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SOP18a: Standard Operating Procedure for Quality Management

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Approved by Wworth JMG (Ian Russell in chair)

Signature

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1 Table of Contents

0	Version Record	1
1	Table of Contents	2
2	Glossary	3
3	Introduction	3
4	Purpose	3
5	Roles & Responsibilities	4
6	Procedure	5
6.1	<i>Procedural flowchart</i>	5
6.2	<i>Quality Assurance (QA) in trials</i>	5
6.2.1	Quality in trial management	7
6.2.2	Quality in trial personnel management	8
6.2.3	Quality in trial design	9
6.2.4	Quality in fulfilling duty of care (e.g. child protection)	10
6.2.5	Quality in trial safety	10
6.2.6	Quality in trial facilities and resources	10
6.2.7	Quality in trial documentation	11
6.2.8	Quality in trial data collection	12
6.2.9	Quality in trial data analysis and reporting	12
6.2.10	Quality in trial computer systems.....	13
6.3	<i>Quality Control (QC) in trials</i>	14
6.4	<i>Quality and audit requirements</i>	15
6.5	<i>Relationships between QA, QC and internal audit</i>	17
7	Training Plan	18
7.1	<i>Training in principle and practice</i>	18
7.2	<i>Training and qualification of internal auditors</i>	19
8	References	20
9	Related SOPs	21
10	Appendices	22
	<i>Appendix 1: Relationship of QA, QC and Audit components of different SOPs</i>	23

2 Glossary

The full Glossary is in Swansea University H drive/Documents/526-WWORTH/Development Group/Glossary.

3 Introduction

Standard Operating Procedures (SOPs) are succinct formal documents designed to achieve consistency in specified trial functions by specifying standard practice in performing those functions (GCP 1.55 & 5.1.1 – [1]). While SOPs should cite relevant legislation & regulations, and key references & evidence, they need not expound theory.

WWORTH SOPs should accord with all relevant regulations, including the European Union Clinical Trial Directive, ICH Good Clinical Practice (GCP) and the current NHS Research Governance Framework. They will seek to distinguish between regulations for clinical trials involving Investigational Medical Products (CTIMPs) and for other research (non-CTIMPs).

This document describes the process of implementing Quality Management (QM) systems into research studies. Under GCP guidelines, the Sponsor organisation is responsible for implementing and developing and maintaining Quality Assurance (QA) and Quality Control (QC) with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement (Section 5.5.1 of GCP guidelines). QC should be applied to each stage of data handling to ensure that all data “produced” are reliable and have been processed correctly (Section 5.1.3). QC should also be applied to procedural checks not involving data wherever relevant e.g. checking for deviations from the protocol, checking patient safety, etc.

To fulfil the QA requirements of GCP, internal audits will be designed to assess and assure the reliability and integrity of a trial’s QC systems and are a way of measuring performance against recognised standards. The Sponsor organisation is responsible for auditing research practice and assuring adherence to current legislation and guidelines (see WWORTH SOP31 Sponsorship and Adoption). As such, it is necessary to audit research against the standards of the Research Governance Framework 2001 (1st Edition), and the Medicines for Human Use (Clinical Trials) Regulations 2004 where applicable, and against the quality systems of GCP intrinsic to the Regulations.

4 Purpose

The purpose of this SOP is to describe the disciplined approach for ensuring that the research, products and services supplied are fully aligned with the

quality and compliance standards expected by the funding body, Sponsor and other regulatory bodies for randomised trials and other rigorous studies within WWORTH.

This SOP is intended as an overview of QA (which involve most SOPs, as SOPs are a core component of QA, but in particular the SOPs listed in Section 9), QC and internal audit, and to inform the process of internal audit of individual trials and of WWORTH. For more specific guidance on monitoring and preparing for external audit and inspection please see WWORTH SOP17 Monitoring and WWORTH SOP18b Preparation for External Audit and Inspection.

5 Roles & Responsibilities

All staff working on trials within WWORTH should be familiar with this SOP, particularly staff working in CTIMPs. Each person allocated a quality role in a trial or for WWORTH should be suitably trained or experienced.

The following people are responsible for implementing this SOP:

- **Chief Investigator (CI)** – responsible for all aspects of the study and will be required to conduct QA and QC tasks for their own section or trial, or for WWORTH.
- **Principal Investigator (PI)** - will be required to conduct QA and QC tasks for their own section or trial, or for WWORTH.
- **Quality Assurance Officer (QAO)** - will guide trials on developing QA and QC procedures.
- **Site Research Teams (SRTs)** – may be required to conduct QA and QC tasks for their section or trial.
- **Trial Data Manager (TDM)** – responsible for the collection and validity of trial data and will be required to conduct QA and QC tasks for their own section or trial, or for WWORTH.
- **Trial Manager /Coordinators (TM/TC)** – will be required to conduct QA and QC tasks for their own section or trial, or for WWORTH.
- **WWORTH Director** -The WWORTH Director has overall responsibility for ensuring that the SOP has been followed in all WWORTH adopted trials.

It is important that people who are responsible for a procedure / product

should not be responsible for checking it as part of a QC check or internal audit as they are less likely to be objectively critical in their examination of its quality. They should however be integral to the QA process, which will ultimately define the quality criteria against which the QC check(s) will be done. They are also likely to be the person identified as being responsible for the rectification of any QC / audit failures.

Under-resourced trials may request WWORTH to perform QC checks on the trial's behalf but overall responsibility will still reside with the CI.

6 Procedure

6.1 *Procedural flowchart*

See the flowchart overleaf for an illustration of how QA, QC and internal audit procedures should be implemented within a trial.

The design of the trial should also include the design a rigorous protocol system against which all products / procedures will be checked. As part of the QC process every QAO will meet every trial team, guide and agree on how QA and QC management principles will be adhered to.

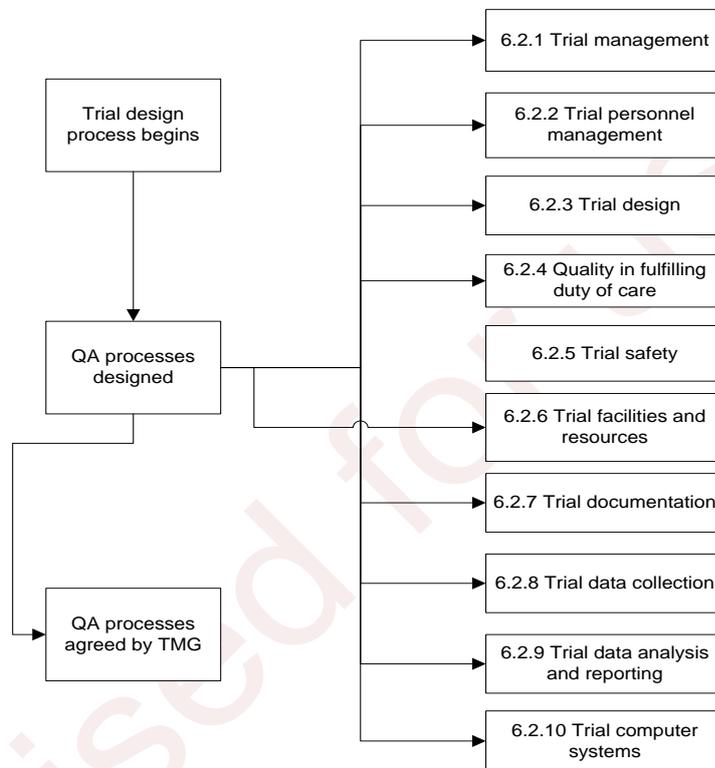
6.2 *Quality Assurance (QA) in trials*

QA is a planned and systematic pattern of all actions necessary to provide adequate confidence that:

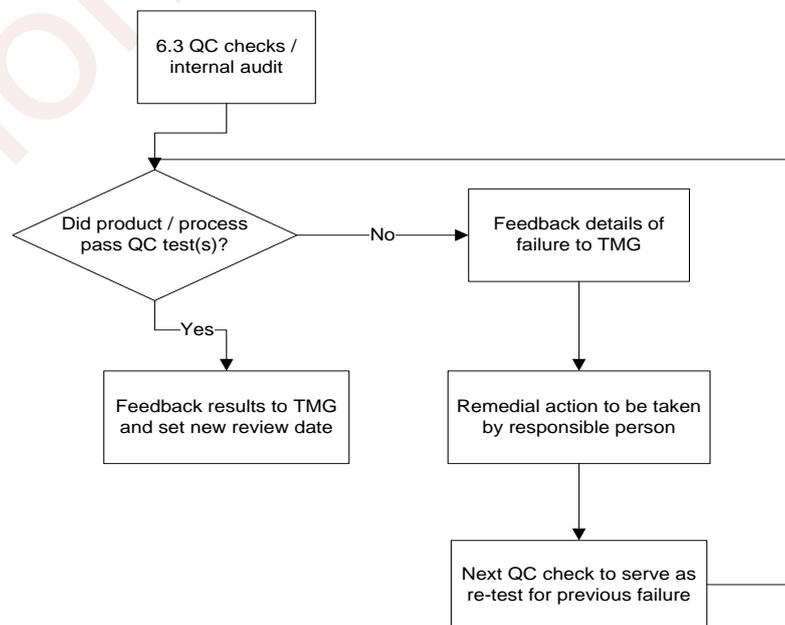
1. The research data output collected was done so consistently and in accordance with established methods. Data checking should involve completing a minimum of 10% check (although some trials will require more extensive data checks). Where errors are found in specific fields, 100% verification of those fields is advised.
2. The trial is being conducted in accordance with study protocol, in a safe manner, and the relevant regulatory issues.

Procedural Flowchart from Section 6.1

a) Quality Assurance



b) Quality Control / Internal audit



QA should be implemented at the outset to design quality into all processes and products. The following actions should be done to implement QA procedures in a trial (or in WWORTH):

- Plan and describe each product and process required or produced by the trial. This should be done using WWORTH SOPs wherever possible and should include quality criteria agreed by the Trial Management Group (TMG). These will be used as a benchmark against which to monitor the product and process' progress over the course of the trial.
- Monitor risks for specific components, or general risks that could adversely affect more than one product or process.
- Identifying all possible remedies to possible risks to create a list of options to be discussed at the TMG should the risk become problematic.
- Requesting agreed remedial action(s) where it is within the TM or WWORTH manager's control; or agenda's item(s) for TMG. A trial's delegation log is used to chart who is responsible for specific remedial action(s) in a study site.
- Since most trials are complex and different, finer details of the implementation of QA should be described in a trial-specific **Quality Plan** produced by the person responsible for quality in each trial, usually the TM or TDM. Subsections 6.2.1 to 6.2.9 describe the **generic** issues of where and how QA should be introduced into trials. These points should be used to create a trial-specific Quality Plan, adapting each sub-section to make it more relevant for the trial wherever possible.

6.2.1 Quality in trial management

1. The protocol should adhere to the guidance stipulated in WWORTH SOP13 Protocol Development and should be periodically reviewed.
2. Charters and agreements should be written to facilitate a clear understanding of the roles and responsibilities of all study sites and any third parties e.g. Data Monitoring and Ethics Committee (DMEC) charters, contracts for randomisation services, laboratory services, etc. (see WWORTH SOP03 Master Site File and WWORTH SOP14 Ethics RG Approval)
3. Definitions of budget targets and budget control measures should be in place, as described in WWORTH SOP13 Protocol

Development.

4. There should be regular progress reports to the TMG, Sponsor, independent monitoring committees, funding body, REC, etc, as required. These reports should use existing proformas where available. Where no existing proforma exists, agree at outset a template to be used to ensure all subsequent reports are standardised.
5. It is advisable to use Project Management (PM) procedures wherever possible to structure and standardise all processes and product requirements (see WWORTH SOP10 Project Management).
6. All meetings and decisions should be appropriately documented for audit purposes.
7. Trial site setup should be done in accordance with principles described in WWORTH SOP16 Site Setup.
8. Ending a trial (prematurely or at a pre-planned closure date) should be done in accordance with WWORTH SOP07 Site Closure.
9. Checks will be in place to monitor for and respond to potential misconduct and serious breaches (see WWORTH SOP32 Detecting & managing misconduct, serious breaches and deviations of GCP/Protocol).

6.2.2 Quality in trial personnel management

1. The personnel records for individuals involved in running the trial both at the Trial Office and at study sites or centres should contain all documentation listed in WWORTH SOP02 Training.
2. The personnel records of trial staff will be reviewed and updated on a regular basis by the TM of that trial, particularly when GCP updates occur.
3. The WWORTH manager is responsible for collating Professional Review (PR) and SOP training logs for all WWORTH staff on a regular basis to confirm the training status and requirements of all staff in accordance with WWORTH SOP02 Training. They will also disseminate details of any training opportunities on a regular basis.
4. For trial staff not employed by WWORTH, the WWORTH Manager should liaise with TM with regard to PR and SOP training logs. If

no TM or TC is in place the CI should delegate the role.

5. For randomised trials, all staff involved in performing randomisation should be appropriately trained by a suitably qualified person (see WWORTH SOP24 Randomisation).
6. For CTIMPs, all local clinical trials pharmacists (LCTPs) involved with a trial will be trained to do a variety of tasks including maintaining the Pharmacy Site File (PSF), performing relevant randomisation procedures, adhering to blinding protocols wherever necessary and storing and dispensing the trial interventions as per protocol. A more extensive list can be found in WWORTH SOP04 Trials Supplies Labelling. Where a manufacturer takes responsibility for this task, they will do so according to their own guidelines.

6.2.3 Quality in trial design

1. The design of the trial should be documented as soon as possible prior to its commencement to demonstrate that will be conducted according to valid statistical principles using the most appropriate outcome measures. This information will also contribute to analysis plan and protocol development (see WWORTH SOP13 Protocol Development, WWORTH SOP25 Outcome Measures, WWORTH SOP26 Economic Evaluation, WWORTH SOP27 Qualitative Methods and WWORTH SOP28 Statistics) and will be used as a benchmark against which the trial's progress will be monitored.
2. The randomisation process should be comprehensively described for each trial in a Randomisation Plan based on guidance in WWORTH SOP24 Randomisation.
3. Service users should be included in trial design and throughout the research process in accordance with WWORTH SOP 09 User Inclusion. Their involvement should be ensured as early as possible in the research process in order to improve the relevance, appropriateness and quality of the proposed research. Most research funders require service user inclusion in trial design and undertaking research. Some of the trial design issues they can be involved with are: considering topic relevance to patients and carers; developing the research question; selecting the research method and data collection tools; ethical issues; identifying issues of relevance to people using health and social care services; considering how service users will be included in undertaking the successful research.

6.2.4 Quality in fulfilling duty of care (e.g. child protection)

1. Another aspect of safety in trials is to fulfil the duty of care to participants and their family members, including child protection. For example, in the Family Links Nurturing Programme (FLNP) trial the field researchers collected data within family's homes, where there was a possibility of observing concerns about child abuse or neglect. The information sheet was amended to ensure that parents were made aware that if the research team were concerned about a child being harmed or neglected, the relevant organisation (for example social services) would be contacted.

6.2.5 Quality in trial safety

1. Trials (and WWORTH where the responsibility is delegated) should provide a co-ordinated system for dealing with trial-related queries from SRTs, external regulatory bodies and research participants and / or their carers such as a trial helpdesk. Any such facility should be "open" during normal working hours and where necessary, an on call rota should be devised. Calls and call outcomes should be documented for audit purposes.
2. Where Trial Steering Committees (TSCs) and DMECs exist they will act as independent monitors of trials and inform the QA and QC processes involved in monitoring trial safety (see WWORTH SOP17 Monitoring).
3. The reporting of all adverse events and reactions, serious or otherwise should be done in accordance with the procedures detailed in WWORTH SOP19a Pharmacovigilance & 19b Urgent Safety Measures.
4. Participant Information Sheets (PISs) and Informed Consent Forms (ICFs) should comply with the criteria stipulated in WWORTH SOP05 Participant Info Consent.
5. Trials should monitor study sites either remotely or at a site visit in accordance with the resources available and the level of risk assigned to the trial (see WWORTH SOP17 Monitoring).

6.2.6 Quality in trial facilities and resources

1. Research facilities used by the trial (and by WWORTH), both at the Trial Office and in study sites and centres should be an adequate size and should be fully resourced to allow tasks to be accomplished in a timely and accurate manner.
2. There should be sufficient storage space to allow the safe and

confidential storage of trial documentation during and after the completion of the work in accordance with WWORTH SOP22a Data Collection Management, WWORTH SOP22b Data Protection Confidentiality and WWORTH SOP08 Archiving.

3. For CTIMPs, IMPs must be received, recorded, handled, stored and dispensed in accordance with the manufacturer's instructions, as specified in WWORTH SOP04 Trial Supplies Labelling.
4. There should be sufficient resources to ensure that viable samples are sent to the laboratories to ensure accurate results, and the timely reporting of those results.

6.2.7 Quality in trial documentation

1. SOPs should be followed explicitly by all trial and WWORTH staff. Where a deviation from the SOP is necessary for a trial, a Modified Operating Procedure (MOP) should be adopted with the relevant agreements of the CI and of WWORTH as necessary (see WWORTH SOP1a on SOPs).
2. All SOPs written by WWORTH and Modified Operating Procedures (MOPs) written by a trial should adhere to the principles stated in WWORTH SOP1a on SOPs and WWORTH SOP1b Document Control.
3. For all types of documentation describing trial procedures, all should have a lead author, a clear purpose and be based on trial-specific document templates and styles as described in WWORTH SOP10 Project Management.
4. For trial protocols specifically, all should be kept current, be formally authorised by the CI and be version-controlled to allow future modifications (e.g. Documentation plans, Analysis plans). Authorisation must be documented for audit purposes.
5. All trial documentation will be archived in accordance with WWORTH SOP08 Archiving.
6. All trial documentation will be made available for any audits (internal or external) and inspections by the relevant regulatory bodies (see WWORTH SOP18b Preparing Audit Inspection).
7. All documents should be made easily available for all trial staff at the Trial Office in the Trial Master File (TMF) and for the SRT, all relevant documents should be filed in the Trial Site File (TSF), as

described in WWORTH SOP03 Master Site File. Local trial staff listed on the trial delegation log should be trained to know of their whereabouts and procedures for their completion.

8. Where documents require password protection, a minimum of two people must know the password to documents, one of which should be the lead author and the other being the next most common user of the document (See WWORTH SOP22a Data Collection Management and WWORTH SOP22b Data Protection Confidentiality).
9. Where documents have a Product Description (PD) it should be adhered to continually. Quality criteria should be included in the PD that must be consistent with the overall trial quality standards. They can be used to determine when the product is fit for purpose by specifying quality criteria, tolerances and procedures for reviewing. Where possible, there should be guidance on the rectification of any QC failures (see WWORTH SOP10 Project Management).

6.2.8 Quality in trial data collection

1. Research data should be recorded by a suitably qualified or trained person listed on the delegation log at the time of data generation wherever possible, directly without transcription (with the exception of qualitative interviews – See WWORTH SOP27 Qualitative Methods), and accurately by the person performing the data collection, as described by WWORTH SOP22a Data Collection Management.
2. Access to data (quantitative and qualitative) should be in accordance with guidelines described in WWORTH SOP22a Data collection management.
3. Where blinding is necessary, the procedures described in WWORTH SOP21 IT Databases and WWORTH SOP24 Randomisation should be observed. Data confidentiality should be respected at all times in accordance with WWORTH SOP22b Data Protection Confidentiality.
4. Use of routine data in trials should be in compliance with the guidelines specified in WWORTH SOP25 Routine Data.

6.2.9 Quality in trial data analysis and reporting

1. The trial statistician should be responsible for the validation and quality of statistical analyses conducted.

2. There should be an independent check of the data received for consistency and face validity in accordance with WWORTH SOP28 Statistics.
3. The Trial Analysis Plan will detail all QC checks to be done by a trial statistician (e.g. multivariate analysis, sensitivity analysis) and should be checked for statistical soundness by an independent statistician (e.g. DMEC statistician) in accordance with WWORTH SOP28 Statistics and WWORTH SOP17 Monitoring.
4. Key analyses should be conducted in accordance with WWORTH SOP28 Statistics.
5. The reporting of all data and trial results to independent monitoring committees, external regulatory bodies and the funding body should be done in compliance with WWORTH SOP17 Monitoring, WWORTH SOP14 RG & Ethics and WWORTH SOP29 Trial Reporting.

6.2.10 Quality in trial computer systems

1. Computer systems used to capture, process and report research data should ensure at least the same level of accuracy, authenticity and security as any paper documentation systems (see WWORTH SOP21 IT Databases).
2. Electronic data should be held in a secure and readable form during acquisition, processing and for as long as regulatory authorities require (see WWORTH SOP18b Preparing Audit Inspection and WWORTH SOP22b Data Protection Confidentiality).
3. Any changes made to electronic data will be appropriately recorded and kept for audit purposes (see also SOP18b Preparing Audit Inspection).
4. Usernames and passwords should be used wherever possible to identify authors and their actions, and to restrict access to electronic documents in accordance with the user's roles and responsibilities as stated on the delegation log (see WWORTH SOP22a Data Collection Management and WWORTH SOP22b Data Protection Confidentiality).
5. Electronic backups and copies of files should be made as required (see WWORTH SOP21 IT Databases).

6.3 **Quality Control (QC) in trials**

QC is a fundamental aspect of research quality to ensure that data are tested and checked to confirm that they are robust and of high-quality using a baseline or benchmark formally documented as part of the QA process for comparative purposes.

Planned QC reviews should be carried out at appropriate intervals by suitably qualified or experienced personnel within the trial or WWORTH and should cover core objectives and ensure that all quality standards are being met. Any QC checks done by staff external to the trial (including WWORTH where the QO has not participated in the QC tasks) are covered under internal audit.

QC reviews should have three components:

A review of the science – there should be a scientific peer review of the trial including its design (e.g. to ensure that the trial has not deviated in its remit to the point where it may violate its contract with the funding body), the type and method of data collection (e.g. to ensure that the patients are being treated safely and ethically) and where time allows, of any results or conclusions available. This review should be independently done by the TSC, although it is good practice for the TMG to review these issues in-house at regular intervals.

Review of the data – There should be routine independent trial reviews by the TSC and DMEC to ensure that results are valid, the trial does not compromise patient safety and that the protocol does not alter to the point where it deviates significantly from the original proposal agreed by the funding body (see WWORTH SOP17 Monitoring).

Review of the processes – Periodic reviews of the trial's processes should be undertaken and reported to the TMG and Sponsor to assure them that the quality level is / remains as expected.

QC reviews should have formal documentation to allow the accurate recording of review activities. Should a product / process fail a QC review, there must be an agreed plan of action for the owner of the product / process to implement to re-establish quality and pass a QC re-test within a fixed, pre-defined time period.

QC should be done at prescheduled intervals, as logged in the protocol, according to the protocol risk assessment (dependent on level of potential internal risk, size of trial etc). The following actions should be performed at a QC check:

- Examine outputs from the QA process, including a randomly selected check of TMF components, and SOP standards against expected quality standards to determine whether there have been any issues with compliance or accuracy.
- Items requiring remedy are logged for remedy and reporting, by either the person responsible for quality from another trial or by another TM, to an agreed schedule. All remedial action must be carried out in a timely manner so that a second QC check of the process can be done. The delegation log is used to chart who is responsible for which remedial action.
- If the random check reveals a significant level of items are out of control, TMG must supervise the remedy and reporting cycle, to ensure the people responsible for the failures have sufficient support to remedy the situation within an appropriate timescale.
- Assess the internal control procedures (e.g. by checking computer security for data transfer, accountability, timely and correct filing and sign-off of deliverables). If internal controls are assessed as strong, this will reduce (but not entirely eliminate) the amount of 'substantive' work internal and external auditors need to do.

6.4 Quality and audit requirements

The purpose of an internal audit is to:

- Ensure participant and staff safety.
- Assist researchers with compliance to regulatory requirements and Swansea University policy.
- Improve research systems and data quality.
- Prepare researchers for external audit processes described in WWORTH SOP18b Preparing Audit Inspection.
- Demonstrate robust research processes to external funders and industry.

The system must also determine the major QA / internal audit risks (i.e. the chance that internal systems or QA will fail, or the auditor will issue the wrong opinion).

ICH GCP requires Sponsors to implement and maintain QA / QC / audit

systems to ensure that trials are conducted and data generated, documented and reported, in compliance with:

- GCP requirements
- MHRA requirements (<http://www.mhra.gov.uk/index.htm>)
- Sponsor requirements (specific to each Sponsor)
- Funder requirements (specific to each Funding Agency)
- NRES (<http://www.nres.npsa.nhs.uk/rec-community/tools-for-reccoordinators/>)
- WWORTH management including Clinical Trials Unit registration with the UKCRC
- Trials Management, including initiation and clinical liaison, including protocol, registration, research ethics and Clinical Trial Agreement (CTA) approvals, staff and participant recruitment, project management, research governance compliance
- Statistics, including data management
- Other statutory and regulatory requirements: e.g. relating to human resources, data protection and confidentiality, IT security, etc.

Internal audits should be done by a nominated internal auditor, who is independent of both the trial and the WWORTH executive management team, either:

- a. at prescheduled intervals, as logged in the protocol, according to the protocol risk assessment (dependent on level of potential internal risk, size of trial etc)

OR

- b. at a randomly selected time for an unannounced spot-check of a random selection of deliverables and processes addressed for (a). [This is designed to counter any perverse incentives to let documentation slip until pre-scheduled dates for QC and internal audit.]

The following actions should be performed at an internal audit:

- Products from the QA and QC processes are examined for WWORTH and ABMU health board.
- Exception reports to TMG for formal remedy cycle.
- Where internal controls are strong, auditors typically rely more on Substantive Analytical Procedures - the comparison of sets of information, to check internal consistency and that unexpected actions have been documented and can be explained. For example, within FLNP data checking procedures, data was checked independently in two parts: 1) For data entry errors, and 2) Inter-rater reliability was checked for coding discrepancies across research sites. Any differences or errors found in data entry were documented and where there were more than 10% of errors, 100% of that measure was checked. Where reliability was inconsistent between research sites further training on coding the measures was provided.
- Where internal controls are weak, auditors typically rely more on Substantive Tests of Detail - selecting a sample of items, and checking hard evidence (e.g. comparison of documentation with actual practice) for those items.
- Timing for remedy would be pre-specified in each trial protocol (varying according to the level of potential risk assessed).

Standards for system and process improvement should be identified and agreed. This is separate from risk remedy, and forms the basis for continuous quality improvement.

6.5 Relationships between QA, QC and internal audit

Each SOP and each TMF component builds to provide QA for each trial and WWORTH. These are monitored for QC, and to inform internal (and external) audit. WWORTH QA, QC and audit use processes central to trial management to provide a cost-effective approach, requiring few additional processes solely for QA or QC.

SOPs related specifically to protocol development, monitoring, TMFs and TSFs, quality management, audit and inspection and safety reporting all inter-relate (see Appendix 1).

QA, QC and internal audit use a cyclical, risk-based approach, based on the pre-scheduled deliverables from each SOP, signed-off, logged and entered in individual TMFs. Each TMF deliverable has a signed cover sheet, the signatures on which are logged centrally, with systems to log

and trace changes, and document and version control (see WWORTH SOP03 Master Site File).

Risk assessments on the basis of regulatory requirements, number of subjects in the trial, the type and complexity of the trial, the level of risks to trial subjects, and any specific identified problems (ICH GCP 5.19.3), and are conducted as part of WWORTH SOP13 Protocol Development.

There is also an assessment of risk during ongoing internal QA, QC and internal audit. Each layer of QA, QC and audit requires and uses a reporting and remedy cycle. The protocol for each trial will specify scheduling for the TMF for, and safe time periods for the responsible person) to:

- Identify, document, and notify risk
- Identify and implement remedy or notify TMG of need for structural or procedural change required for process that is out of control

7 Training Plan

7.1 *Training in principle and practice*

All WWORTH staff involved with trials must undertake the appropriate generic and trial-specific training to ensure that they meet with the specific employers' mandatory training requirements and the specific requirements of the trial. For example, for SU staff, all new employees must attend induction, fire and safety training (as well as role-specific training courses, e.g. laboratory safety). For new staff, additional training requirements should be identified alongside the specific role requirements and the WWORTH Unit Manager should make provision for the new staff member to attend the necessary courses as soon after appointment as is practicably possible.

It is the responsibility of the WWORTH Unit Manager (alongside the CI or TM) to identify all the SOPs that are relevant to a specific trial and in which the new member of staff should be trained. The WWORTH UM or the SOP author will provide group training for trial staff and/or one-to-one training, as required for new staff in relation to the specific SOPs identified. Training records should be filed both by the main employer and the staff member, in accordance with the specific employer requirements. Trial specific training should be filed in TMF or TSF as appropriate and every individual involved in a trial should have an individual training record (see WWORTH SOP02 Training).

Where the tasks specified in the individual SOPs are delegated to WWORTH staff, CIs/PIs or TMs, these delegated staff must ensure that they have attended a training course on GCP and keep up-to-date through attending refresher courses.

It is the responsibility of the CI/PI to ensure that all staff allocated duties on the study delegation log template of responsibilities are suitably trained in the activities linked to those duties (see WWORTH SOP16 Site Setup, Appendix 9 and Appendix 10).

Each trial should maintain a central training log and ensure that WWORTH has access to that log, not least to integrate the logs of staff who work on more than one trial. Similarly trials should ensure that each site maintains a local training log, not least to integrate the logs of staff who work for more than one sponsor.

Training in principle will take place during the WWORTH SOP meeting to approve the SOP. The SOP will become effective after the training in principal.

Training in practice will be effective once a staff member has completed the SOP's tasks. The staff member will sign the "training in practice log" (WWORTH SOP02 Training). New staff members will receive one-on-one training from either the author of this SOP or a suitable person from WWORTH on use of this SOP.

7.2 Training and qualification of internal auditors

Quality monitors and WWORTH staff should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor trial procedures effectively. A monitor's experience and/or training should be documented. This would normally include attendance at a dedicated GCP monitoring course, and previous operational responsibilities with at least two trials in the capacity of assistant to the TM, TDM or equivalent role.

Quality monitors should be familiar with the IMP, the protocol, PIS and ICF (ICH GCP 5.18.2), as well as WWORTH SOPs, GCP and applicable regulatory requirements. The WWORTH manager should be familiar with all WWORTH SOPs, GCP and applicable regulatory requirements, and the portfolio of trials under WWORTH management.

The internal auditor should be independent to the trial (or to WWORTH for a WWORTH review) to conduct audits appropriately. An auditor should be qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented (ICH GCP 5.19.2). Internal Auditors will normally be employed by Swansea University, but should not

be required to audit tasks, structures or procedures on any trials where they have an operational role.

Each trial will be responsible for ensuring the adequate training of its internal auditors. WWORTH will maintain a register of people authorised for auditing duties.

8 References

1. European Medicines Agency (2002). *Guidelines for Good Clinical Practice*. London: EMeA. (CRMP.ICH/135/95).
www.emea.europa.eu/pdfs/human/ich/013595en.
2. International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) 1996 [accessed July 2009]
<http://www.ich.org/LOB/media/MEDIA482.pdf>
3. International Conference on Harmonisation of Good Clinical Practice (ICH-GCP) website [accessed July 2009] <http://ichgcp.net/>
4. Research Governance Framework for Health and Social Care 2nd Ed 2005 [accessed July 2009]
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

Bibliography

CT-Toolkit (2004) Monitoring Procedures, accessed 16.05.07 (http://www.ct-toolkit.ac.uk/route_maps/stations.cfm?current_station_id=319&view_type=map)

European Medicines Agency (EMeA) website [accessed July 2009]
<http://www.emea.europa.eu/>

European Union Clinical Trials Directive 2001 [accessed July 2009]
www.wctn.org.uk/downloads/EU_Directive/Directive.pdf

Henry Stewart A. Two-Day Practical Briefing on Designing, Writing, Approving and Implementing SOPs in Clinical Research. [cited 2008 March]
<http://www.henrystewart.com/conferences/march2003/N03628/programme.html>

Institute of Clinical Research. Standard Operating Procedures: Clinical Research Operational Standards for Professional Practice. 5 May 2006. [cited 2008 March]

http://www.instituteofclinicalresearch.org/documents/Professional_Standards/SOPs.pdf

Marinus A. Quality assurance in EORTC clinical trials. European Journal of Cancer 2002; 38 (4):159-161

Medicines for Human Use (Clinical Trials) Regulations 2004 [accessed July 2009] <http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm>

Nicholson P, Henley P, Wilkins M. Quality Control and Quality Assurance CRO/SOP/025 Version 2. Imperial College. [cited 2008 August] <http://www3.imperial.ac.uk/pls/portallive/docs/1/45143714.PDF>

NWORTH website “Standard Operating Procedures” [accessed July 2009] <http://www.bangor.ac.uk/imscar/nworth/specservices.php?menu=3&catid=2236&subid=0>

9 Related SOPs

SOPs form a QA function and as such, all WWORTH SOPs are integral to the QA process. The list below describes the WWORTH SOPs specifically referenced by this SOP:

WWORTH SOP01a on SOPs
WWORTH SOP01b Document Control
WWORTH SOP02 Training
WWORTH SOP03 Master Site Files
WWORTH SOP04 Trial Supplies Labelling
WWORTH SOP05 Participant Info Consent
WWORTH SOP07 Site Closure
WWORTH SOP08 Archiving
WWORTH SOP09 User Inclusion
WWORTH SOP10 Project Management
WWORTH SOP13 Protocol Development
WWORTH SOP14 Ethics RG Approval
WWORTH SOP16 Site Setup
WWORTH SOP17 Monitoring
WWORTH SOP18b Preparing Audit Inspection
WWORTH SOP21 IT Databases
WWORTH SOP22a Data Collection Management
WWORTH SOP22b Data Protection Confidentiality
WWORTH SOP23 Routine Data
WWORTH SOP24 Randomisation
WWORTH SOP25 Outcome Measures
WWORTH SOP26 Economic Evaluation

WWORTH SOP27 Qualitative Methods
WWORTH SOP28 Statistics
WWORTH SOP29 Trial Reporting
WWORTH SOP31 Sponsorship and Adoption
WWORTH SOP32 Detecting & Managing Misconduct, Serious Breaches and
Deviations of GCP/Protocol

10 Appendices

Appendix 1: Relationship of QA, QC and audit components of different SOPs.

Appendix 1: Relationship of QA, QC and Audit components of different SOPs

#	Title	Main purpose	Purpose notes
03	Master file & site file	To describe the process of maintaining a TMF/TSF for a trial of IMPs or “other research”.	Appendix 1 lists all essential docs, including: documents of QA procedures and copies of risk assessment reports . References pharmacovigilance . <i>Applicable to individual TRIAL</i>
13	Protocol development	To describe the process of protocol development	To describe the process of protocol development both in the instance where the primary authors of the protocol are within WWORTH and when they are not. This includes Risk Assessment . <i>Applicable to individual TRIAL</i>
17	Monitoring	To describe how trial monitoring will be planned and carried out by trials and by WWORTH.	This SOP applies only to trials where all monitoring responsibilities have been delegated to WWORTH, which is most likely in cases where Swansea University is the Sponsor. For the purposes of this SOP, the term monitor will be used to refer to any member or committee designated by WWORTH to undertake specific monitoring task <i>Applicable to individual TRIAL</i>
18a	Quality Management	To describe the QA, QC and internal audit procedures for both clinical trials and WWORTH.	The purpose of an internal research or trial unit audit is to: <ul style="list-style-type: none"> • Ensure participant and staff safety • Assist researchers with compliance to regulatory requirements and College policy • Improve research systems and data quality • Prepare researchers for external audit processes • Demonstrate robust research processes to external funders and industry <i>Applicable to individual TRIAL and the WWORTH</i>

18b	Preparing for external audit and inspection	To describe the processes necessary to prepare, host and participate in a Sponsor's regulatory inspection by the Competent Authority.	<p>Both audits and inspections take place to examine 'systems' and look for good control of processes and opportunities for process improvement. The same "principles" should be applied in preparation for internal departmental audits and Site inspections. This might involve audits of informed consent forms, adherence to the protocol (including subject eligibility criteria) and adverse event reporting. Maintenance of a central study file is therefore essential to assist in any audit.</p> <p><i>Applicable to individual TRIAL</i></p>
19a & 19b	(a) Pharmacovigilance and (b) Urgent Safety Measures	To describe the process of Safety Monitoring and Pharmacovigilance	<p>Monitoring the use of medicines/ IMPs, assessing their harms and benefits, raising awareness of them by reporting adverse events ('AEs') or adverse reactions ('ARs') and following through actions recommended in the wake of AEs/ARs is fundamental to improving the efficacy and safety of IMPs. The unifying description for this area of CTIMP activity is 'pharmacovigilance'.</p> <p>The word pharmacovigilance applies precisely to CTIMPs. For non-CTIMPs, the following must be decided during protocol development:</p> <ol style="list-style-type: none"> 1. the level of recording of adverse events appropriate for the trial 2. expected reactions to the intervention must be defined <p>procedures for reporting AEs, SAEs, SARS, and SUSARs must be established, following the general principles of this SOP except for the involvement of the MHRA</p> <p><i>Applicable to individual TRIAL and the WWORTH</i></p>