inflamed, the drum intact, translucent and pearly grey with normal mobility. Purulent discharge from the ears suggests acute otitis media with tympanic membrane perforation, or chronic serous otitis media.

5. Growth: plot weight and height on the Road to Health Chart. Compare with previous growth. If the child has been previously investigated by a doctor for failure to thrive (FTT), stunting, and/or microcephaly, and a medical cause has been excluded, vaccination can occur providing no other contraindications exist. If the child has a medical cause for any of these, vaccination can continue provided the condition does not conflict with exclusion/elimination criteria. If the child has not been previously investigated, referral to a doctor is required.

6. A child has FTT if they are less than six months of age and have had weight loss or no weight gain over the past month. If the child is six months of age or older FTT is present if they have had weight loss or no weight gain over the past two months.

   Hydration: recent change in body weight provides the most accurate indication of the degree of fluid depletion. Children with severe dehydration have a fluid deficit equal to or greater than 10% of their body weight. This is indicated by any combination of two of the following signs: lethargy or unconsciousness, inability to drink or poor oral intake, sunken eyes, or reduced skin turgor. In a severely malnourished child the eyes may always look sunken, even if the child is not dehydrated.

   Children with moderate dehydration have a fluid deficit equalling 5 - 10% of their body weight. This is usually indicated by any combination of two of the following signs: restlessness/irritability, sunken eyes, drinks eagerly/thirsty and reduced skin turgor. Referral is required and vaccination should be withheld. Children with moderate or severe dehydration should not be vaccinated and should be referred immediately to the clinic for assessment.
Mild dehydration is less than 4% of bodyweight loss. Few clinical signs are evident. Advice regarding the continuation of breastfeeding/oral fluid rehydration should be given. These children can be vaccinated if no other elimination/exclusion criteria exist.

7. Skin: many children will present with scabies or skin sores. Study staff should be able to treat both of these as per standard treatment manuals. Severe cases or other skin conditions should be referred to the clinic for assessment. Minor skin conditions are not a reason for exclusion or delay in vaccination.

Treatment of current conditions by study staff

- Study staff can treat certain conditions detected at screening if a formal agreement has been reached with the community’s clinic staff and/or district medical officer. These may include scabies, headlice, otitis media, and diarrhoea.

- Treatment must follow standard treatment manuals (e.g. CARPA).

- Any decision to treat minor conditions needs to be discussed with the site coordinators and documented appropriately. Community clinic staff must also be informed of the diagnosis, the treatment dispensed and any follow-up that is required.
Adverse events

Adverse event reporting is mandatory in clinical trials to monitor the safety of the investigational product. Adverse events may be serious (SAEs) or non-serious (AEs) and their management differs accordingly. While GCP guidelines dictate the timeliness, nature and extent of reporting of adverse events, sponsors may have additional requirements or more specific definitions of adverse events that study staff must be conversant with. These will usually be outlined in the study protocol.

Study coordinators/investigators should read the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) which is available from the Therapeutic Goods Administration.

Serious Adverse Events

Definition

Any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacitation
- Requires in-patient hospitalisation, or prolongs of hospitalisation
- Is a congenital anomaly/birth defect in the offspring of a study subject
- Is an important medical event that may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above.

SAE Reporting Procedures

1. Parents are given information on SAE definitions and reporting procedures at the enrolment visit. This information can be supported by supplying contact phone numbers for SAE notification on:
   - a study subject identification card, and
   - a type of keepsake such as a key ring or fridge magnet.

2. Parents should be encouraged to contact research staff as soon as an SAE occurs. (A 24hr number/answering machine should be provided).

3. Parents should be solicited for SAEs at the beginning of each study visit.

4. For all visits following enrolment the research staff review the patient’s medical records for SAEs prior to study procedures.

5. Clinic/hospital staff in study regions should be informed of SAE reporting requirements. This can be facilitated by the application of stickers to the front of a study subject’s medical record outlining the requirements. In some situations, alerts may also be placed on hospital patient information systems. Staff should be encouraged to report notification of any SAE to the study coordinator/investigators immediately upon learning of the event.

6. The records of Aerial Medical Services and hospital admissions departments should be checked at least twice per week for evacuations/admissions of study subjects from remote communities.

7. Study staff should phone remote clinics once a week to solicit for SAEs.
8. Once a month, the list of study participants can be crosschecked against DHCS hospital morbidity data to identify any participants who were not identified by the procedures listed above.

**Notification Requirements**

Designated SAE coordinators are responsible for reporting SAEs to the sponsor and Principal Investigator/Study Medical Officer within 24 hrs of the original notification to research staff. It is good practice for the PI/Medical Officer to be contactable 24 hours a day. The PI is responsible for assigning causality and severity and deciding whether the child should be withdrawn from the trial.

The review of SAEs by the Investigator/Study Medical Officer should be done as soon as possible after learning of the SAE.

Usually, the minimum information required for reporting within the 24 hour time frame is:

- Patient identifiers (initials and enrolment number)
- Study vaccine has been administered, and
- Nature of the event.

Adverse event report forms are provided by the sponsor and are included in the CRF.

Adverse events following immunisation are also notifiable in the NT under public health legislation. SAE coordinators should therefore also report adverse events in vaccine trials to the Centre for Disease Control, Department of Health and Community Services.

Adverse events should be documented in terms of a medical diagnosis(es). When this is not possible, the adverse event should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit.

The flow of serious adverse event reports is outlined in the Figure 3. Follow up of the SAE will require access to the participant’s clinic or hospital medical record, and potentially an interview with his/her parents or guardians. Serious adverse events and adverse drug reactions must also be reported to the TGA and the HREC. The sponsor will usually undertake this task.
A Framework for Developing Standard Operating Procedures for Pre-licensure Vaccine Trials in the Northern Territory

Figure 3. Sequence of events - Serious Adverse Event reporting

Staffing

SAE monitoring and follow-up is time consuming and labour intensive. Each event takes on average one working day to address adequately. Studies should therefore ensure that staffing quotas are sufficient to manage the workload. The number of expected events that would usually occur in the study population can be estimated from Hospital Morbidity Datasets and deaths data.
Other Adverse Events

AEs include both reactogenicity data and any other health events reported by the parent/clinic that may be relevant to monitoring the safety of the product. These may be solicited or unsolicited events.

Solicited events generally include reactogenicity data and parental responses to a question such as:

“Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?”

At each visit/assessment, all adverse events either observed by research staff or reported by the parents/guardians of subjects spontaneously or in response to a direct question are generally recorded in the CRF and evaluated by the investigator. The detail to be collected will be decided by the sponsor and will be outlined in the study protocol and in the CRF. Similarly the sponsor will indicate how pre-existing conditions, hospitalisations for elective procedures, or changes in severity or frequency of any of the above are to be managed.

Reactogenicity

Reactogenicity refers to the intensity of localised and systemic symptoms that result from vaccination. Data are usually collected on all subjects enrolled in the study and sponsors will generally have a system for recording and scoring intensity and frequency of these symptoms. These will be outlined in the study protocol.

In many studies, reactogenicity data are collected in diary cards maintained by study subjects or their parents/guardians. They are completed daily, usually at bedtime. This method may not be reliable in Aboriginal communities and interviewer assisted questionnaires will need to be used. Standardisation of measurement will need to be addressed in staff training. Similarly the frequency of parental interviews will need to be carefully considered with respect to resources and budget and the requirements of regulatory agencies.

Local (injection site) adverse events

Symptoms at the injection site that are usually assessed include pain, redness and swelling. Any information collected by interview by study personnel will need to be transcribed into the appropriate pages of the CRF. Study staff should instruct the parent(s)/guardian(s) to contact the investigator immediately if severe signs or symptoms should occur.

General adverse events

Systemic symptoms are generally assessed and recorded for the same period and in the same manner as the local solicited symptoms. These may include:

- Drowsiness,
- Fever,
- Irritability/fussiness; and
- Loss of appetite.

The sponsor will have a system of scoring the severity, intensity and frequency of these events, which will be documented in the protocol.
Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any, to the administration of the study vaccine(s).

The degree of certainty with which an adverse event can be attributed to administration of the study vaccine(s) (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc) will be determined by how well the event can be understood in terms of one or more of the following:

- reaction of similar nature having previously been observed with this type of vaccine and/or formulation;
- the event having often been reported in literature for similar types of vaccines; or
- the event being temporally associated with vaccination or reproduced on revaccination.

Other possible contributors to the event include:

- Medical history
- Other medication
- Protocol required procedure
- Lack of efficacy of the vaccine
- Erroneous administration
- Other causes which must be specified.

Following-up of adverse events and assessment of outcome

Investigators should follow-up subjects with serious adverse events until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject/patient is lost to follow-up; or, in the case of non-serious adverse events, the subject/patient completes the study. Clinically significant laboratory abnormalities as well as any adverse event are followed up until they have returned to normal, or a satisfactory explanation has been provided.

Similarly, any serious adverse event that is brought to the attention of the investigators after the subject has completed the study (or the study itself has terminated) must be reported to the sponsor.

Concomitant vaccine administration

In case of concomitant administration of multiple vaccines and absence of a concurrent control group (e.g. in open label, non-randomised effectiveness studies), it will not be possible to determine causal relationship of general adverse events to the individual vaccines administered. The investigator should, therefore, assess whether the adverse event could be causally related to vaccination rather than to the individual vaccines.

In this situation, discussion needs to be held with the Data Safety Monitoring Board convened for the trial regarding the most appropriate method for monitoring safety. This may occur through comparison of hospital morbidity/deaths data in the study population to those in the general population or non-study regions. In the NT these data can be provided fortnightly by DHCS Business Information Unit.
Data management

Aims
- To ensure data collected in the study is timely, complete, reliable and valid.
- To maintain subject confidentiality.
- To ensure data is available for auditing and regulatory purposes.

Objectives
- Describe the requirements of sponsor, ethics guidelines and regulatory authorities regarding data collection and storage.
- In collaboration with the sponsor, develop standardised data collection instruments.
- Develop instructions regarding the completion and storage of data collection instruments.

Case Report Forms

Sponsors will provide Case Report Forms (CRFs). These are data collection instruments (either paper or electronic) that contain all study specific details for each study subject. CRFs are the formats in which data is transferred to the sponsor’s data management facility. The CRF design/layout cannot be altered or changed and they are the permanent record of a study subject’s history in the study. Completion and storage of CRFs must be consistent with GCP guidelines and the requirements of the sponsor.

Pages in paper-based CRFs are generally produced in carbon-copy triplicate. The top copy is forwarded to the sponsor, the second copy to study headquarters and third is retained at the study site. These are always stored in locked cabinets. If remote data entry (RDE), i.e. electronic CRFs, is used, databases are password protected with access restricted to the investigators and data entry personnel. Data are transferred electronically to the sponsors data management facility where there are cleaned and analysed. A complete dataset can be returned to the study site for local analysis if required.

If any additional information is to be collected by an investigator that is not included in the CRF, additional data forms and databases must be developed by the investigators. These must also be approved by the relevant HREC and by the sponsor. That additional data are being collected must also be stated in the patient information sheets.

CRF procedures

Prior to screening the first potential participant, the investigators are usually required to provide to the sponsor a list showing the signature and hand-written initials of all individuals authorised to make or change entries on CRFs. Similarly, the sponsor must be notified if the authorised individuals should change during the study.

It is the responsibility of the investigator or co-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink fountain or ballpoint pen.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified, where necessary, by the authorised individual making the change. The original entry must not be obliterated, overwritten or erased when a correction is made.
The sponsor will indicate a time frame in which CRFs must be completed by investigators after each study visit or after the last data becomes available. As soon as the subject has completed/withdrawn from the study and the CRF is completed the principal investigator or delegate should sign the study conclusion pages of the CRF to confirm that they have reviewed the data and that the data are completed and accurate. An original (top copy) CRF or log sheets must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

**Load considerations**

- Local workbooks based on the CRF are preferable for remote community settings. This allows additional notes and details to be added, and reduces the amount of data queries from the sponsor that could arise from errors in the CRF. Workbooks (like medical records) constitute source date and must be kept in a locked file where clinic sites are located.

- Workbooks, screening and recruitment logs should be hand delivered to central office on a weekly basis, where staff would be responsible for transcribing data into CRFs and other study database CRFs should be stored in a secure facility at the study’s central headquarters.

- Given mobility between communities, it may be necessary to have copies of pages of the workbooks kept in several sites. This allows data from a visit to be recorded if a subject is located at a centre other than where their original workbook it kept. The page should then be faxed through to head office and to their original study site. This ensures a complete CRF and workbook is kept for every child, regardless of where a study visit occurs.

**CRF Quality Assurance**

Study coordinators and/or investigators should review CRFs regularly for errors and completeness and quality of data. Basic checks should include:

1. Each page/section is completed, legible and signed.
2. Errors have been correctly amended.
3. All header pages have been fully completed.
4. All adverse events are fully recorded.
5. All concomitant medications have been fully and accurately recorded.
6. All source documents that need to be kept with the CRF are in the correct place.

**Source data/documents**

Source data is the place where original study data are recorded. This could be in workbooks, medical records, lab report forms etc. These data should be preserved so that CRFs can be checked against them.

The sponsor's Study Monitors will perform Source Data Verification (SDV) at each visit. The purpose of SDV is to ensure data quality and reliability. The monitor will require ready access to CRFs and source data and may require the assistance of study coordinators in completing the SW.
SDV of CRFs occurs for all study participants. Examples of items usually included in SDV are as follows:

- Demographic data
- Evidence that participation in a trial is recorded in medical records
- Evidence of informed consent
- Evidence that entry criteria have been met
- Documentation of medical history, concurrent illnesses and concomitant medications
- Results of study measurements
- Details of adverse events
- Laboratory reports
- Evidence of correct prescribing
- Numbers of study visits

**Data queries**

Data queries are generated by the sponsor and occur when errors or inconsistencies are detected in the data at the sponsor’s data management facility. They may also arise during site visits by the study monitor and are usually rectified at this time. For the former, the sponsor’s study monitor will contact study sites and completion of specific paperwork is required.

Upon notification of an error the study coordinator is responsible for informing the investigator and for performing or delegating the necessary tasks to address the query. This will require access to source data and/or contacting the local clinic to obtain further information. Corrections are then returned to the sponsor’s study monitor.

Data queries may arise after the study has been completed and study documents have been archived. In this situation, wherever possible, the investigator should assist in clarification or correction of errors detected after study finalisation within 48 hours of their being brought to the attention of the investigator.

In many studies, data queries are frequent and time consuming. Therefore the training of staff in data entry, transcription and the timely completion of CRFs is crucial to minimising the amount of queries that occur.

**Storage of data**

Sponsors generally require the investigator/institution to maintain all study documentation until at least two years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of the clinical development of the investigational product.

Documents and databases should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of the information.
Similarly, the sponsor-specific study documentation should be retained until at least two years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the sponsor. The sponsor should inform the investigator/institution in writing of the need for record retention and should notify the investigator/institution in writing when the study-related records are no longer needed.

The Therapeutic Goods Administration in Australia requires the sponsor to retain records for a minimum of 15 years following the completion of a clinical trial.

Local considerations

The requirements for storage of data and biological specimens from clinical trials may be inconsistent with the principles of research control and ownership in Aboriginal communities (see NH&MRC guidelines for the conduct of research pertaining to Aboriginal and Torres Strait Islander peoples2). In some circumstances, particularly the storage of biological specimens, it may be culturally unacceptable. This issue must be discussed in detail with communities and Aboriginal organisations during the planning phase of the study and formal agreements obtained in writing.

All data/CRFs must always be kept locked in a secure area of the administering institution. At Menzies School of Health Research, archive space must be negotiated with the institute’s Business Manager. The sponsor may also agree to assist with archiving at the completion of the study. This should be negotiated before study start.
Vaccine accountability

Vaccine accountability describes the process of monitoring vaccine supply, storage and usage. It is a requirement of GCP that all doses of vaccines supplied for studies can be accounted for at all times, and accountability processes will always be included in study audits and inspections by the Study Monitor and regulatory authorities.6

Aims

To ensure that all vaccines can be tracked from the point of manufacture through to administration to a study participant, or its final destruction.

To ensure vaccine integrity is maintained.

Objectives

- Maintain documentation of vaccine supply from manufacturer to research staff, and the return of unused vaccines
- Implement best practice vaccine storage and cold chain monitoring procedures
- Identify which vaccine was given to each study participant
- Store vaccine packaging until study completion, or as otherwise directed by the sponsor

Documentation required at the study site

The sponsor will provide vaccine accountability report forms and distribution logs. These are to be maintained by the investigator/pharmacist and must be available for inspection at any time. Specific documentation required includes:

- Details about receipt of supply at the study site and when.
- Evidence that vaccines have been stored in the correct conditions (i.e. cold chain monitoring records.
- Dispensing records, which subjects have received what and when
- Details of returned subject packs and their contents.
- Details of the collection of returned packs by the sponsor.
- Details of destruction of unused vaccines.
- Details of any loss of vaccines or unreturned packs.

Supply and storage of study vaccines

Study vaccines will be delivered by air from the manufacturer. Depending on the size and location of the study in the NT, it is recommended that the research team develop their own storage and distribution system. Given the multiple sites from which vaccines are distributed in the NT, and the multiple courier systems that are used, a central facility facilitates greater vaccine storage and distribution quality assurance.

Use of a central DHCS pharmacy will be dependent on the quantity of vaccines to be stored and most will expect some payment for services provided. Distribution of vaccines from a DHCS pharmacy should be through direct transfer to study staff, or through a contracted courier. Reliance on the current system for distribution of vaccines in the NT will lead to some problems with ensuring timeliness, correct transport procedures and completion of the required vaccine accountability reports.
The sponsor will conduct an audit of the vaccine storage facility prior to the first delivery of study vaccines to ensure it meets GCP standards and the sponsor’s SOPs.

**General procedures**

- The sponsor will provide numbered doses of study vaccines, sufficient to administer the required number of doses specified in the protocol to all study subjects. An additional amount is usually supplied for replacement in case of breakage or bad storage conditions. All vials need to be accounted for on a distribution log provided.

- The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products will be handled and stored safely and properly, that investigational products will only be dispensed to study subjects/patients in accordance with the protocol; that any unused vaccine (including placebo) will be returned to the sponsor.

- At any time the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of usage and returned stocks. Account must be given of any discrepancies.

- Certificates of returns must be signed with the assurance from investigator/pharmacist that all unused dosage forms for the study have been returned - including all opened and unopened packages.

- Unused vaccines will be disposed at the sponsor’s office in accordance with their SOPs.

- The sponsor will collect unused supplies on completion of the study. Used vaccine vials can be disposed on site according to local biosafety standards for disposal of biological waste material.

- In case a vial of vaccine is broken or unusable, the investigator should replace it with a replacement vaccine vial. Although the sponsor need not be notified immediately in these cases, documentation of the use of the replacement vial, and the reason for using it, must be recorded by the investigator on the vaccine administration page of the CRF and on the vaccine accountability form.

**Receipt of vaccines from the manufacturer**

- Enter details of receipt (e.g. time, location, receiver etc) into vaccine distribution log.

- Assess vaccine integrity through inspection of packaging and cold chain monitors.

- Advise sponsor immediately if problems are identified.

- Place vaccines in fridge.

- Notify investigator of receipt of vaccine.

**Storage**

- All vaccines must be stored in a safe and locked place with no access for unauthorised personnel. If using a pharmacy, a locked box must be provided.

- Most vaccines must be kept in the refrigerator (+2°C to +8°C) and must not be frozen.
Guidelines for the storage of vaccines in fridges should be adhered to.

Storage temperatures should be monitored continuously. Fridges should be equipped with digital thermometers and a continuous electronic temperature data logger. Monitoring should occur by:

a) daily recording of the thermometer temperature on a chart (available from the sponsor or the Centre for Disease Control, Darwin); and

b) fortnightly download and review of data logger outputs.

Fridges should be linked to a 24 hour temperature failure alarm system. It is advisable to have a back-up refrigerator in case of power failure/breakdown.

**Distribution**

- Study staff advise pharmacist/vaccine supply coordinator of requirements including ID numbers and amount and time required.
- At time of collection complete details of distribution log with pharmacist.
- Check batch IDs and amounts.
- Ensure vaccines are packed appropriately for transport.

**Transport**

- Vaccines should be transported in portable fridges equipped with digital temperature monitors and data loggers. Several brands are available and the sponsor will assist with selection. The frequency of temperature monitoring is as described above.
- If portable fridges are not available/feasible, vaccines should be packed as specified in The Australian Immunisation Handbook 7th Edition.3

**Use of the vaccine**

- Check heat/freeze monitors included in transport packaging.
- Check subject ID with vaccine ID (or alternatively allocate vaccine ID to CRF).
- Visually check vaccine as per manufacturer’s instructions to assess integrity.
- Administer vaccine as per protocol.
- Dispose of vial in sharps container.
- Record details of vaccine administration in the workbook and the CRF.
- Record details of vaccine administration (i.e. subject ID, date and time) on vaccine packaging.
- Return packaging to pharmacy/central storage site for accounting and recording on distribution log.
“A Framework for Developing Standard Operating Procedures for Pre-licensure Vaccine Trials in the Northern Territory”
Ethics

The NH&MRC has released guidelines on the ethical conduct of research involving humans. The section of the guidelines relevant to the conduct of clinical trials in Australia should be reviewed and understood in the planning phase of the trial. Other documents which dictate the conduct of clinical trials, which should be kept at study headquarters, include:

1. the World Medical Association Declaration of Helsinki;
2. where relevant, the CPMP/ICH Note for Guidance on Good Clinical Practice (CPW/ICH-135/95: Annotated with TGA comments), and the ISO 14155 Clinical Investigation of Medical Device, both of which are available from the TGA; and
3. any requirements of relevant Commonwealth or State/Territory laws.

Ethics Committee Applications in the NT

There are three Human Research Ethics Committees in the NT:

1. **The Top End HREC**
   PO Box 41096
   Casuarina NT 0811

2. **The Central Australian HREC**
   PO Box 2234
   Alice Springs NT 0871

3. **The Tiwi Health Board**
   (the latter relies on approval from the Top End HREC)
   PO Box 4347
   Darwin NT 0801.

Applications are generally expected to be submitted four weeks before the committees meet. In addition to the scientific protocol and ethics application, the following information must also be supplied for pre-licensure pharmaceutical trials:

- study protocol;
- the Investigator’s Brochure (supplied by the sponsor);
- patient Information Sheets and Consent forms and any advertisements; and
- the TGA approval for use of the product in research (supplied by the sponsor).

The sponsor may also require statements from the chairs of the ethics committees that the committees meet ICH GCP requirements and those of the NH&MRC for the constitution and conduct of HRECs, 2:7 and that the committees will accept standard clinical trial indemnity procedures used by sponsors. A copy of this indemnity is provided in the Appendices.
Administrative procedures

Monitoring, auditing and inspections

Monitoring of the study by the sponsor will occur regularly throughout the study. The primary purpose of these visits is to ensure that the study is being conducted according to the protocol, GCP guidelines and company SOPs. Visits may be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject has completed. Monitoring visits occur at a frequency determined by the sponsor but generally once every eight weeks, and they usually take one to two days to complete. The visits entail review of source documents supporting the adequacy and accuracy of CRFs (SDV), review of documentation required to be maintained, and checks on vaccine accountability. Investigators and study coordinators must be available to assist with the inspections.

Audits and inspections can also be conducted by regulatory agencies, particularly if the study is a pivotal trial (i.e. a major contribution to an application for marketing authorisation of a new product). The sponsors Study Monitor will assist investigators in preparing for these.

They will be especially interested in the following items:

- HREC approval;
- Vaccine accountability;
- Approved study protocol and amendments;
- Informed consent of the subjects (written or witnessed oral consent);
- Medical records supportive of CRF data; and
- Reports to the HREC and the sponsor and record retention.

Study files

GCP guidelines specify the minimum documentation requirements for clinical trials. The sponsor will assist in establishing a comprehensive filing system for essential documents. These should be maintained in a secure and central location. They should be readily accessible during monitoring and auditing visits.

Reporting

Detailed reporting before, during and after the trial will be required. These include progress reports to the sponsor, ethics committees, service providers, communities and administering institutions. Reports are deemed essential documents and may be audited.

The roles and responsibilities of all study staff with respect to reporting and documentation requirements should be clearly specified at the start of the planning phase for the trial. A schedule of reports should be developed to ensure continuity, timeliness and completeness of reporting.
All documented internal communications can be considered essential documents and should be retained during the study. These may include faxes, memos, letters, and emails. It is advisable to develop a field manual/guide for internal communications and study policies. An example of the contents of this manual is as follows:

1. names and contact numbers of investigators, study coordinators, SAE coordinators and all study sites;
2. study staff confidentiality agreement statement and proforma;
3. routine field site reporting proforma and calendar;
4. policies for the requisition, supply, use and care of study equipment and vehicles;
5. procedures for the requisition, supply, storage and care of study drug;
6. policies for access to study files, filing cabinets and databases;
7. incident reports, including:
   a) staff and study subject injury or other incident reports;
   b) protocol violation/deviation reports and procedures;
   c) vaccination errors; and
   d) laboratory errors.
8. procedures and documentation pertaining to approvals to deviate from the study protocol; and
9. lines of communication for:
   a) administrative purposes;
   b) protocol questions;
   c) medical questions;
   d) data questions;
   e) adverse events; and
   f) media and public enquiries/complaints.

Human Resources

It is both an ethical and GCP requirement that all staff employed on a clinical trial have the appropriate qualifications and expertise. The investigators will be required to supply the sponsor with detailed CVs for all staff engaged on the project.

Staff training programs must also be comprehensive and ongoing. In the NT, the minimum training requirements for staff prior to study start include:

- Vaccine provider accreditation course (developed by DHCS and coordinated by Staff Development Services at a cost of $50 per person);
- Cross-cultural awareness;
- GCP;
- Bush survival skills and 4WD training;
- Data collection and quality assurance;
• Informed consent;
• Scientific protocol, SOPs and outcome measurements. Protocol Amendments and modifications.

No changes to the study protocol are generally allowed unless discussed in detail with the sponsor and filed as an amendment/modification to the protocol.

Any amendment/modification to the protocol must be adhered to by the participating centre(s) and will apply to all subjects. Written HREC approval of protocol amendments is required prior to implementation (unless the amendment is required for immediate patient safety); administrative changes should be submitted to HRECs for their information only.

Study Termination

The investigators, sponsor and administering institution usually reserve the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible written notification should be tendered within an agreed time period.

Sponsors will have an internal SOP for the termination of a study. Some procedures that can be expected are:

• Written notification to the HREC. A copy of this letter and their response is to be forwarded to the sponsor.
• Written notification to stakeholders such as service providers and communities. Copies of these letters and the distribution list should be forwarded to the sponsor.
• All paper and electronic copies of sponsor specific documents such as the scientific protocol, investigators brochure and patient information sheets are to be returned to the sponsor.
• Screening, recruitment and vaccine accountability logs are returned to the sponsor.
• Any unused vaccine and packaging are to be returned to the sponsor.
• Study files are to be archived in a secure facility.
References


Appendix

GUIDELINES FOR COMPENSATION FOR
INJURY RESULTING FROM
PARTICIPATION IN A COMPANY-SPONSORED
CLINICAL TRIAL

Preamble

The Australian Pharmaceutical Manufacturers Association (APMA) favours a simple and expeditious relation to the provision of compensation for injury caused by participation in clinical trials. The Association therefore recommends that a member company sponsoring a clinical trial should provide a written assurance to the investigator - and through him or her to the relevant Ethics Committee - that the following Guidelines will be adhered to, without legal commitment, in the event of injury caused to a Subject attributable to participation in the trial in question. Non-members of APMA are encouraged to adhere to the principles outlined in these Guidelines. These Guidelines are an adaptation of those used by the Association of the British Pharmaceutical Industry (ABPI), for use in Australia.

1. Basic Principles

1.1 Notwithstanding the absence of legal commitment, the company should pay compensation to Subjects suffering personal injury (including death) in accordance with these Guidelines.

1.2 Compensation should be paid when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the Subject in the trial.

1.3 Compensation should be paid to a child injured in utero through the participation of the Subject's mother in a clinical trial as if the child were a Subject with the full benefit of these Guidelines.

1.4 Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints.

1.5 Where there is an adverse reaction to a medicinal product under trial and injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly by the medicinal product under trial.

1.6 Neither the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the Subject has freely consented (whether in writing or otherwise) to participate in the trial should exclude a Subject from consideration for compensation under these Guidelines, although compensation may be reduced or excluded in the light of the factors described in paragraph 4.2 below.

1.7 For the avoidance of doubt, compensation should be paid regardless of whether the Subject is able to prove that the company has been negligent in relation to research or development of the medicinal product under trial or that the product is defective and therefore, as the sponsor, the company is subject to strict liability in respect of injuries caused by it.

“A Framework for Developing Standard Operating Procedures for Pre-licensure Vaccine Trials in the Northern Territory”
2. **Type of Clinical Research Covered**

2.1 These Guidelines apply to injury caused to Subjects involved in Phase 2 and Phase 3 trials, that is to say, Subjects under treatment and surveillance and suffering from the ailment which the medicinal product under trial is intended to treat but for which a registration or listing approval does not exist or does not authorise supply for administration under the conditions of the trial.

2.2 These Guidelines do not apply to injuries arising from studies in non-patient volunteers (Phase I), whether or not they are hospitalised. Such studies should be subject to a separate contract with participants in the study.

2.3 These Guidelines do not apply to injury arising from clinical trials on marketed products (Phase 4 where a registration or listing approval exists authorising supply for administration under the conditions of the trial, except to the extent that the injury is caused to a Subject as a direct result of procedures undertaken in accordance with the protocol (but not any product administered) to which the Subject would not have been exposed had treatment been other than in the course of the trial.

2.4 These Guidelines do not apply to clinical trials which have not been initiated or directly sponsored by the company providing the product for research.

2.5 Where trials of products are initiated independently by doctors under the appropriate Therapeutic Goods Act 1989 exemptions, responsibility for the health and welfare of Subjects rests with the doctor alone (see also paragraph 5.2 below).

3. **Limitations**

3.1 No compensation should be paid for the failure of a medicinal product to have its intended effect or to provide any other benefit to the Subject.

3.2 No compensation should be paid for injury caused by other registered or listed medicinal products administered to the Subject for the purpose of comparison with the product under trial.

3.3 No compensation should be paid to Subjects receiving placebo in consideration of its failure to provide a therapeutic benefit.

3.4 No compensation should be paid (or it should be reduced as the case may be) to the extent that the injury has arisen:

   3.4.1 through a significant departure from the agreed protocol;

   3.4.2 through the wrongful act or default of a third party, including a doctor’s failure to deal adequately with an adverse reaction;

   3.4.3 through contributory negligence by the Subject.

4. **Assessment of Compensation**

4.1 The amount of compensation paid should be appropriate to the nature, severity and persistence of the injury.

4.2 Compensation may be reduced, or in certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the Subject can reasonably be expected to accept):
4.2.1 the seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warnings given;

4.2.2 the risks and benefits of established treatments relative to those known or suspected of the trial medicine.

This reflects the fact that flexibility is required given the particular Subject's circumstances. As an extreme example, there may be a Subject suffering from a serious or life-threatening disease who is warned of a certain defined risk of adverse reaction. Participation in the trial is then based on an expectation that the benefit/risk ratio associated with participation may be better than that associated with alternative treatment. It is, therefore, reasonable that the Subject accepts the high risk and should not expect compensation for the occurrence of the adverse reaction of which he or she was told.

4.3 In any case where the company concedes that a payment should be made to a Subject but there exists a difference of opinion between company and Subject as to the appropriate level of compensation, it is recommended that the company agrees to seek at its own cost (and make available to the Subject) the opinion of a mutually acceptable independent arbiter, and that this arbiter's opinion should be given substantial weight by the company in reaching its decision on the appropriate payment to be made.

5. Miscellaneous

5.1 Claims pursuant to the Guidelines should be made by the Subject to the company, preferably via the investigator, setting out details of the nature and background of the claim and, subject to the Subject providing on request an authority for the company to review any medical records relevant to the claim, the company should consider the claim expeditiously.

5.2 The undertaking given by a company extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial but not to treatment extended beyond the end of the trial at the instigation of the investigator. The use of unlicensed products beyond the trial period is wholly the responsibility of the treating doctor.

5.3 The fact that a company has agreed to abide by these Guidelines in respect of a trial does not affect the right of a Subject to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Any payment made to a Subject by the Company will be made without admission of liability and Subjects may be asked to accept that any payment made to them is in full settlement of their claims.

5.4 A company sponsoring a trial should encourage the investigator to make clear to participating Subjects that the trial is being conducted subject to the APMA Guidelines for Compensation for Injury Resulting from Participation in a Company-sponsored Clinical Trial and to have available copies of the Guidelines should they be requested.