## PURPOSE:

The purpose of this Standard Operating Procedure (SOP) is to describe the process for quality assurance reviews of research and clinical trials which are part of research quality improvement and education processes including internal and external audit and inspection.

## SCOPE:

This SOP applies to reviews, audits and inspection by:

1. Internal quality assurance activities - which may be conducted on:

* Any research study conducted at Epworth, including clinical trials, research studies (HREC reviewed and non-HREC pathway studies), and quality assurance (QA) projects.
* Research and clinical trial systems and processes.
* Third party vendors contracted to perform research and/or clinical trial activities for Epworth.

1. Externally conducted reviews, audits, and inspections of research and clinical trial activity:

* Including those conducted by ethics committees, external sponsors, and regulatory bodies.

## APPLICABILITY:

This SOP applies to all Epworth employees, non-employed staff and Visiting Medical Officers (VMOs) and to all relevant external persons and parties engaged in the research or clinical trial activities at Epworth.

## DEFINITIONS:

**Audit** - a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s) – ICH GCP 1.6.

**CAPA** – Corrective and preventive actions identified to understand an event and prevent its reoccurrence. Process documented using a CAPA form.

**CTC –** Clinical Trial Coordinator

**For-cause audit** - audit of a study selected because a complaint, non-compliance, adverse event or other specific issue.

**GCP –** Good Clinical Practice

**OfR –** Office for Research

**On-site audit** – audit of a study conducted by OfR staff.

**Procedural audit** - audit of a process or procedure.

**Random audit**- audit of a study selected on standard risk-based criteria and not selected as a result of a complaint, non-compliance, adverse event or other specific issue.

**Self-audit** – audit of a study conducted by the study team by completion of the audit tool and returned to the OfR.

**Themed audit** – audit of a series of studies (or parts thereof) or processes related to a common theme.

**VMO** - Visiting Medical Officers

## PROCEDURE:

The procedure includes information on:

* When to provide information to the OfR after external reviews, audits and inspection of research and clinical trials are conducted.
* Elements and processes of quality assurance activities conducted by the OfR including defining the annual schedule, planning, preparation, conduct, reporting of outcomes to teams, follow-up and CAPA, organisational reporting.

### 5.1 Reporting External Quality Activities to the OfR

5.1.1 External Quality Activities including external audits and inspection of studies conducted at the Epworth may be undertaken the sponsor, the Human Research Ethics Committees, or a regulatory body.

5.1.2 The study team should provide reports and information on CAPAs or other subsequent improvements resulting from external reviews, audits and inspection of studies to the OfR in a timely manner.

5.1.3 The OfR will maintain a log of externally conducted reviews, audits and inspections.

5.1.4 The OfR will periodically analyse and report on the collected reports and data to identify common outcomes and trends.

5.1.5 Where quality improvement and/or education learnings are identified, the OfR will liaise with internal and external stakeholders to prepare/update processes and information as necessary.

### 5.1.6 The OfR will disseminate the quality improvement and/or education learnings to researchers and research teams and report teams as outlined in 5.7 Reporting Audit outcomes.

### 5.2 Conduct of Internal Audits

In compliance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines1 (hereafter referred to as GCP), audits performed by Epworth HealthCare will:

* be systematic, risk based, and independent examination of study-related activities and documents.
* Aim to establish whether the evaluated study related activities were conducted, and the data recorded, analysed and accurately reported according to the protocol, Epworth procedures and policies, GCP and applicable regulatory requirements.

### 5.2.1 Annual Audit Schedule

The OfR will conduct study audits according to this SOP and the annual Audit Plan provided in Table 1.

The audits may be conducted as random, themed or for-cause audits.

The selection of studies, processes and/or vendors to be audited will be risk-based and including considerations:

* If there is a specific trigger for the audit (i.e., adverse event/s, complaint).
* Type of research i.e., clinical trials are generally classed as higher risk, however risk may vary depending on the individual characteristics of the study, the participants, the study team and other factors listed in this section.
* Quality Assurance projects will not routinely be audited but may be audited in for-cause audits or audits of research systems and processes.
* the number of patients recruited
* the phase/complexity of the study
* the status of the study
* concerns regarding data integrity
* experience of Clinical Trial Coordinator (CTC)/Research Nurse/Coordinator and Principal Investigator (PI)
* turnover of staff
* findings from Sponsors
* high incidence of Serious Adverse Events (SAEs)
* periodic audit cycles
* new vendor; change in location.

Audits will be performed according to the applicable annual Quality Plan prepared and updated from time to time by the OfR and approved by the Group Director of Research and Development. The type and frequency of internal audits may vary, depending on the risk or process being audited. Additional audits may be undertaken if significant potential or actual quality and/or safety issues arise.

The OfR delegate who is ‘independent’ (i.e. not a member of the study team) will act as the auditor.

* **Table 1:** Annuals Audit Plan for internal research audits

|  |  |  |
| --- | --- | --- |
| Audit Type | Planned Audits / year | Conduct/review team |
| On-site audits | 6 | Conducted by the OfR |
| Self-audits | 33 | Conducted by the study team.  Reviewed by the OfR |
| Procedural and themed audits | 2 | Conducted by the OfR with assistance by other Epworth stakeholders as required |
| Third party vendors | As required | Conducted by the OfR with assistance by the study team |

### 5.2.2 Conduct of On-Site Audits

On-Site audits are conducted by OfR staff.

OfR staff will notify the study team of the audit in writing and liaise with the study team to organise the audit schedule and access to documentation, personnel and facilities required for the audit. Audits should be held within two weeks from the date of notification.

The audit may be conducted as on-site, remote or combination of these modes depending on site location and availability of OfR and/or research personnel.

The process for conduct of on-site audits is described in Appendix 1.

**5.2.3 Conduct of Self Audits**

Self-Audits conducted by the study team by completion of the audit tool and returned to the OfR.

OfR staff will notify the study team of the audit request in writing and provide the audit tool, request for any other information and instructions for completing the audit.

The study team will complete the audit tool and gather any other requested information.

The study team should submit the completed audit tool and requested information within three weeks from the date of notification by the completion date.

The OfR will review the submitted information and provide a written response to the study team within 10 business days.

Information to be reviewed by the auditor is dependent on the audit scope and usually includes (but is not limited to):

* HREC approvals (initial and amendment(s))
* Research Governance authorisations (initial and amendments)
* regulatory and ethics correspondence
* the ISF, including Pharmacy documents, if applicable
* Signed participant PICFs
* participant source data
* protocol deviations
* adverse events
* Investigational Product receipt, accountability, storage and disposal
* management of biological samples
* equipment maintenance
* qualifications and training of staff.

Comparison of source data against the data entered into the CRFs (or data collection forms) will occur. The number of CRFs reviewed will be dependent upon the number of participants recruited and the risk profile of the trial.

Trial team members may be interviewed regarding details of the conduct of the study.

The process for conduct of self-audits is described in Appendix 2.

### 5.2.4 Conduct of Research Procedural and Themed Audits

The processes for the conduct of procedural and themed audits will be determined based on the purpose, scope of the audits.

Procedural and themed audits may include, but are not limited to, obtaining Epworth research governance authorisation and other approvals, regulatory requirements (i.e., Therapeutics Goods Administration requirements), consent and consenting procedures, SAE reporting, drug storage, documentation of a study, training processes and compliance etc.

OfR staff will liaise with relevant staff across the organisation as required to request assistance for the conduct of procedural and themed audits. This may include requests for feedback on processes, participation in focus groups/meetings and documentation.

The process for conduct of on-site audits is described in Appendix 3.

### 5.2.5 Research Vendor Audits

As part of the oversight process for vendors, audits of vendors may occur to initially determine whether to use the vendor as well as determining their ongoing suitability for research and clinical trial work. Research and Clinical trial vendors who may be audited include, but are not limited to, vendors providing research and clinical trial services of imaging, data collection/management, pathology and pharmacy.

The OfR will determine the frequency and scope for Vendor Audits in liaison with the Group Director of Research and Development, and Group Director Clinical Governance (as required).

The process for conduct of vendor audits is described in Appendix 3.

### 5.3 Preparation, Approval and Distribution of the Audit Report

The OfR is responsible for the preparation of a draft audit report within 10 working days after the completion of the audit. Audit observations will be classified as:

* **Critical**: Where significant and unjustified departure(s) from applicable regulatory requirements has occurred with evidence that (1) the safety or wellbeing of study participants either have been, or have significant potential to be, jeopardised and/or (2) the clinical data are unreliable. Critical observations may include serious breaches of the protocol or GCP as defined in SOP-QA-02 (see Related Documents). Formal documented corrective and preventive actions are required as per SOP-QA-02. Immediate suspension of the practices or study may be required. Immediate escalation to Epworth senior management is required.
* **Major**: If not resolved or left unaddressed, the observation(s) could adversely impact the safety or wellbeing of study participants or the integrity or reliability of the site’s data. Major observations may include serious breaches of the protocol or GCP. Formal documented corrective and preventive actions are required and site practices must be modified as per SOP-QA-02. Major observations may also include repeated or frequent occurrence of minor findings or known non-compliance which has not been corrected or the corrective action has been ineffective.
* **Minor**: Although requiring attention, the observation(s) would not significantly impact the integrity of the site’s data or jeopardise the safety or wellbeing of the study participants. Documentation of the deviation is required and site education or modification of site practices may be advisable. Formal corrective action is required.
* **Recommendations**: A suggestion (not non-compliance) for improvement to a current process, procedure, operation and/or quality system.

The audit report will be reviewed by the Group Director of Research and Development within 10 working days of receipt from the auditor.

The approved audit report will be distributed to the relevant auditees by the Research Operations Manager.

### 5.4 Auditee Response to the audit report

Internal auditees will be required to review and provide a response to the audit report within 20 business days from receipt of the audit report from the auditor.

The response will include:

* Acknowledgement of the findings by the Epworth PI.
* Responses to the findings appropriate to address the nature and rating of the finding.
* CAPA to manage all findings that require action (as per SOP-QA-02 Management of Serious Breaches and CAPA Process).

**5.5 Closure of the Audit**

Once the auditor deems the responses to the audit report are adequate, the auditor will finalise the audit report and close the audit.

Final, signed audit reports will be stored securely with restricted access in the OfR.

### 5.6 Sharing Audit Observations with Sponsors

The audit report and responses from internal Epworth audits should not generally be distributed to external trial Sponsors.

It is the responsibility of the CTC and/or the PI to communicate with the Sponsor on the audit observations in line with trial-specific requirements. Issues confirmed as critical must be escalated to the Sponsor immediately.

### 5.7 Reporting Audit outcomes

Audit outcomes will be reported at least quarterly to:

* **Group Director of Research and Development**
* Chief Medical Officer
* Group Research Governance Committee
* Patient Care Committee
* Other committees as required.

Issues confirmed as critical must be escalated to the Group Director of Research and Development, **and** Chief Medical Officer immediately.

Outcomes of audits will be analysed at least annually and will be reported to the Chief Medical Officer and internal committees as required.

Analysed audit outcomes will be reported to clinical trial teams via meetings, forums (including the Clinical Trial Meetings) and Research Matters newsletters.

## REFERENCES:

1. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>

## RELATED DOCUMENTS:

### 7.1 Related Forms and Templates

N/A

### 7.2 Related SOPs

* SOP-QA-02 Management of Serious Breaches and CAPA Process

## VERSION CONTROL

|  |  |  |  |
| --- | --- | --- | --- |
| **Document History** | | | |
| **Version** | **Date** | **Summary of Changes** | **Authors** |
| 1.0 | 26 APR 2019 | N/A First Issue | Helen Christensen  (RQC) |
| 2.0 | 23 Nov 2019 | * Removal of reference to internal supporting templates.   Minor formatting and grammatical corrections. | Helen Christensen  (RQC) |
| 3.0 |  | * Update to current SOP template. * Update scope to clarify audits may be conducted on any research study conducted at Epworth, including quality assurance (QA) projects, non-HREC and HREC reviewed research studies, and clinical trials. Change trial to study/ies throughout the document. * Define types of audits for on-site, self, procedural and themed audits. * Add discussion and table for the Annual Audit Schedule. * Add requirement for Reporting External Quality Activities to the OfR   Move and extend audit conduct information for specifics audits to appendices. | Sarah Rickard (GMRO) |

**APPENDIX**

## APPENDIX 1 - CONDUCT OF ON-SITE AUDITS

### 1.1. Scheduling an Audit with Study Team

OfR staff will notify the study team of the audit in writing and liaise with the study team to organise the audit schedule and access to documentation, personnel and facilities required for the audit.

The audit may be conducted as on-site, remote or combination of these modes depending on site location and availability of OfR and/or research personnel

### 1.2 Notification of Study Audits

The OfR will send written notification (letter/email) to the PI and study coordinator/CTC/Research Nurse confirming:

* the audit date(s)
* required personnel
* the purpose or the audit
* the scope of the audit
* access to specific documents, information, systems, and training as applicable to the study (see below)
* study status overall
* Research Governance authorisations (initial and all amendments)
* HREC approvals (initial and all amendments)
* regulatory and ethics correspondence
* study protocol and all protocol amendments
* Signed participant PICFs, or other evidence of consent or waiver of consent as applicable to the study
* Investigator Site File (ISF), including Pharmacy documents
* Case Report Form (CRF) – if an eCRF is being used, the auditor should discuss the ease of getting access to the eCRF or whether the printing of line listings from the database is best for reviewing the data
* data collection forms
* trial manual, including worksheets and source data specific templates
* CRF guidelines and any other study related plans
* monitoring follow-up visit letters
* a listing of SAEs and Protocol Deviations
* participants’ source data and medical records
* communications
* other documents, as required.
* any additional specific needs for the audit e.g., desk space, visits to laboratories, clinical trial centres/units.
* Request for the study coordinator/CTC/Research Nurse to arrange appointments for the auditor with supporting departments (e.g., Pharmacy, Pathology, Imaging), if applicable.

### 2. Conducting the Audit

#### 2.1 Introductory Meeting

1. OfR staff will hold an introductory meeting with the study Principal Investigator and study coordinator/CTC/Research Nurse (or other auditees depending on audit type) at the beginning of the audit or early in the study audit schedule.

2. Attendance of the study Principal Investigator and study coordinator/CTC/Research Nurse is mandatory requirement of the audit process.

3. The purpose of the introductory meeting is to allow the OfR staff to:

* introduce themselves.
* meet the key personnel in the study team.
* confirm the:
* purpose of the audit program is to support research quality improvement and education across the research platform.
* reason for selection of this study as random, themed, or for cause.
* scope and objectives of the audit.
* availability of personnel for audit support and interviews, including vendors, as applicable.
* review and confirm the audit schedule.
* ascertain how the study and/or processes are conducted and confirm roles and responsibilities.
* indicate the tentative time and date for the closing meeting.

#### 2.2 Review of study documentation

1. Information to be reviewed by the auditor is dependent on the audit scope and usually includes (but is not limited to):

* HREC approvals (initial and amendment)
* Research Governance authorisations (initial and amendments)
* regulatory and ethics correspondence
* consent documentation and processes including signed participant PICFs
* participant source data
* protocol deviations
* adverse events
* the ISF, including Pharmacy documents, if applicable
* Investigational Product receipt, accountability, storage and disposal
* management of biological samples
* equipment maintenance
* qualifications and training of staff.

2. OfR staff may compare source data against the data entered into the CRFs (or data collection forms) will occur. The number of CRFs reviewed will be dependent upon the number of participants recruited and the risk profile of the trial.

3. Study team members may be interviewed regarding details of the conduct of the study.

#### 2.3 Exit Interview

At the end of an audit, an exit meeting will be held with the auditees to present and discuss the observations from the auditing activities. OfR staff will emphasise the critical and major observations. The exit interview will also provide the auditee with an opportunity to ask questions and clarify the observations from the audit.

## APPENDIX 2 – CONDUCT OF SELF-AUDITS

### 1.1. Notification of Self-Audit

OfR staff will send written notification (letter/email) to the PI and study coordinator/CTC/Research Nurse confirming that the study has been selected for Self-Audit and confirm the:

* scope of the audit and objectives of the audit
* overview of the purpose of the audit program is to support research quality improvement and education across the research platform.
* reason for selection of this study as random, themed, or for cause.
* instructions on how to conduct the audit and complete a CAPA (if required).
* due date for submission of the audit information to the OfR.
* OfR review and process for follow-up information/clarification.
* Timeline for issue of audit report.
* Process for responding to the report.
* Process for OfR internal reporting, quality, and educational improvements.

## APPENDIX 3 – CONDUCT OF VENDOR AUDITS

The OfR will determine the frequency and scope for Vendor Audits in liaison with the Group Director of Research and Development, and Group Director Clinical Governance (as required).

The process for conduct of on-site audits is described in Appendix 1.

The auditor will notify the vendor in writing of the request for a vendor audit and negotiate a specific date(s) and time to conduct the audit.

The auditor will confirm in writing with the vendor:

* the audit date(s)
* required personnel
* the purpose or the audit
* the scope of the audit
* any additional specific needs for the audit e.g., desk space, visits to laboratories, clinical trial centres/units.

The auditor will request documents pertaining to the vendor’s processes as well as any documents related to specific trials prior to the audit.