**[Study name] Monitoring Plan**

|  |  |
| --- | --- |
| **Purpose**   * This monitoring plan has been developed to tailor the monitoring activities of the generic ITCC SOP 5.18 Monitoring as they apply to the [insert name] study. * This is to ensure the monitoring for the [insert name] study meets all the requirements for a pre-registration study, and that the monitoring program is adaptive, comprehensive and focusses on review, training and mentorship. | |
| **Full title:** | ***Specify full title for the study*** |
| **Abbreviated title:** | ***Specify abbreviated title for the study*** |
| **Trial Registration** | *Specify trial registration on ACTRN* |
| **Coordinating  Principal Investigator** | *Name*  *Position*  *Organisation*  *Address*  *Phone*  *Fax*  *Email* |
| **Study sponsor** | *IMPACCT Trials Coordination Centre (ITCC), University of Technology Sydney*  *235 Jones Street*  *Ultimo NSW 2007*  *Australia*  *Email: itcc@uts.edu.au* |

**Definitions**

**Coordinating Centre**

The Coordinating Centre is the IMPACCT Trials Coordination Centre (ITCC) located at the University of Technology Sydney. The National Manager and Project Officer at this centre work closely with the Coordinating Principal Investigator, all Principal Investigators, the local site staff, the Study Statistician, and the Central Randomisation Service to manage the operational study procedures.

**Coordinating Principal Investigator (CPI)**

The investigator who leads the study protocol development. The Coordinating Principal Investigator in a multi-centre study also takes responsibility for the coordination of investigators at different sites.

**Monitoring**

The act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOP’s, GCP, and any applicable regulatory and legislative requirements.

Monitoring is a process internal to the clinical study, where the study management, investigators or other groups within the study can monitor their own progress and ensure that the study complies with internal and external requirements.

This process differs from an Audit which is a process conducted by personnel external to the study. Monitoring enables problems and deficiencies to be detected and corrected at an early point, to be dealt with prior to auditing and to assist sites’ ability to meet study requirements. Monitoring enables the study team to be confident about undergoing an external audit process.

Monitoring of Palliative Care Clinical Studies Collaborative (PaCCSC)/Cancer Symptom Trials (CST) clinical studies is the responsibility of the Coordinating Centre.

**Monitor**

An individual trained in research who has also undergone specific training on audit related activities. Within the ITCC, the monitors include the project officers and research assistants who, in conjunction with the PaCCSC/CST National Project Officer, monitor the PaCCSC/CST/ITCC investigator sites.

The study monitor is thoroughly familiar with the study protocol, investigational product, consent processes and related study requirements.

The study monitor has completed training at the ITCC. The monitor is responsible for:

* Verifying that the principal investigator has adequate qualifications and resources (facilities, equipment and staff) and that these remain adequate throughout the trial period
* Verifying that the principal investigator follows the approved protocol and all approved amendment(s), if any and that the investigator and the site staff are performing the specified trial functions, in accordance with the current approved protocol and any other written agreement and have not delegated these functions to unauthorised individuals.
* Verifying that written informed consent was obtained before each subject's participation in the trial.
* Verifying that only eligible subjects are enrolled
* Verifying that source documents and other trial records including essential documents are accurate, complete, kept up-to-date and maintained.
* Checking the accuracy and completeness of the Case Report Form entries by performing on-site and remote data verification
* Answering study related questions
* Providing additional support to the site in order to successfully complete their
  + Recruitment and regulatory obligations
  + Resolution of outstanding data queries
* Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations
* Documenting and reporting visits
* Completing a monitoring log for filing at the study site.

**Monitoring Log**

A record of all monitoring visits conducted at a specific site for a specific study. The monitoring log is held at each site for each study. It is signed by the monitor at the end of each monitoring visit.

**Monitoring Report**

A written evaluation by the monitor of the outcomes from the monitoring visit.

**Principal Investigator (PI)**

The person responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Principal Investigator is the responsible leader of the team. The Principal Investigator is qualified by education, training and experience to assume responsibility for the proper conduct of the study, is thoroughly familiar with the use of the investigational product and is aware of (and complies with) the applicable regulatory requirements. The qualifications of the Principal Investigator are appropriate to their role in the study.

**NOTE TO INVESTIGATORS**

* ***This study monitoring plan template contains instructions and sample text in italics. Investigators should carefully consider the suggested text under each section, and then modify, remove or replace as appropriate to their study.***
* ***This instruction page should be removed once the study monitoring plan is completed.***

**Procedure**

1. **Trial Summary**

|  |  |
| --- | --- |
| Primary objectives | *The* ***primary objective*** *is to determine …..* |
| Study timelines | *Commence recruitment ….*  *Complete recruitment ….*  *Closure and analysis ….* |
| Planned number of participants | *…. completed to primary endpoint* |
| Planned number of Centres | *….* |
| Participant numbering system | *Study code-site code- screening number*  *(xx-xx-xxx)* |
| External partners | *[Company]* |
| Case Report Form (CRF) | *Paper completion of data collection worksheets, data entry into electronic CRF (eCRF) in online database [specify RDMS]* |
| Data entry and query responsibilities | *Data entry by site staff.*  *Checking, validation and query management by the IMPACCT Trials Coordination Centre (ITCC)* |
| Randomisation | *Developed by [Company/process], central randomisation by a telephone call and follow-up using email by PaCCSC/CST National Manager /delegate or using Randomisation tool in REDCap* |
| Data and Safety Monitoring Committee (DSMC) | *[Details]* |

1. **Trial start up**

*The IMPACCT Trials Coordination Centre (ITCC) will approach and select all trial sites to participate in the trial. The ITCC will facilitate the application for the relevant HREC and local approvals by the individual sites and will provide guidance, as necessary. The ITCC will facilitate the set up and approval of all site agreements and co-sponsorship agreements (if appropriate).*

*The trial will not be allowed to commence at participating sites until all necessary approvals have been granted and all essential documentation listed in Table 1 is confirmed present in the Investigator Site File (ISF) and has been verified by the ITCC.*

***Table 1: Investigator Site Folder documentation***

|  |  |  |
| --- | --- | --- |
| ***Document*** | ***Original kept*** | ***Frequency of update*** |
| *Funding agreement* | *ITCC* |  |
| *Trial registration* | *CPI* | *Annual* |
| *HREC approval* | *Lead site; copies in ISF* | *Annual* |
| *Local approval*  *(Site Specific Assessments)* | *ISF* | *Annual* |
| *CTRA* | *ITCC and ISF* | *On protocol amendment* |
| *CTN* | *Online; copy of acknowledgement in ISF* | *Each new site* |
| *Principal Investigator CV* | *ISF* | *Annual* |
| *Staff Signature and Delegation Log* | *ISF* | *Ongoing* |
| *Individual/Group Training Record* | *ISF* | *Ongoing* |
| *Site Initiation Record of Attendance* | *ISF* | *N/A* |

*The ITCC will work with the site staff to ensure that all required trial materials are present at site in sufficient quantities prior to initiation as detailed in Table 2.*

***Table 2: Quantities of trial material per site***

|  |  |  |
| --- | --- | --- |
| ***Material*** | ***Quantity required*** | ***Re-supply procedure*** |
| *Investigator Site File* |  | *None* |
| *Pharmacy Folder* |  | *None* |
| *Participant Data Collection Worksheet folder* |  | *Download via RedCap Forms and Documents and Print* |
| *Patient Questionnaires* |  | *Download via RedCap Forms and Documents and Print* |
| *Study drug* |  |  |
| *[Other]* |  |  |

1. **Site initiation**

*All sites undergo site initiation prior to the trial starting. The site initiation training is delivered virtually using a web-based video conferencing platform (e.g Zoom or Microsoft Teams) per ITCC SOP 5.7. Site initiation will take the following format.*

1. *Investigators and study coordinators/ study nurses*
   1. *A virtual site meeting presented by the Coordinating Principal Investigator and members of the ITCC team will cover a review of the study protocol highlighting study specific procedures and elements and where representation from each site is required. This meeting will be recorded.*
   2. *A follow-up teleconference will be conducted with the PIs who were unable to attend the virtual site meeting after self-review of the site initiation training materials has been completed.*
   3. *Where staffing changes during the course of the study, further training will be provided to new staff at each site.*
   4. *Additional training sessions will also be provided highlighting an overview of the principles of Good Clinical Practice (GCP), relevant legislation, roles and responsibilities of investigators and site staff and drawing attention to ITCC Standard Operating Procedures (SOPs). These sessions will also cover monitoring and study management including record keeping and essential document filing and maintenance, informed consent, contracts and invoicing and data management including data collection worksheets and data entry. [For new sites, these additional training modules will be presented virtually by the ITCC over a series of short sessions and for existing sites, these training modules will require self-review of the training slides].*
   5. *The training agenda outlines the staff expected to attend each session.*
   6. *The final agenda, listing the final training, the staff in attendance and the training slides will be provided post training.*
   7. *The agenda, attachments and attendance are to be filed in the ISF and Trial Master File (TMF).*
   8. *Any training conducted with other staff after the initial training presentations are to be documented using an individual or group training record form.*
2. *Pharmacies*
   1. *Each pharmacy will be provided with an electronic zip. Folder structure pre-filled with the required template documents .*
   2. *Each pharmacy, including the clinical trials pharmacist and any other person. who may have trial related activities, attend a teleconference where the study protocol and procedures are discussed.*
   3. *Where staffing changes during the course of the study further training will be provided to new staff at each site.*
   4. *A log of the attendees is to be filed in the ISF and TMF.*
3. **Types of monitoring**
   1. **Central monitoring**

*Trial activities will be monitored centrally throughout the trial and will form part of the trial reporting. Central monitoring activities undertaken by the ITCC involve the development and maintenance of two separate REDCap projects for each trial:*

*1. Forms and Documents project: A repository of essential documents including ethics and regulatory documents, HREC approved study documents such as protocol, consent forms, questionnaires and other assessment tools, recruitment and retention materials as well as data collection worksheets, guides and instructions, master documents for the Investigator Site File (ISF) and site initiation training materials.*

*2. Tracking project: This project functions as a Clinical Trial Management tool to internally monitor all aspects of the trial at site level including ethics (central and local) and regulatory approvals, site initiation training and site activation, recruitment, site monitoring including issues and protocol violations as well as invoicing and payments.*

*Central monitoring will include the following:*

1. **Investigator Site File**

*An electronic Investigator Site File (ISF) folder structure containing the ISF index is provided to each PI prior to study initiation.*

*Each site will refer to the Study ‘Forms and Documents’ project in REDCap to access the approved forms and documents for the study and populate the ISF. These documents include but are not limited to:*

* + *Contact details*
  + *Protocol and product information*
  + *Regulatory documents to date including HREC approval letters, Trial Registry listing and approved documents*
  + *Template documents for training, delegations, logs, reporting forms*
  + *Template Participant Data Collection Worksheets and eCRFs*
  + *Questionnaires and licences*

*Updates of these documents and the ISF will be ongoing throughout the study.*

* *The Study ‘Forms and Documents’ project in REDCap will be updated by the ITCC as new study forms and documents become available.*
* *Correspondence related to regulatory approvals and reporting will be copied to the ITCC for review.*
* *Any irregularities, lack of reporting or errors will be addressed by direct communication between the ITCC and the site concerned.*
* *In addition, the ITCC will develop and maintain the Study ‘Tracking’ project in REDCap to ensure each site has ongoing ethical and local approval with the correct study documents.*

1. **Recruitment**

* *Recruitment across the entire study and by site will be monitored via the eCRF database and the Study ‘Tracking’ Project for unexpected high recruitment, general recruitment rates and deviations, and apparent problems (refer also to Guidance 10, Site Management Plan).*

1. **Randomisation**

*For studies utilising Central Randomisation Service:*

* *Notification of randomisation will take the form of an emailed or faxed notice to the ITCC.*
* *This notification will be reviewed against eligibility data for consistency and accuracy.*
* *The randomisation numbering will be checked by the Central Randomisation Service to ensure compliance with the schedule.*
* *For studies with specific timeframes during which randomisation must occur: The time of randomisation, measured as the time of the email request to the Central Randomisation Service, will be documented and reviewed during monitoring activities in order to determine correct protocol procedures were followed. Randomisation must occur within [specify protocol timeframe].*

*For studies utilising Randomisation Tool in REDCap:*

* *The randomisation schedule is uploaded to REDCap and the allocation for each participant is obtained directly by the delegated pharmacist, downloaded and filed in the pharmacy study folder.*
* *Notification of randomisation will take the form of an emailed notice to the ITCC.*
* *This notification will be reviewed against eligibility data for consistency and accuracy.*

1. **Safety reporting**

* *Serious adverse events (SAEs) will be circulated to the ITCC through the submission of a Serious Adverse Event Report (Template 40) and data entry of the event into the [RDMS] within 24 hours of knowledge of the event. Failure of a site to report an SAE to the ITCC within this timeframe will be reported as a protocol deviation, unless the event meets the exemption criteria for 24 hour reporting defined in the protocol.*
* *The onward reporting and follow-up will be tracked and monitored by the ITCC*
* *Individual safety reports will be circulated to the Data and Safety Monitoring Committee (DSMC)/Medical Monitor and* *relevant Scientific Advisory Committee and local hospital Ethics Review Committee for review within 24 hours of the ITCC becoming aware of the event, as applicable. Summary reports will also be circulated at the committee teleconferences to be conducted twice per annum.*

1. **Data quality**

* *The study specific Data Management Plan (Template 10) will be followed.*
* *Data quality checks will include monitoring of data entry for primary outcome, patient safety, regulatory compliance, visit timeframes, eCRF completion rates and accuracy, data validation, data queries and resolution.*

*1. REDCap will be checked via a download and visual review of the data for the following critical data elements*

*• Eligibility*

*• Primary endpoints*

*• Safety*

*• Administration of study medication*

*2. Study termination (Study end/withdrawal/completion)*

*3. Manual check of REDCap data for completeness prior to final invoice payment*

1. **Internal ITCC monitoring**

*In addition to the central monitoring of recruitment site activities, the ITCC will also monitor internal activities within the [insert name] study. These activities will include:*

* *Compliance with SOP 5.18 Monitoring timeframes*
* *Time taken to complete processing of agreements, contracts and invoices*
* *Monitoring study site staff changes including completion of required training and collection of relevant essential documents for new study team members and appropriate maintenance of the staff signature and delegation log (all current staff are listed with stop dates entered for staff no longer on the study).*
* *Outlying information from the tracking of Key Performance Indicators (KPIs) and recruitment*
* *Compliance with requests from the DSMC and relevant Scientific Advisory Committee*
* *Updating of monitoring training skills*
* *Verification of Source Data upon receipt of Source Documents in the form of paper data collection worksheets.*
* *Review site staff completing paper data collection worksheets and performing study assessments are appropriately delegated by the PI by checking against current staff signature and delegation log.*
* *Monitoring study site staff changes including completion of required training and collection of relevant essential documents for new study team members and appropriate maintenance of the staff signature and delegation log (all current staff are listed with stop dates entered for staff no longer on the study).*

1. **Periodic telephone monitoring visits:**

*Periodic telephone calls between the ITCC monitor and site staff (PI and/or primary study coordinator or study nurse) will be performed as remote monitoring visits after the first X participants are enrolled and throughout the study recruitment period (Refer to Figure 1).*

*The first monitoring visit will occur within X days of completion of the second participant. If recruitment is slow, the first monitoring visit will take place within X days of the completion of the first participant. Completion will be defined as reaching primary endpoint (Day X) or the participant’s last visit/contact if withdrawal occurs prior to Day X.*

*A second telephone monitoring visit will be scheduled at all recruiting sites at the study 50% sample size being reached and will include review of the last two participants enrolled at each site when this milestone is reached.*

*An additional telephone monitoring visit will be scheduled at all recruiting sites when the study sample size has been reached (100%) and will include review of the last two participants randomised at each site.*

*More frequent telephone visits may be conducted for high risk sites exhibiting persistent quality issues, reduced protocol/GCP compliance or other trial site issues.*

*[Alternate text for studies requiring additional monitoring): The frequency of subsequent telephone calls will be determined by the recruitment rate and risk assessment of the site; either every X months (only if no new participants have been recruited since the last visit) or after every X completed participants, whichever occurs first. At each scheduled telephone monitoring visit, the monitor will select a random sample of participants to review. Only every X participants enrolled into the study will be monitored. Specific participants may be selected in the event of known issues (reported Protocol violation or significant SAEs). The number of participants monitored may also be increased for high risk sites exhibiting persistent quality issues, reduced protocol/GCP compliance or other trial site issues.]*

*Prior to the scheduled telephone visit, a copy of the most current staff signature and delegation log, training log/records and monitoring log will be requested to facilitate monitoring activities. Preparation for the telephone visit will include a review of received data collection worksheets for participants to be monitored. These will be reviewed for compliance with the ALCOACCEA principles of GCP good documentation practice. Discrepancies within the source documents (e.g. inconsistent dates or data) will be sent to the site for clarification using a corrective action sheet.*

*The focus of the telephone visits will be to review and obtain verbal confirmation that the following data elements are documented in the participant’s medical records/clinical notes:*

*• Informed consent process and documentation*

*• Eligibility including confirmation of admission details, confirmation that all assessments/measures required to confirm eligibility criteria were completed, review of concomitant medications for potentially exclusionary treatments, review of medical assessment for potentially exclusionary co-morbidities/health conditions*

*• Primary endpoints including completion of all required measures and assessments at each visit, checking accuracy of calculated scores for clinician assessments*

*• Consistency of dates and compliance with visit schedule*

*• Compliance with administration of study drug*

*• Safety and adverse events including review of medical assessments such as vital signs/ physical examination and concomitant medications that may indicate unreported adverse events*

*• Study termination: reviewing reason for cessation/withdrawal/completion and verification of the daily assessments in the days prior to that event*

*In addition, the following other items will also be reviewed during the call to assess overall site health and compliance:*

*• Protocol deviations and violations*

*• Recruitment activities, eCRF data entry and completion of participant data collection worksheets*

*• Discuss and resolve issues identified during data verification activities*

*• Site staff changes and resources at the site*

*• Assess any requirement for additional site staff training*

*• Unresolved corrective action items or site issues*

* + - *Recurring issues such as those related to consent, documentation, delegation of duties, and issues related to organisation, access to information or source data*

*• Availability of important regulatory and essential documents in the ISF such as CVs, training records, HREC/RGO documentation, Serious Adverse Event Reports etc*

*Any significant deviation from the planned monitoring timelines will be explained and documented in the monitoring visit report and the monitoring plan amended if appropriate*

*Each participant monitored will have a single page summary completed, which will be filed electronically in the TMF. The completed and returned Corrective Action Sheet will be scanned and filed electronically in the TMF after having been checked for resolution of the errors found.*

*Telephone monitoring visits and documentation will be in accordance with SOP 5.18 Monitoring.*

* 1. **On-site monitoring**

*The majority of the monitoring activities will follow a centralised, risk-based approach. The requirement for and frequency of on-site monitoring visits will be determined by a risk assessment of each site and the application of monitoring triggers or requests by the DSMC/Medical Monitor or the relevant Scientific Advisory Committee.*

*The trigger for on-site monitoring will be determined by the participant enrolment rate, quality issues, trial site compliance or other trial site issues. The triggers for on-site monitoring may include any combination of:*

*• Increased incidence of protocol violations*

*• Continued or sustained deviations from the Data Management Plan such as missed visits, missing participant data collection worksheets or eCRF data entry, numerous data outliers*

*• Where the central documents of the ISF fails to document compliance with regulations, protocol or study administration and review of the on-site file is indicated*

*• Repeated issues related to consent procedures, incorrect PICF use, failure to report Serious Adverse Events, missing primary outcome data*

*On-site visits made as a result of any single or combination of triggers will be preceded by an email and teleconference to discuss the issues, to seek clarification, and to plan ways to redress and avoid future problems.*

*On-site monitoring will involve review of the Investigator Site File (ISF) in full to determine appropriate compliance with filing of essential documents, a review of the participants, and a discussion with the study team regarding:*

* *The protocol, specifically to include any updates or amendments to the study design*
* *Compliance and implementation issues*
* *Recruitment*
* *Compliance and understanding of data management procedures*
* *Additional training as appropriate such as GCP, assessments, equipment, etc.*

*Review of the participant study files and medical records will focus on the following items:*

* *Consent*
* *Eligibility*
* *Data to primary endpoint/cessation, looking at the reason for cessation/withdrawal/completion, and then verification in the daily assessment in the days prior to that event*
* *Safety*
* *Investigational product accountability*

*Each participant monitored will have a single page summary completed, to be filed in the electronic central files, the completed and returned Corrective Action Sheet will be scanned and filed electronically after having been checked for resolution of the errors found.*

*On-site monitoring visits and documentation will be in accordance with 5.18 Monitoring SOP.*

* + 1. **Pharmacy monitoring**

*Each pharmacy will be monitored by a trained unblinded monitor, who will monitor in accordance with established SOPs. This may be through the use of an outsourced provider contracted by the ITCC for the purpose of supply of the investigational product, and pharmacy monitoring. An agreement is to be established for the delivery of these services.*

*The frequency of monitoring will be determined by recruitment rate and the capacity of the pharmacy to hold the returned study drug, to coincide with monitoring of another nearby pharmacy, and the study completion.*

*The pharmacy monitor will provide a monitoring report. This report will determine if there are any actions required by the ITCC to assist the site pharmacy to address the findings. A copy of the report will be filed in the TMF, and a copy will be sent to the pharmacy for filing within the pharmacy study folder.*

# Protocol deviations and violations

*All protocol deviations and violations identified by the ITCC through the completion of central/remote and on-site monitoring activities will be tracked and documented in accordance with SOP 4.5 Protocol Deviations and Violations.*

**Figure 1. Monitoring visit schedule**

File training materials in ISF

Commence Training log

Commence SSDL

**Site Initiation**

**Recruit 2 participants**

**Monitoring trigger**

**Repeat monitoring triggers or major finding**

On-site monitoring

Telephone monitoring

Telephone monitoring

**Central monitoring of:**

**ISF updates**

**Recruitment**

**Safety**

**Data quality**

**50% sample size reached**

Telephone monitoring

(Last 2 participants)

**100% sample size reached**

Telephone monitoring

(Last 2 participants)

**References**

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