A Standard Operating Procedure (SOP) is a detailed written instruction used to achieve uniformity when performing specific functions, and is used to set out the way practice and procedures need to be performed. SOPs are written instructions and records of procedures agreed and adopted as standard practice.

The definitive version of the Centre for Healthcare Randomised Trials (CHaRT) SOP book appears online, not in printed form, to ensure that the up to date version is used. Hardcopy printouts are UNCONTROLLED COPIES. If you are reading this in printed form check the version number and date to ensure you are working to the current version.

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT CHECKING IT IS THE LATEST VERSION.
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<td>01</td>
<td>None, new procedure. Launch of SOP book</td>
<td>21/04/09</td>
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<td>02</td>
<td>Review and update of all chapters and web links</td>
<td>24/06/10</td>
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<td>03</td>
<td>Review and update of all chapters and web links, referencing the UoA-NHSG SOPs where appropriate and referencing to Q-pulse for all CHaRT specific templates &amp; policies. Details of SOP authors on front page renamed to “Lead Authors” and listed by roles. The names are given in a new section “Lead Author History” below. More detailed chapter specific “Version History” sections have been added at the end of each chapter.</td>
<td>15/10/12</td>
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<td>Review and update of all chapters and web links, referencing the SOP-QA (formally UoA-NHSG-SOPs) where appropriate for locally sponsored studies and referencing to Q-pulse for all CHaRT specific templates &amp; policies. The following chapters were renamed: Chapter 8 ‘Final Trial Reporting’ to ‘Trial publications and Dissemination’, and Chapter 13 ‘Consumer issues’ to ‘Patient and Public Involvement’.</td>
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<td>05</td>
<td>Review and update of all Chapters and web links; removal of word ‘issues’ from Chapter headings; removal of Health Psychology chapter (chapter 12); inclusion of Chapter on randomisation (chapter 11); inclusion of NEW Chapter on IT infrastructure (chapter 9); inclusion of NEW Chapter on embedded qualitative evaluations (chapter 14) and as a result the re-ordering of Chapters where required.</td>
<td>19/04/18</td>
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<td>06</td>
<td>Review and update of all Chapters, hyperlinks and web links where required. All links to Q-Pulse have now been clearly highlighted &amp; staff have been directed to use the software for accessing these. Any new templates, examples or guidance documents, relevant to CHaRT procedures, have been added. Significant changes have been made to Chapters 5, 6 and 10 to ensure all procedures, especially regulatory ones, are current and up-to-date, and Chapter 15 includes two new sections; these describe the process for supporting Patient and Public Involvement (PPI) partners and the best methods for documenting PPI.</td>
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<td>05/08/15</td>
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Note: Within this document there are a number of associated documents that are accessed via Q-Pulse. The titles of these documents appear in the text coloured red. All CHaRT staff will have a specific login to Q-Pulse and have access to this software via their PCs.
## ABBREVIATIONS

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<th>Description</th>
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<tr>
<td>CE</td>
<td>European Conformity</td>
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<tr>
<td>CHaRT</td>
<td>Centre for Healthcare Randomised Trials</td>
</tr>
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<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CRF</td>
<td>Case Report Forms</td>
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<td>CSO</td>
<td>Chief Scientist Office</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
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<tr>
<td>CTIMP</td>
<td>Clinical Trial of an Investigational Medicinal Product</td>
</tr>
<tr>
<td>CTU</td>
<td>Clinical Trials Unit</td>
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<tr>
<td>DAHS</td>
<td>Division of Applied Health Sciences</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<td>DMP</td>
<td>Data Management Plan</td>
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<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
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<tr>
<td>EME</td>
<td>Efficacy and Mechanism Evaluation Programme</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Clinical Trials Database</td>
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<td>EU</td>
<td>European Union</td>
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<td>FTP</td>
<td>File Transfer Protocol</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GRP</td>
<td>Good Research Practice</td>
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<tr>
<td>HEAP</td>
<td>Health Economics Analysis Plan</td>
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<tr>
<td>HSRU</td>
<td>Health Services Research Unit</td>
</tr>
<tr>
<td>HS &amp; DR</td>
<td>Health Services and Delivery Research</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>ImpEC</td>
<td>Improving Experiences of Care</td>
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<tr>
<td>IRAS</td>
<td>Integrated Research Application System</td>
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<td>ISD</td>
<td>Information Services Division</td>
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<td>ISF</td>
<td>Investigator Site File</td>
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<tr>
<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number</td>
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<td>IP</td>
<td>Intellectual Property</td>
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<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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CHAPTER 1: STANDARD OPERATING PROCEDURE (SOP) DETAILS

[version: v06.0100.06]

LEAD AUTHOR
CHaRT Director.

BACKGROUND
The Standard Operating Procedure (SOP) for the design, conduct, analysis, reporting, documentation and quality assurance of randomised controlled trials (RCT) and other high quality trial designs in the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit (HSRU), University of Aberdeen (UoA).

PURPOSE
The purpose of this chapter is to provide details of the aims of the SOP book; their structure (format, style, content); who is responsible for them and how they are maintained.

APPLICABILITY
- Essential for those members of staff involved in the production and maintenance of the SOP.
- Useful background reading for all members of staff observing the SOP in their work.

STANDARD OPERATING PROCEDURE (SOP) DETAILS

1.1 Overview of SOP  [version: v06.0101.06]
Clinical trials are expected to be run to exacting ethical, regulatory and legal standards and it is paramount that all CHaRT clinical trials are conducted in compliance with: the study protocol and CHaRT SOP book, the University of Aberdeen’s Handbook for Research Governance (www.abdn.ac.uk/staffnet/research/research-governance-304.php) and the Institute of Applied Health Science’s Research Governance and Quality Assurance policy www.abdn.ac.uk/iahs/research/research-governance-guidance.php#panel321, the UK Policy Framework for Health and Social Care Research (www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/) and the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (SI1031: www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf) and any updates. For locally sponsored studies, the joint University of Aberdeen and NHS Grampian’s sponsor SOPs (SOP-QA: www.abdn.ac.uk/clinicalresearchgovernance/sops/index.php) must be complied with and, where relevant, the Sponsor’s Quality Management System Matrix should be completed documenting which of the Sponsor SOPs have been read. This should be held in staffs’ training records (see Section 16.3). For externally sponsored studies, the relevant corresponding requirements, which may include local SOPs, may need to be integrated. International trials must conform to all relevant national requirements.

Currently, only Clinical Trials of an Investigational Medicinal Product (CTIMPs) are required to comply with the UK Medicines for Human Use (Clinical Trials) regulations. However, to ensure consistency of quality assurance across all clinical trials adopted by CHaRT, all trials (CTIMPs and non-CTIMPs) need to adhere to the appropriate regulations and are run in compliance with the principles of Good Clinical Practice (GCP). Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the ICH Declaration of Helsinki, and that the clinical trial data are credible.
Chapter 1: Standard Operating Procedures (SOP) details

This SOP book describes how CHaRT conducts its trials, covering all aspects including: the scientific issues of design and analysis; ensuring a trial is properly authorised; conducting studies to the principles of Good Clinical Practice (GCP); specific issues for disciplines that comprise the core competencies required for a multidisciplinary trial (statisticians, trial managers, IT professionals, health economists, health psychologists, clerical staff, clinical staff); ensuring quality throughout; describing the processes for documentation and archiving study materials and training issues.

The aim of this SOP book is to have a simple core set of generic processes that need only routine minor review (every two years) and modification, with occasional update to respond to major external change in the ethical, regulatory and legal framework. For a specific trial, all the detail of the processes will be contained in the study guidance (see Section 5.4.1), which in particular will document any departure from the CHaRT SOP.

1.2 Style of SOP
To facilitate ease of maintenance and readability, the SOPs appear in book form – that is, we do not have individual SOPs each formatted to an identical template. The book comprises chapters (covering a theme e.g. trial management issues), and chapters will comprise headings, which in turn will cover specific items.

1.3 Contents of SOP
In general, a specific item and/or a chapter will be expected to cover:

- **Lead author:** State the role of the person responsible for leading the authoring of the chapter.
- **Background:** Briefly discuss the background to the SOP, making reference to regulatory guidance, if applicable. Consider the driving forces or why the SOP is necessary.
- **Purpose:** Describe the procedure to be followed and the setting in which the SOP applies.
- **Applicability:** Define the scope of responsibility for the SOP.
- **SOP title:** Describe the procedures and specific items that relate to the chapter.
- **Cross reference:** Mention any relevant chapters or sections within this book that are not already referenced within the text of the chapter, as well as SOP-QA, where relevant. In addition, include any publication or further reading if appropriate.
- **Version history:** Summarise the significant changes made to the SOP chapter from the previous version.

1.4 Format of SOP
To make the Book > Chapter > Section style workable, the following administration format is adopted.

- **For a chapter:**
  - Chapter X: <Title> e.g. Chapter 10, Statistical issues
  - Version: <Version number> e.g. xx.ccss.yy - where xx is the overall protocol ‘counter’, cc is the chapter identifier & ss the section identifier (always ‘00’ for a chapter); yy is the version of this chapter.

- **For a section:**
1.5 SOP responsibilities
The overall responsibility for the SOP book is held by the director of CHaRT. The CHaRT Quality Assurance (QA) manager will oversee the document control of this book and is responsible for managing and facilitating the SOP review, delegating responsibility for authoring chapters on a common theme (e.g. data management, statistics, trial management, and so on) to the appropriate theme leader (senior IT development manager, senior statistician, senior trials manager, and so on). Individual sections within these chapters, covering a specific item, may be delegated by the theme leader to individual staff members as appropriate.

1.6 SOP review
The SOP book will be formally reviewed every two years from the issue date, or earlier should substantive changes in the external environment in which randomised controlled trials are conducted necessitate such a review. The CHaRT director and the SOP committee (see Section 1.9 below for membership) are responsible for identifying new requirements, detecting obsolescence, and updating current material. The review of the chapters within the SOP book will be coordinated by the designated theme leader (lead author). The CHaRT QA manager is then responsible for collating and formatting the chapters of the SOP book, updating the version numbers for the various chapters and sections of the book (see Section 1.4 for details) and updating the ‘Version History’ section of the book.

Once finalised, the SOP book will be reviewed by the University of Aberdeen/NHS Grampian research governance and quality assurance managers to ensure local compliance. Thereafter, the CHaRT QA Manager will arrange for the completed version of the SOP book to be reviewed by the director of CHaRT for final approval, will add the appropriate Issue Date; Effective Date and Review Date, and then the CHaRT director and QA manager will add wet signatures. The SOP issue date is the date the SOP book is issued and made available to all CHaRT staff. The effective date will be one month after the issue date to allow sufficient time for CHaRT staff to be trained.

1.7 SOP training
CHaRT recognises that to ensure its staff are conversant and compliant with the SOP book, training is a key issue. All CHaRT staff are required to be familiar with the content of the SOP book (and relevant detail of the study guidance (see Section 5.4.1 for details) for all trials they have responsibilities for). The QA manager will organise general SOP overview training sessions which take place for both new and established CHaRT staff. A note of this training is held by the QA manager. Specific training sessions are usually in specialist groups e.g. statisticians, IT, trial managers, clerical staff, senior staff and in addition in generalist groups for generic issues.
1.8 SOP location [v06.0108.03]
An electronic version of the currently approved SOP book is available on Q-Pulse and at w3.abdn.ac.uk/hsru/CHaRT/public/content/ShowPage.aspx?page=CHaRT-SOPs. The original signed copy of the SOP book is held by the QA manager (or delegate) in a secure location within HSRU. The QA manager (or delegate) also has another hard copy that is available for controlled use and distribution. Superseded versions of the original copy and electronic copy of the SOP book will be archived as appropriate.

1.9 SOP committee [v06.0109.04]
The CHaRT SOP committee is responsible for all aspects of the specifications, authoring, maintenance, and distribution of the CHaRT SOP. The committee is chaired by the CHaRT director, who is responsible for the conduct of all CHaRT’s activities, and comprises the QA manager, senior trials managers, senior IT development manager, research manager(s), and HSRU’s senior statistician, senior health economist, HCA programme director and PPIE coordinator. Membership will be reviewed as a specific item every two years and is detailed in the ‘Lead Authors’ History’ at the start of the SOP book.

1.10 Standardisation [v06.0110.02]
CHaRT’s philosophy is to demonstrate all processes used in its trials are of high quality, and fit for their purpose. There is a commitment to re-use existing, proven tools, possibly customising them to new situations in new trials. Standardisation is therefore a key objective. A resource repository containing a number of templates and examples (protocols, patient information leaflets, CRFs, committee reports, statistical analysis plans) is managed and document controlled using quality management specific software (Q-Pulse), and should be consulted when planning a new trial.

CROSS REFERENCE
All CHaRT SOP chapters.

VERSION HISTORY

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<td>Updated SOP details to include Lead Author &amp; Version history; updated 1.6: SOP review to include details on sponsor oversight.</td>
<td>Jan 2012</td>
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<tr>
<td>04</td>
<td>Updated section 1.1 to include information on externally sponsored studies, section 1.6 to detail the issue and effective dates, and section 1.8 to amend the location of the SOP book from the Shared drive to Q-Pulse.</td>
<td>Aug 2015</td>
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<td>Minor wording amendments, updated Section 1.9 to include addition of new lead authors.</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Minor changes to wording in section 1.1 including information on local Sponsor Quality Management System matrix.</td>
<td>Feb 2020</td>
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CHAPTER 2: CHART DETAILS

LEAD AUTHOR
CHaRT director.

BACKGROUND
To describe the setting and environment in which CHaRT operates.

PURPOSE
The purpose of this chapter is to provide the context in which CHaRT conducts its business, as an academic clinical trials unit specialising in the design, conduct, analysis and reporting of publicly funded trials, within the setting of the University of Aberdeen. CHaRT achieved full registration as a UK Clinical Research Network Trials Unit in November 2007, which was renewed in 2012 and again in 2017, and CHaRT has a long-term goal of maintaining and consolidating that status.

APPLICABILITY
- It is not essential reading but should be useful background for all members of staff, particularly those involved in writing or maintaining the SOP Book.

CHaRT DETAILS
2.1 CHaRT setting
CHaRT is concerned with collaborating on all aspects of the design, conduct, analysis and reporting of randomised clinical trials of important healthcare questions, and funded by the public sector.

It is administratively part of the Health Services Research Unit (HSRU), which is itself part of the Institute of Applied Health Sciences (IAHS), which is part of the School of Medicine, Medical Sciences and Nutrition in the University of Aberdeen.

Members of CHaRT are therefore employed by the University of Aberdeen, and as such are subject to the rules and regulations of the University. CHaRT itself is likewise obliged to follow University policies and procedures. These policies include those governing:

- recruitment (including all employment laws)
- training (including professional development)
- research practices (including research misconduct)
- research governance and quality assurance
- intellectual property (IP)
- financial issues
- promotion procedures
- data confidentiality

This SOP book is written with these structures in mind. If any text within the SOP book is found to be in conflict with these University policies, it will be amended at the earliest opportunity.
2.2 CHaRT organisation
Organogram of CHaRT
Chapter 2: CHaRT details

Organogram
A part of CHaRT’s remit is to conduct all of the Health Services Research Unit (HSRU) RCTs in HSRU’s two major programmes – Health Care Assessment (HCA) and Improving Experiences of Care (ImpEC), alongside supporting trials from out with HSRU and/or Aberdeen.

CHaRT is administratively part of HSRU, and all its staff are members of HSRU. The director of CHaRT is a senior member of HSRU staff, and reports to the director of HSRU. A senior CHaRT management group comprises the senior trials managers, senior IT development manager, senior statistician, research managers, QA manager and CHaRT PA/secretary, and the CHaRT director to whom they report. Other members of CHaRT (trial managers, programmers and data co-ordinators) report to their line manager. The senior CHaRT management group receives input from senior leads in statistics, health economics, and clinical disciplines as required.

- **Trial management:**
The trial management function is 100% devoted to CHaRT activities and is managed by the senior trials managers who report directly to the CHaRT director. There are various models of engagement for the provision of trial management for CHaRT trials. Generically, these models involve either complete trial management support from CHaRT or a more supervisory, mentoring type role where an experienced CHaRT trial manager provides oversight and guidance to a trial manager who is not located within HSRU (typically, they would be at a study office at the clinical lead’s site). In such engagements, it is usual that the local trial manager would be governed by the sponsor’s SOP(s), as applicable.

- **IT/applications:**
The IT/applications programming function is approximately 90% CHaRT activity, the remaining 10% being non-trial HSRU activity (e.g. web-based disease registries, observational studies) so for administrative convenience this whole function is run by CHaRT. The programming group is managed by the CHaRT senior IT development manager, with input from a senior programmer.

- **Statistical group:**
The statistical group is managed by the HSRU senior statistician, who is core funded by the Chief Scientist Office (CSO). Although CHaRT is configured in such a way that in principle it could obtain statistical support from other academic units (see Section 12.10: Partnerships with external statisticians), it routinely gets support from the HSRU statistical group since they have the track record and work to the agreed SOP.

- **Health economics:**
The provision of health economics expertise is approached on similar lines: HSRU has joint appointments with the Health Economics Research Unit and this is the first port of call for provision of health economics expertise. For collaborative projects where the clinical lead is outside HSRU, CHaRT has collaborated with non-Aberdeen health economists (see Section 13.8: Partnerships with external economists).
• **Clinical, methodological and other input:**
  CHaRT receives input from various sources (e.g. from clinical and methodological leads within HSRU) and more broadly from the IAHS and externally; including links through the UKCRC CTU network and their subgroups (QA, IS, statistics, PPI). This input usually comprises assisting with understanding of clinical contexts and understanding of patient and public perspectives for trial participation, assessing evidence bases, helping with grant applications, and advertising on clinical networks and professional bodies.

• **Finance:**
  To remain competitive in attracting funding, and to deliver trials consistently on time and budget, providing value for the public funders (the taxpayers), CHaRT has developed an internal costing model for its trials. The costing of a new trial and the subsequent management of the trial budget is a collaboration between senior CHaRT staff and the Unit business manager, who in turn negotiate and facilitate on CHaRT's behalf with the wider University finance office.

**CROSS REFERENCE**
All CHaRT SOP chapters.

**VERSION HISTORY**

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<td>Jul 2015</td>
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LEAD AUTHOR
Quality Assurance manager.

BACKGROUND
Clinical trials rely on the goodwill of participants; are time consuming for the research staff; and tend to be expensive to fund. It is therefore a prerequisite that all trials in CHaRT are conducted to a high quality – to avoid putting participants at unnecessary or pointless risks, since a trial of an unimportant question or a trial conducted to a poor standard would not provide meaningful evidence; to allow the research staff to work efficiently in the knowledge that their efforts are combining to produce valuable insights; to reassure the funders that public money is being used appropriately and to good effect; and to demonstrate to the sponsor of the trial that their interests are safeguarded.

PURPOSE
To describe the rationale and processes for all quality assurance (QA) activities within CHaRT. QA is the set of processes by which CHaRT can demonstrate that its work has been carried out at or above the relevant required level of performance.

APPLICABILITY
- Essential reading for all CHaRT staff.

QUALITY ASSURANCE (QA)
3.1 Overview of QA in CHaRT

The responsibility for all QA activity resides with the HSRU QA manager. The QA manager is a senior member of CHaRT staff, and has scheduled monthly QA meetings with the director of CHaRT and/or the director of HSRU. The QA manager also interacts regularly with the CHaRT senior management group (see section 2.2: CHaRT organisation) and monthly with the HSRU operations management group.

The QA manager’s primary responsibilities are:
- overseeing and advising on assessments of quality on CHaRT’s projects (see section 3.2: Internal assessment of QA procedures);
- overseeing CHaRT’s co-operation with external auditors & monitors (such as NHS Grampian), regulators (such as Medicines and Healthcare products Regulatory Agency (MHRA)), and so on (see section 3.3: External audit and monitoring of QA procedures) and;
- training (see section 3.4: Training).

The QA manager is also expected to facilitate any activity designed to detect or arising from the discovery of “Fraud and misconduct” (see section 3.5).

3.2 Internal assessment of QA procedures

CHaRT’s internal QA procedures operate at two levels (a) CHaRT generic procedures, and (b) trial specific procedures.
3.2.1 CHaRT generic procedures

(I) Quality assurance of CHaRT staff: The CHaRT director and line manager will ensure that staff have appropriate qualifications and experience to deliver their responsibilities by having: up-to-date CVs; complete and accurate training records; and a system of periodic annual review to identify training gaps.

(II) Quality assurance of buildings/work environment: It is the responsibility of the University of Aberdeen’s Estates Department’s Maintenance Team to ensure that the building(s) that staff work in is maintained and fit for purpose.

All computing and IT equipment are supported and tested by IT services. Any other electrical office equipment is tested by Estates (or sub-contracted to an external company by Estates). Faults affecting any equipment are reported to the Unit business manager. All staff and students are trained on the use of equipment and provided with simple instructions as and when required.

The Unit’s health and safety inspection and work-station assessments are carried out in accordance with the IAHS’s Health & Safety Policy. Although staff routinely work in CHaRT offices, if they are required to work anti-social hours or in potentially uncontrolled environments e.g. home visit to a participant to collect outcome data via a face-to-face interview etc., care will be taken that staff understand potential risks and are able to follow procedures to minimise those risks e.g. taxi transport in anti-social hours; having a colleague present in an uncontrolled environment, as described in section 13: “Working in the community” of the IAHS health, safety and well-being policy available on Q-Pulse.

3.2.2 Trial specific procedures

The type of trials CHaRT engages in are usually long-term studies of complex interventions involving investment of considerable sums of public money. They are multidisciplinary in nature, involving core competencies such as experienced trialists, trial managers, IT professionals, statisticians, health economists, and qualitative researchers, interacting with clinical staff and participants. It is essential that trials are properly designed, conducted, analysed, reported and archived. The evidence that these procedures have been carried out to the required standard is through the production of trial study documentation, which are developed using the repository of approved standardised templates available on Q-Pulse. The appropriate study specific Project Management Group (PMG) (see section 5.10.1) is then responsible for reviewing and commenting on this documentation. In addition, if any deficiencies are found, the senior trials manager will negotiate a correction plan with the responsible staff, including the QA manager and/or CHaRT director, and will monitor that its implementation has been successful. If the deficiency is generic or has ramifications for other trials, that will be addressed by the senior CHaRT management group.

3.3 External audit and monitoring of QA procedures [v06.0303.04]

The QA manager will act as point of contact for all external audits of CHaRT (for example, from NHS Grampian R&D and/or University of Aberdeen (refer to SOP-QA-29 for locally sponsored studies)), other non Aberdeen Universities or NHS Trusts with whom CHaRT is collaborating; and regulatory bodies such as the UK MHRA (refer to SOP-QA-30 for locally sponsored studies). The QA manager will facilitate CHaRT’s response to such external audits, providing requested documentation, making sure staff are available, responding to requests during visits, and then co-ordinating CHaRT’s response to any requirements identified in the auditor’s report.
Chapter 3: Quality Assurance (QA)

For all external study specific monitoring, the QA manager will assist the trial office team: with any preparation for the visit; being available for the monitoring visit (if required); with coordinating the response to any findings raised in the monitor’s report.

For both audits and monitoring visits, where generic (non-trial specific) ‘Observations’ or ‘Findings’ have been reported and may affect or have an impact on other trials, the QA manager will liaise with senior trials manager(s) and/or CHaRT senior management group to ensure all trial teams are made aware of this. In addition, changes may need to be made to specific CHaRT processes.

3.4 Training  [v06.0304.02]

CHaRT understands the need for a properly trained workforce, and that training is a constantly evolving requirement. It is therefore committed to identify, meet and document its staff training and development needs (see section 16.3 for further information). All staff are expected to keep an up-to-date ‘Staff Development Manual’, or an equivalent, which will include their CV, annual review objectives, staff training courses attended. The responsibility of the QA manager is to review periodically review the training records, and liaise with the HSRU business manager and other responsible staff (such as the CHaRT director, the CHaRT senior trials manager, and the CHaRT senior IT development manager) to assure compliance.

3.5 Fraud and misconduct  [v06.0305.03]

If during any routine or ad-hoc inspection of trial documentation, or any correspondence or within any conversations with staff within or out with CHaRT, the QA manager (or delegate) has reason to suspect the possibility of fraudulent behaviour or behaviour which might amount to research misconduct, they must, without delay, inform the CHaRT director, in strict confidence. If the CHaRT director is potentially compromised in any way, they should alert the director of HSRU (or their superior).

CHaRT staff, as University employees, are required to be aware and abide by the University policies on issues of research misconduct. For further information see the University’s Policy & Procedure on Public Interest Disclosure (whistleblowing) www.abdn.ac.uk/staffnet/governance/policies-proceedures-plans-and-guidlines-399.php and local Sponsor guidance on Study Management: Management and Monitoring www.abdn.ac.uk/clinicalresearchgovernance/study-management/management.php.

CROSS REFERENCE

Section 5.4: Trial protocol
Chapter 16: CHaRT staff training

VERSION HISTORY

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<td>Jan 2012</td>
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<td>Minor changes to title of section 3.2 to say ‘assessment’ instead of ‘audit’ and 3.3 to include ‘monitoring’. Details of study-specific monitoring visits added. Minor changes &amp; updates.</td>
<td>Apr 2015</td>
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<td>Apr 2018</td>
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<td>Jan 2020</td>
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Chapter 4: Collaboration

CHAPTER 4: COLLABORATION  [v06.0400.03]

LEAD AUTHOR
Research managers.

BACKGROUND
CHaRT receives core funding from the Chief Scientist Office (CSO) of the Scottish Government Health and Social Care Directorates, the University of Aberdeen, and competitive grant funding from many public funders such as: NIHR HTA, HS and DR, PHR, EME, CSO, and other research councils and charities. It is important that CHaRT has rigorous and transparent criteria for developing collaborations with research partners.

PURPOSE
To describe the criteria upon which CHaRT’s engagement will be based.

APPLICABILITY
• Essential for all senior CHaRT staff involved in strategic decision making.
• Desirable background reading for all CHaRT staff.

COLLABORATION
4.1 CHaRT collaboration criteria  [v06.0401.03]
CHaRT is expected to justify its selection of trials and defend the strategic balance of its portfolio at annual and quinquennial reviews by an independent international panel.

The management of the selection of the trials adopted into the CHaRT portfolio is the responsibility of the CHaRT director and the CHaRT research managers. The criteria for selection of trials can be found at: www.abdn.ac.uk/hsru/what-we-do/trials-unit/planning-a-trial-553.php They are supported in this process by the CHaRT Advisory Group which meets regularly (6-8 weeks) to discuss opportunities for trials that have arisen. Views from the various stakeholders are solicited and discussed, to assess the suitability of a trial for adoption and work up for funding. Arrangements for CHaRT’s engagement will vary for each trial depending on the collaboration sought.

Reflecting our academic remit, CHaRT collaborates as an intellectual partner in the research, not as a service provider. It expects to lead the methodological design of the trial; to take responsibility for the management of the trial; and to use the most appropriate technologies for the analysis and reporting of the trial. Variations on this model of engagement are undertaken. However, in all instances CHaRT anticipates making a significant intellectual contribution to the research, and for its staff members to be recognised for their contribution as grantholders and authors as appropriate.
### CROSS REFERENCE

**Chapter 2: CHaRT details**

### VERSION HISTORY

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<td>Feb 2020</td>
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CHAPTER 5: TRIAL INITIATION

LEAD AUTHORS
Senior and deputy senior trials managers.

BACKGROUND
The initiation (or set-up) phase of a trial is demanding. There are a number of legally required processes that need to happen (the authorisations – ethical, regulatory e.g. Clinical Trial Authorisation, financial e.g. insurance and indemnity, and site contracts). There is usually a relatively short, fixed time frame from being awarded the grant to starting recruitment (typically no more than six months). In addition to the obligatory authorisations, the multidisciplinary study team must effectively organise the trial materials such as the protocol, the case report forms (CRF), patient information leaflets (PIL), the consent form and any other study documentation; and the study databases and IT applications (such as the randomisation system). This requires good communication and planning between the various groups – the clinicians, statisticians, programmers, trial methodologists, trial managers and so on. A trial manager usually plays a pivotal role in this phase.

PURPOSE
To describe the essential processes in developing a trial from successful grant proposal to first randomised participant.

APPLICABILITY
• Essential reading for all CHaRT staff involved in launching a study, in particular the trial managers.

TRIAL INITIATION
5.1 Trial authorisations

5.1.1 Sponsorship
All CHaRT trials need a sponsor (see the following link for a description of “sponsor” www.ct-toolkit.ac.uk/glossary/?letter=S&postcategory=-1. The sponsor(s) is usually the substantive employer of the Chief Investigator (CI). Therefore, for trials led from Aberdeen, this will usually be the University of Aberdeen and NHS Grampian as co-sponsors (refer to SOP-QA-4 for details on applying for sponsorship for locally sponsored studies). When the CI is based out with Grampian it is the trial manager’s responsibility to check with the CI that sponsorship has been obtained. It is usual (obligatory, if the University of Aberdeen and/or NHS Grampian is the potential sponsor) for an organisation considering taking on the role of sponsor to institute a risk assessment, to establish whether their responsibilities will be executed properly by the study team. It is the trial manager’s responsibility to liaise with the sponsor about the risk assessment.

As indicated above, the sponsor’s role is an important one in the configuration of a clinical trial. CHaRT as a trials unit will undertake to communicate promptly and effectively with the sponsor(s) to satisfy and reassure the sponsor(s) that the sponsor’s obligations on the authorisations, the financing and the progress reporting (including emerging safety data) of the trial are being met. This will include providing information before the start of a trial for the purposes of risk assessment by the sponsor(s) and submission of core documentation to the sponsor(s) for sign off prior to submitting applications for regulatory approvals.
The trial manager should be satisfied that the appropriate insurance and indemnity is in place, by verifying this with the sponsor.

5.1.2 Ethical
The need for independent review of the ethics of medical research is obligatory.

CHaRT will always comply with the relevant process in force. Currently, for our UK trials this is the Health Research Authority (HRA) - [www.hra.nhs.uk/](http://www.hra.nhs.uk/) and the Integrated Research Application System (IRAS) [www.myresearchproject.org.uk/](http://www.myresearchproject.org.uk/) who maintain the established UK-wide framework for review of research.

Prior to study start-up, all trials must have favourable opinion from a Research Ethics Committee (REC). The application form can be found at: [www.myresearchproject.org.uk/](http://www.myresearchproject.org.uk/). A trial manager will usually own the IRAS for the study. A trial manager will establish with the CI who is taking responsibility for preparing and submitting the ethics application. The trial manager must have a copy of the full ethics submission and approval, filed in the TMF. It is usual that each document submitted to REC with the initial submission is versioned as version 1. Any deviation to this should be documented on a version log. Please see [SOP-QA-10](#) for further information for locally sponsored studies.

In exceptional circumstances, a trial may fall outside the remit of HRA and as such ethical review should be sought elsewhere.

5.1.3 Management approval
Management approval (sometimes referred to as Capacity and Capability (C&C) or R&D approval) must be obtained from the appropriate bodies prior to any research commencing (this may be from the R&D department of an NHS Trust, R&D department of an NHS Board, primary care general practice, primary care dental practice, Research Network or similar depending on where the research is to take place). Similar to the ethics favourable opinion, no recruitment at a centre must take place until R&D approval is in place for that site. Please see [SOP-QA-10](#) for local procedures on applying for R&D approvals.

There are different mechanisms in place for seeking R&D approval between nations.

Links to further details of the coordinating centres in England, Scotland, Wales and Northern Ireland are given below:

4. Northern Ireland: Health and Social Care Application Gateway. [research.hscni.net/approval-research-hsc](http://research.hscni.net/approval-research-hsc)
5.1.4 Regulatory

It is not always obvious what is or is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) under the EU Directive. It is the trial manager’s responsibility to verify that each trial has been checked against the published algorithm: (assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algorithm.pdf) and if there is any doubt, the CI or Sponsor should seek an expert adjudication from the UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA).

Studies involving a device that is not European Conformity (CE) marked may fall under the Medical Devices Regulations. See www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device for further information and how to apply. Queries as to whether a study would fall under the Medical Devices Regulations can be directed to the MHRA.

If any international sites are involved, the trial manager should work with the CI to ensure that all relevant national authorisations and processes are obtained and maintained as appropriate.

If the research is a CTIMP taking place in the UK, a clinical trial authorisation (CTA) or a Clinical Trial Notification (CTN) must be submitted to the MHRA. Detailed guidance on the application for a CTA or CTN can be found at: www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/index.htm.

Prior to submitting a CTA or CTN application, a EudraCT number is required to uniquely identify the study and is allocated by the European Medicines Agency following protocol registration on this website (EMA; see eudract.ema.europa.eu).

It is vital that the CHaRT trial team work closely with the lead clinical trials pharmacist or appropriate team member(s) to ensure that all procedures and facilities are appropriate, and any pharmacies involved with the trial are fully informed and adhering to the specific trial criteria.

5.1.5 Legal and financial

There are usually a number of legal issues that need to be addressed in a multicentre clinical trial. It is also important that the financial arrangements are in place before the trial starts. Sub-contracts are issued between the sponsor and the appropriate Trust/Board, Practice, Care Home or other appropriate body, including details of any research funds available to the sites. It is the responsibility of the CI or his/her designated team member to instruct and monitor contract activity. Please refer to SOP-QA-13 for further information on the generation of contracts for locally sponsored studies. All financial and contractual details should be considered confidential. It is the CI’s (or delegate’s) responsibility to verify that contracts between the sponsor(s) and individual recruiting centres are in place and up to date, and bring any queries and/or variations to the attention of the sponsor(s). Recruitment at an individual site should not commence until this signed agreement is in place.

Contracts with any third parties are also likely to be required, for example with companies supplying Investigational Medicinal Products or devices, or carrying out laboratory tests. Please refer to SOP-QA-16 for further information for locally sponsored studies.
For high value purchases (£50,000 or more) the sponsor is likely to require a tendering process before procurement of goods or services. Examples of an invitation to tender are available on Q-Pulse. The sponsor procurement policy is likely to include financial thresholds above which quotes may be required (this may be for purchases of £1000 or more). For locally sponsored studies, contact the University of Aberdeen procurement team (www.abdn.ac.uk/staffnet/working-here/purchasing-procurement-1110.php).

If services or products are being provided free of charge by a company or organisation, a contract or agreement is likely to be required. For locally sponsored studies, contact the University of Aberdeen R&I team (www.abdn.ac.uk/business-info/research-innovation/).

5.2 Trial registration

All trials will be registered on a publically available registry. Currently these include:

- The International Standard Randomised Controlled Trial Number (ISRCTN) Registry (www.controlled-trials.com)
- The National Institute of Health Trials Registry (www.clinicaltrials.gov)
- Research registry (www.researchregistry.com) – although this is not preferred for trials.

If a funder/sponsor has a policy for registration, usually that will prevail.

It is a requirement for publication by leading journals and by the Research Ethics Committees (RECs) that the trial be registered before any participants are randomised.

At the end of the study, there is usually a requirement to upload the results to the trials registry (see section 5.1.4 and section 7.2). For CTIMPs there is also a requirement to register the trial on the European Medicines Agency (EMA; see eudract.ema.europa.eu) (see section 5.1.4). At the end of the study, results must also be uploaded onto this portal.

In addition, most, if not all CHaRT trials will be eligible for National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio support: www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/run-your-study/crn-portfolio.htm

5.3 External relations

It is the duty of all CHaRT staff to maintain professional and courteous relations with all external bodies that CHaRT will collaborate with. This will include other University departments (within Aberdeen, across the UK and further afield), other Clinical Trials Units, professional bodies, government departments, NHS bodies, charities, funding agencies, and regulators. CHaRT works hard to project and maintain an image of excellence and reliability, and it is important that CHaRT staff promote this image at all times by their attitude and conduct.

5.3.1 Funders

CHaRT's long-term sustainability rests in part on maintaining its successful and established partnership with major funders such as National Institute for Health Research (NIHR) Health Technology Assessment (HTA), Medical Research Council (MRC) and Chief Scientist Office (CSO). It is therefore important that CHaRT staff establish and maintain good relations with
funders and that they understand and meet their contractual obligations to the funder. It is particularly important that in the event of any difficulties or dissatisfaction expressed by the funder, senior CHaRT staff are made aware of the situation.

Both background and any potential foreground IP issues will be considered by the funder at trial start-up and throughout the project. Advice can be sought from the sponsor(s).

5.4 Trial protocol

All CHaRT trials are required to have a trial protocol. Protocol templates are available on Q-Pulse. For locally sponsored studies, please refer to SOP-QA-3 for protocol guidance for use in high risk trials and CTIMPs. The trial protocol is a statement of the scientific objectives of the study, with clear detail on the methods and conduct and with input from all relevant disciplines. The trial protocol is usually based on an extension of the final approved grant submission. Members of the trial Project Management Group (PMG) are usually expected to take responsibility for drafting the protocol.

Trial protocols should be published in a peer-reviewed journal (preferably in open access mode) and should include the SPIRIT checklist1 items. CHaRT, in collaboration with the CI, will take responsibility for this. Refer to specific journal guidelines as to when protocol papers will be accepted (for example before recruitment closes or before analysis starts). See Chapter 8: Trial publications and dissemination for more detail.

5.4.1 Study guidance

It is important to distinguish the trial protocol from the study guidance (sometimes referred to as an operations manual), the former is the scientific statement of the trial’s aims and methods; the latter is a very detailed description of study processes that deliver the trial. The study guidance is intended to grow organically as the study progresses, documenting problems and their solutions, and also ensuring their consistent implementation across centres in a trial.

5.5 Case report form (CRF)

For the purposes of the SOP a Case Report Form (CRF) encompasses clinical case report forms and also patient reported outcomes such as Questionnaires, which may be paper or electronic (eCRF).

The CRFs record the study data. Wherever possible, tried and tested formats from previous trials should be used or adapted when designing the CRFs for a new study. Templates are available in the CHaRT resources repository on Q-Pulse. For validated tools, licence agreements may be required.

CRFs are developed alongside the study protocol and dummy tables (if necessary CRFs may be modified after feedback). See Section 6.8 for further details about amendment processes for key documents.

The development of the CRFs is a multidisciplinary task, needing input from:

- investigators
- those responsible for the data collection e.g. study nurses
- statisticians
- health economists (as appropriate)
- health psychologists (as appropriate)
- IT application programmers
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- trial managers
- patient and public involvement (PPI) partners
- study committees (Trial Steering Committee (TSC), Data Monitoring Committee (DMC))

CRFs need to be subject to systematic checks against the study protocol and version controlled. CRFs must be clearly set out, the data being collected matching the trial dummy tables (see section 12.2). CRFs will be incorporated into training materials and the Investigator Site File (ISF), and sent out to the sites by CHaRT and/or maintained by CHaRT on the trial web portal, as stipulated in the trial protocol.

All participant completed questionnaires should be submitted to REC for approval; CRFs are not usually submitted to REC unless explicitly requested.

The final versions of the CRFs will be versioned as version 1. At the outset of a study, if required, the programming team will build version 1 of the eCRFs (see also section 6.8 for amendments).

5.6 Informed consent

Consent is an essential element for all participants in clinical trials. It is usual for participants to be informed of their role in the study and consent to it by indicating their willingness to participate by signing and dating an informed consent form. Any deviation to this process will be documented in the trial protocol.

For most studies, the key requirements of this process are that the participant is able to give consent; that they do so voluntarily; that they understand what they are consenting to; and that the consent is properly documented (the consent form template is available on Q-Pulse). Please refer to SOP-QA-9 for locally sponsored studies.

Traditionally, the mechanism for imparting the information to a participant to give them the opportunity to start comprehending their potential role in the trial is the patient information leaflet (PIL; this template is available on Q-Pulse, please also see www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/ for further guidance on the content of these leaflets). The time that potential participants will have to consider participation will be detailed within the protocol. They also need to be given adequate access to trial staff to discuss any concerns they have.

Once informed consent has been satisfactorily given, the participant must be given a copy of the consent form for their retention. The protocol should document whether or not signed copies of the consent forms are returned to the trial office. The original "wet-ink" signed consent form should be retained in the ISF (see section 5.8.2). Informed consent forms are a very important component of the essential documentation of a trial.

Particular attention needs to be paid when eliciting the consent of vulnerable groups; these include participants with temporary or permanent cognitive impairment (for example, trials in an emergency setting when a person might be unconscious; or trials in people with dementia or mental health conditions); trials in children; trials in people with learning difficulties or language issues; and so on. Refer to the relevant national guidance on incapacity (see www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/). If consent is not possible and assent or verbal agreement is sought, this procedure will be fully detailed in the trial protocol together with the mechanism for subsequently gaining fully informed consent, where relevant.
5.7 Other documentation [v06.0507.01]
In addition to the documents described in Sections 5.4, 5.5 and 5.6, other documentation will be required to be drafted prior to trial initiation. This may include covering letters for questionnaires or other trial supplies, advertising materials etc., Investigational Medicinal Product Dossier (IMPD), Investigator Brochure (IB), and drug labels etc.

5.8 Essential documentation [v06.0508.05]

5.8.1 Trial master file index (TMF)
The trial master file index (TMF) must include all essential documentation related to the trial and can be a hard copy, electronic or a hybrid system. A TMF index template is available on Q-Pulse. The index should be very clear about what essential documents are held as hard copy (and their location) and what essential documents are held electronically (and their location; for example, on the shared network or the study website). Any essential information or documents missing must be explained in a file note (a template can be found on Q-Pulse). Maintenance of the essential trial documentation is the responsibility of the trial manager(s).

5.8.2 Investigator site file index (ISF)
The trial's investigator site file index (ISF), like the TMF, can be a hard copy, electronic or a hybrid system. An ISF index template is available on Q-Pulse. The ISF index should be very clear about what essential documents are held as hard copy (and their location) and what essential documents are held electronically (and their location). The ISF must include all essential documentation related to the trial relevant to the individual site. Any missing information or documents or deviations must be explained in a file note. It is the responsibility of the Trial Manager (or member of the study team) to provide each site with an initial ISF and thereafter any updated documents. Sites who maintain a hard copy of their site file must take responsibility for keeping their ISF up to date.

Please refer to SOP-QA-7 and SOP-QA-8 for further details on establishing and maintaining a TMF and ISF for locally sponsored studies.

5.9 Site selection and initiation [v06.0509.04]
Sites are identified in a variety of ways, such as those listed in the grant application, sites we have worked with before, and new sites. When considering selection of sites, the trial manager should document communication about the suitability of the site. A trial site expression of interest form template, which may include recruitment target, is available on Q-Pulse and can be used for this purpose. For locally sponsored studies, please also refer to the SOP-QA-40.

It is important that sites recruiting participants into a trial are prepared sufficiently to transact the study processes competently and efficiently. It is usual for CHaRT to provide training to site staff in study processes, including informed consent, randomisation, CRF completion, data entry on a study web portal, adverse event reporting and query receipt and resolution and other issues as appropriate. The pre-site initiation questionnaire, which is available on Q-Pulse, may be a helpful tool to inform discussion during the site initiation. All CRFs and trial procedures should be reviewed with particular emphasis given to consenting procedures.

Roles and responsibilities of individual site team members should be included in the trial’s site delegation log (a template can be found on Q-Pulse). It is essential that those with delegated responsibilities are fully aware of their responsibilities (e.g. informed consent, randomisation, data entry, clinic visit scheduling, adverse event reporting, query processing, etc). A copy of
the signed delegation log should be kept in the ISF and TMF. For locally sponsored studies, refer to the SOP-QA-6.

Site visits/training can take place prior to appropriate legislative procedures being in place but no participant recruitment can start until all necessary approvals have been issued. Site initiation may be carried out by visiting sites, holding central study training days or by telephone/video conferencing to train study staff at the recruitment sites in the study processes. This should be undertaken before the first participant is recruited into a study at the site.

It is emphasised that training may need to be repeated over a long trial, or as and when needed (e.g. when new staff join a centre). Any training gaps identified, are to be rectified as soon as practicable.

Prior to visits/training, the trial manager will try to ensure that local team members involved in the study have the opportunity to familiarise themselves with the protocol and all essential documentation (see section 5.8). Any procedures that are not clear can be discussed during the site visit training. If possible, all those involved in the study locally (e.g. PI, recruitment officer, research nurse, physiotherapist, pharmacist etc.) should attend the relevant sections of the initiation meeting/training session.

5.10 Trial monitoring [v06.0510.05]
The sponsor usually conducts a risk assessment for randomised controlled trials. The risk assessment contributes to the creation of a CHaRT trial specific monitoring plan. For locally sponsored studies, a trial monitoring plan template is available on Q-Pulse. For studies sponsored elsewhere, the sponsor may provide a template. This should be reviewed and updated when appropriate throughout the trial.

The trial monitoring plan details the scope, level and type of checking (e.g. all consent forms, all primary outcomes, 10% of a selected minimisation covariate, 10% of questionnaires) with a responsive plan depending on what was found (e.g. >3% error would trigger more extensive checks).

In addition, the trial monitoring plan describes the trial oversight, training and central monitoring arrangements. We may use monitoring solutions (for example during the preparation of DMC reports) which identify spurious or unusual data patterns in accruing data. This central monitoring indicates potentially problematic centres and allows investigation and targeted monitoring in a proactive rather than reactive manner.

5.10.1 Trial oversight
The five main groupings that contribute to the oversight and governance arrangements for each trial are: the funder(s), the sponsor(s), the Project Management Group (PMG); an independent Trial Steering Committee (TSC); an independent Data Monitoring Committee (DMC). The membership and remit of these committees, including frequency of meetings and expected progress reports, will be referenced in the trial protocol and detailed in the TSC and DMC charters. Templates of these documents are available on Q-Pulse. Please refer to SOP-QA-17 for further information on creating the necessary management and oversight committee for locally sponsored studies.

• The funder is likely to require regular progress reports and will provide guidance on issues encountered within the study (see section 5.3.1).
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- The role of the sponsor (see section 5.1.1) is to have ultimate responsibility for the study and ensure that trial is being conducted in accordance with the principles of GCP and the relevant regulations.
- The PMG will consist of the grantholders, those responsible for the day-to-day management of the trial (usually the trial manager) and can include a Patient and Public Involvement (PPI) representative.
- The role of the TSC is to monitor and supervise the progress of the trial. The membership usually consists of an independent chair, together with at least two other independent members. It is normal that members of the PMG be invited to the TSC meetings (in particular the CI, trial manager and statistician). The CHaRT TSC charter template, which can be found on Q-Pulse, was developed using the MRC CTU template TSC Charter version 1.02, 13-Mar-2006.
- The role of the DMC is to monitor accumulating trial data during the course of the trial and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial. CHaRT has adopted the DAMOCLES charter for DMCs and suggests to the independent DMC members that they adopt the Terms of Reference. A copy of the CHaRT DMC charter template can be found on Q-Pulse. It is important that closed progress reports to the DMC, since they may contain unblinded analyses, are held in strict confidence and are only accessed by authorised personnel. In general, they should not be seen by other members of CHaRT or the individual study team, including the CI, the trial manager, and so on. Closed reports, and the closed session should be securely archived by the statistician preparing the report, for later inspection if the need arises. An open DMC progress report is frequently prepared, and this can be seen by all members of CHaRT and the individual study team.

The independent members of the TSC and DMC should meet to agree their terms of reference. The Funder or Sponsor will determine whether this should be prior to the first randomisation.

5.11 Patient and Public Involvement (PPI)  [v06.0511.03]

A crucial aspect of the design of CHaRT trials is that the question being investigated is of importance to potential participants and uses outcomes that measure dimensions of the condition that matter to the person with the condition. The most effective way of ensuring that these conditions are maximized is to involve people with everyday experience (i.e. individuals who are able to contribute a patient and/or wider public perspective) in the design and delivery of the trial (see Chapter 15: Patient and Public Involvement for more detail). CHaRT has an unambiguous commitment to the involvement of members of the public in as many of its trial processes as possible. Such involvement will be sought as early as possible in the development process for the trial – ideally from the grant application stage. PPI input should be sought on at least the patient facing documents prior to seeking REC approval. Membership of specific trial Committees such as the PMG and the TSC are also recognised ways of involving patients and/or the public.
Chapter 5: Trial Initiation

CROSS REFERENCE
Chapter 6: Trial conduct and management
Chapter 8: Trial publications and dissemination
Chapter 15: Patient and public involvement

Reference:
1 www.spirit-statement.org/

VERSION HISTORY

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<td>Total revision and re-ordering of this chapter; particularly to sections 5.1, 5.4 and 5.7.</td>
<td>Jan 2012</td>
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<td>04</td>
<td>Updates to sections 5.1, 5.6, 5.7 and 5.8. Further clarity on section 5.4.2 Case Report Form; including updates to relevant web links</td>
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<td>Updates to sections: 5.1.3. R&amp;D approval paragraph to include information on the different R&amp;D procedures across the UK; 5.1.4. addition of paragraph on studies using devices; 5.1.5. merging of Legal and Financial paragraph. Addition of two new sections 5.7 other documentation and 5.8 essential documentation (previously within Chapter 6).</td>
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<td>06</td>
<td>Minor clarifications to sections 5.1.2, 5.1.4, 5.4.1, 5.5, 5.8 and 5.10. Revision of text to reflect C&amp;C procedures (5.1.3); addition of text about tendering procedure and services/products (5.1.5); addition of text about uploading results at the end of study and revision of text in relation to CRN function (5.2); revision of text around publication of trial protocol (5.4); revision to text to clarify version of consent to be retained in the ISF, clarification around consent in vulnerable groups (5.6); revision of text around delegated responsibilities (5.9); addition of text around funder progress reports, revision of text around role of the DMC and timing of agreeing terms of reference for TSC and DMC (5.10.1).</td>
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CHAPTER 6: TRIAL CONDUCT AND MANAGEMENT

LEAD AUTHOR
Senior and deputy senior trials managers.

BACKGROUND
Although trial design is of fundamental importance (an important question investigated with optimal methodology) it is said that a successful trial is “10% science, 90% process”. Having established and proven techniques for conducting the trial is therefore crucial.

PURPOSE
To describe the CHaRT processes in conducting a trial from the first randomisation (or screening) through to the last participant, last visit and study reporting, and document generic issues for trial management of CHaRT trials.

APPLICABILITY
• Essential reading for all CHaRT staff involved in trial conduct, in particular the trial managers and data coordinators.

TRIAL CONDUCT AND MANAGEMENT

6.1 Good Clinical Practice
Good Clinical Practice (GCP) is an ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve participation of human subjects. Compliance with the principles of this standard provides public assurance that the rights, safety and well-being of trial subjects are protected. It is imperative that all staff working within CHaRT have appropriate training in GCP (a level of knowledge that reflects their exposure to the principles). For CTIMPs, staff will be required to attend a GCP specific training course; in addition, staff should refer to www.legislation.gov.uk/uksi/2004/1031/part/4/made for further information on GCP in clinical trials relating to the Medicines for Human Use Regulations 2004. For non-CTIMPs, staff are required to attend the local Good Research Practice (GRP) training course. Also refer to SOP-QA-34 for locally sponsored studies.

For non-CHaRT staff working on CHaRT trials e.g. Principal Investigators (PIs), Research Nurses (RNs) etc., GRP or GCP training should be commensurate with the local team members’ roles and responsibilities and the type of study they are working on.

6.2 Trial monitoring
The CHaRT trial monitoring plan as detailed in Section 5.10 should be followed. In addition, trials may be subject to monitoring/audit by external bodies (e.g. R&D Departments, MHRA; see Section 3.3 for more information and refer to SOP-QA-28 for locally sponsored studies).

6.3 Governance arrangements
Research Governance applies to everyone working in health care research (including CIs, PIs, RNs, laboratory staff and CHaRT staff). For further details, refer to the relevant sponsor’s guidance. For studies sponsored by the University of Aberdeen, refer to the University of Aberdeen / NHS Grampian web pages for research governance issues related to clinical research studies: www.abdn.ac.uk/medical/researchgovernance/clinicalresearch, and the
6.4 Progress reporting [v06.0604.05]
The funder of the study will have a format and timeline for reporting. It is the responsibility of the trial manager and/or CI that he/she is clear when progress reports are due and on which template. The report to the funder should be delivered on time, addressing all issues, in particular any areas of concern.

In addition, an Annual Progress Report (APR) which can be found at www.hra.nhs.uk/research-community/during-your-research-project/progress-reporting/ should be sent to the REC 12 months after the date on which the favourable opinion was given and subsequently annually thereafter until the end of the study. It is the responsibility of the CI/trial manager to ensure these reports are submitted on time. Please refer to the SOP-QA-21 for full details on preparing and submitting APRs for locally sponsored studies.

For CTIMPs, it is the sponsor’s responsibility to prepare and submit the annual Development Safety Update Report (DSUR) to the Medicines and Healthcare products Regulatory Agency (MHRA), but this may be delegated to the CI (and any such delegation should be documented in the (co-)sponsorship agreement and/or the trial protocol). Please refer to www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues for details on submitting a DSUR, which is completed using the Common European Submission Portal (CESP). The DSUR should also be copied to the sponsor and REC. The trial manager is usually involved with this process. The CESP submission details should be used as evidence of the DSUR submissions and should be retained in the TMF and forwarded to the sponsor. Please refer to the SOP-QA-21 for details on preparing and submitting DSURs for locally sponsored studies; examples of recent DSUR reports are available on Q-Pulse. The DSUR preparation may highlight if there is a requirement for a substantial amendment to update the reference safety information (SmPC or IB). Please refer to SOP-QA-14 for details for the use of these regulatory documents. Reconciliation of the Serious Adverse Event (SAE) log against the SAEs recorded on the study website should be undertaken before preparing the line listings for the DSUR. Consideration should be given to MedDRA coding of SAEs prior to preparing the line-listings. In order to access the MedDRA coding you will need a MedDRA ID before logging in to their website https://tools.meddra.org/wbb/. Please liaise with the senior Trials Managers for details on accessing the MedDRA ID.

The trial manager should also comply with any requests from local R&Ds for individual progress reports.

6.5 Safety reporting [v06.0605.05]
Serious Adverse Event (SAE) procedures (including who is responsible for reporting) must be detailed within the trial protocol for all interventional studies (including both CTIMPs and non-CTIMPs). The local PIs, CI or their medically qualified deputies are usually responsible for assessing seriousness, causality, severity and expectedness. See the HRA guidance for clarification on definitions and reporting procedures/timelines for both CTIMPs and non-CTIMPs: www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/.

All SAEs, that require to be recorded as part of the study protocol, should be recorded on the appropriate SAE form which is available on Q-Pulse. For locally sponsored studies, please also
refer to the SOP-QA-22 for further details on identifying, recording and reporting SAEs in CTIMPs and SOP-QA-39 for AEs in medical device clinical investigations.

All electronic SAEs recorded remotely in CHaRT trials are automatically flagged to relevant members of the trial team (which may include the CI, trial manager and senior CHaRT management) to ensure appropriate follow-up. CHaRT may facilitate the CI in the reporting of an SAE to the relevant parties (e.g. sponsor, DMC, TSC, REC, regulator) in the appropriate timescale, once it has been generated and assessed. The details of such arrangements should be stated in the trial protocol and fully specified in the study guidance/operations manual and associated legally binding contracts.

6.6 Breach reporting  
Breach reporting of the conditions and principles of GCP or the trial protocol should be recorded on the CHaRT breach report form which can be found on Q-Pulse. Possible breaches should be discussed with the trial CI, Senior Trials Manager or the CHaRT director, or outwith CHaRT (e.g. with NHS R&D Director or sponsor) as appropriate, as soon as it becomes apparent that a possible breach has occurred.

An initial assessment of seriousness should be made by the CI. A serious breach is one which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial. The CHaRT non-compliance and breaches guidance document can be found on Q-Pulse.

If the breach is potentially serious it should be reported to the sponsor as soon as possible (usually within 24 hours). The sponsor, together with other key stakeholders (e.g. the CI, trial manager, R&D Director/Manager) will undertake an assessment and consider whether a corrective and preventive action plan is required. If the breach is confirmed as serious, the sponsor, or delegated research team member, will notify the REC within 7 days of becoming aware of the serious breach. The MHRA should also be informed within 7 days of confirmation of the serious breach. The Notification of Serious Breaches of GCP or Trial Protocol Form should be used to inform both the MHRA and the REC – www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

Please refer to the SOP-QA-25 for locally sponsored studies for further information on the notification of serious breaches of GCP and/or the trial protocol in all interventional research.

If the breach relates to a data protection issue, the data breach should also be reported to the Sponsor’s Data Protection Officer as soon as possible (usually within 24 hours). Please see website for full details: www.abdn.ac.uk/staffnet/governance/data-protection-6958.php#panel8626.

6.7 Urgent safety measures  
An Urgent Safety Measure (USM) occurs when a research participant or participants are identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant(s). In such circumstances, the sponsor, Chief Investigator or any Principal Investigator may make changes to the conduct of a study without first giving notice to the REC or obtaining a favourable opinion. If a USM is implemented, the sponsor should be notified
immediately. The REC should also be informed by telephone, ideally within 24 hours. Notice in writing should follow to the REC within 3 days.

For CTIMPs, a USM can be implemented without giving notice to the MHRA. The MHRA should be informed by telephone, ideally within 24 hours. Notice in writing should follow within 3 days. A substantial amendment covering the changes made as part of the USM should be submitted within two weeks of the notification to the MHRA.

Where a USM requires amendment to study documentation, this should be submitted to REC (and MHRA if applicable) as soon as possible and marked as being in response to a USM.


6.8 Amendments [v06.0608.05]

Refer to the funder’s contract to review whether any proposed amendment requires their approval before submission to sponsor and / or REC. Sponsor(s) will review and approve any proposed amendments prior to submission. SOP-QA-19 provides further details on how to submit substantial amendments for locally sponsored studies.

The amendment tool and full guidance, which can be found at www.myresearchproject.org.uk/help/hlpamendments.aspx, should be used for all amendments for project-based research. The tool categorises the amendment and provides tailored guidance on how to submit. It will identify any review bodies the amendment needs to be sent to, based on the changes that are being made to the study.

The Notice of Substantial Amendment/annex 2 form can be generated by completing the tool. This version of the form can then be submitted to the REC and the MHRA (as required) when making a substantial amendment to a trial. It also provides detailed information about the amendment to participating sites.

Once you have completed the amendment tool, you should follow the submission guidance provided in the submission guidance tab of the tool. If the amendment needs to be submitted, then the amendment tool, together with all the supporting documents, should be uploaded into via IRAS and submitted using the online system.

Any changes/updates to documentation must be agreed through informed discussion at appropriate trial meetings.

The R&D approval processes varies depending on the geographic location of participating sites. See www.myresearchproject.org.uk/help/hlpnhshscr.aspx for further details.

The amendment shall only be implemented once all the necessary approvals have been received. The trial manager should ensure that the processes and timing of amendment notification/approval are implemented. Rather than submitting multiple amendments in close succession, one amendment covering all changes may be preferable.
Chapter 6: Trial conduct and management

For CTIMPs, if a substantial amendment is being made to the protocol, take the opportunity to ensure that the reference safety information (SmPC/IB) is reviewed and updated if appropriate. Please refer to SOP-QA-14 for details for the use of these regulatory documents. Any change that the trial team wish to make (in terms of the version of the reference safety information) is considered a substantial amendment. Changes to the version of the reference safety information may have implications as to how any safety events are assessed during that DSUR reporting period and therefore consideration should be given to the implementation date of any change to the reference safety information (see MHRA blog for more details; mhrainspectorate.blog.gov.uk/2016/03/02/reference-safety-information-for-clinical-trials/ and mhrainspectorate.blog.gov.uk/2017/01/18/reference-safety-information-ii/).

An amendment log should be maintained summarising the key changes, together with new version numbers and dates of any revised documents.

Following the receipt of relevant approvals, at the point of implementation, amended documents should be distributed to appropriate sites. Sites will be instructed to destroy any unused hard copies of older versions and mark any hard copy versions in their investigator site file (ISF) as superseded. New versions will be incorporated in training materials.

Any planned amendments to CRFs should be discussed with the programming and statistics teams so that the study database and Statistical Analysis Plan (SAP) can be updated as required (see Section 10.2.3 for details on Change Management in relation to databases). A change request form (see Q-Pulse) is required for any changes to the data collection tools built on the study website. All changes to the protocol or the CRFs should be consistent. If there are any changes to REC approved CRFs (for example questionnaires), approval of the new version must be obtained before these are implemented (see Section 6.8).

6.8.1 Amendment processes for key documents

The first version of documents submitted for regulatory and/or ethical approval is usually Version 1 (see section 5.1.2). Amendments made subsequent to or as a condition of regulatory/ethical favourable opinion (as applicable) will generate a new version. A version control document should be used to record changes made to key documents (available in Q-Pulse).

6.9 Error correction [v06.0609.04]

Error correction on a hard copy paper case report form (CRF) is undertaken by crossing through the incorrect data with a single line, adding the correct data and signing/initialling and dating the change in permanent ink. Justification of why the amendment has been made (such as a copy of a letter from an investigator clarifying data) may be attached to the CRF or noted on the eCRF. Under no circumstances is correction fluid (e.g. Tippex) to be used. The CHaRT guidance document completion of CRFs can be found on Q-Pulse. For locally sponsored studies, please also refer to SOP-QA-27 Good Documentation Practice. There is an electronic audit trail for all amended electronic data on CHaRT trial databases.

Any personal identifiable data that does not form part of the content of a CRF form in completed CRFs received by CHaRT centrally will be obscured at the time of data entry or prior to archiving (e.g. if a participant writes their name or other identifying information on a CRF, this is covered over upon receipt by pen and/or sticker). There are cases where personal identifiable data should not be redacted (e.g. a letter written by a participant to the trial team, a prescription).
These should be discussed on a case-by-case basis. Please refer to the SOP-QA-12 for local sponsored guidance on managing research data in CRFs.

6.10 Query processing

The frequency that queries are generated is dependent on the size of the trial and data collected. The standard method of data entry by study personnel is via a dedicated software programme or study web portal, hosting a remote data capture application authorised by CHaRT. Some validation can be built into the data capture application whereby the data entry person will be asked to clarify or confirm impossible or improbable entries at the point of entry. Care should be taken in respect of the amount and the range of validation that is included, so as not to restrict users. To clean the data, further queries will be generated at specific times (e.g. weekly, monthly, or at important milestones; such as several weeks before a database lock for a DMC Report). Data queries can be generated within the study website. The resulting queries will be distributed to the responsible person (PI, nurse or recruitment officer etc.) at each centre, who will investigate and attempt to resolve the query, and update and correct via the study web portal, or via the study office at CHaRT.

6.11 Filing

With the large volume of documentation required for each trial a satisfactory filing system of both hard copy and electronic data is essential. The filing system should be segmented so that individual trials remain separate. It is the responsibility of all CHaRT staff to ensure that data are held securely and confidentially.

Access to all electronic trial data must be restricted to authorised team members. Hard copies of CRFs should also be stored securely.

6.12 Study meetings

Study meetings, whether ‘in-house’, PMG, TSC or DMC should have a designated chair. Constitution of these committees is described in section 5.10.1. For significant meetings an agenda should be made available to all attendees in advance and should be referred to during the meeting to ensure that all items are systematically reviewed as required. Meetings should be organised in sufficient time (will vary depending on the geographic location of those who will be attending and the type of meeting). Clear details will be sent to attendees with regard to location and, when appropriate, travel options. It may be appropriate for meetings to be held via tele- or video-conference.

It is common practice within CHaRT to hold regular (e.g. fortnightly) ‘in-house’ meetings for trials that are in start-up, with reduced frequency while the trial is ongoing, increasing in frequency again during the close down phase. Membership of the ‘in-house’ group will include appropriate CHaRT personnel.

Minutes of meetings should be taken by the data co-ordinator, trial manager, or another team member and filed appropriately.

6.13 Site contact/follow-up

Recruitment and clinical follow-up at sites can go on for many months within an individual trial. Building and maintaining good relationships with site staff is essential. Strategies to improve and enhance these relationships and maintain lines of communication should be adopted whenever possible, in agreement with the Project Management Group. Common strategies
include newsletters, teleconferences and providing study specific merchandise such as pens and post-it note pads. See guidance on maintaining site and participants' motivation guidance document on Q-Pulse for further information. Opportunities may arise to research different strategies to maintain site contact and build good relationships. These may require the approval of the relevant trial committees, sponsor, funder, REC and so on.

6.14 Participant contact  [v06.0614.04]
The protocol will describe the process for initial approach to participants and how subsequent contact is made. Local contact is covered during the initial site training and detailed in the study operations manual. Contact by central CHaRT personnel will normally be following participant consent and is also documented in the protocol and / or study guidance.

All CHaRT staff must be aware of their duty of confidentiality and will maintain a professional approach to all participant contact. Contact may be made via post, telephone, text message and email by designated team members. If a trial participant has a query that the team member cannot answer (e.g. a clinical query), the team member is responsible for passing that query to a relevant person for resolution.

Where research involves NHS patients, data or facilities, in addition to requiring NHS R&D permission for the trial, members of the trial team may need to be covered by an appropriate Human Resource agreement with the NHS organisation hosting their research. The NHS Research Passport algorithm, which can be found at www.hra.nhs.uk/planning-and-improving-research/best-practice/research-passport/, provides guidance on whether CHaRT personnel will require an honorary NHS contract or letter of access depending on the level of patient contact they have throughout the trial. In addition, NHS R&D departments may also provide guidance.

6.15 Participant follow-up  [v06.0615.05]
6.15.1 Within trial
Participant follow-up is detailed within the trial protocol (see Section 5.4). Participant contact preferences may be recorded such that correspondence is delivered by for example, post and email. When questionnaires are sent from CHaRT, it is normal practice that participants who fail to return them will be sent reminders approximately three weeks following the initial distribution (although this time-frame may be shortened in some trials). Second reminders (by post, telephone or email) may also be used. It may be appropriate to adopt, or research, other strategies to enhance retention and response to questionnaires. It is important that all such methods of contact with participants, and their frequency, is pre-specified in the trial protocol and any relevant approvals (e.g. REC) obtained.

Before generating any participant contact (for example questionnaires or end of study results letter) the study website should be updated with any known changes to patient status (e.g. withdrawal from follow-up or death).

We will aim to accommodate the needs and requests of trial participants, e.g. that a CHaRT member of staff telephone them to complete questionnaires.
Depending on the trial design/population and length of follow-up, it is important to keep participants informed of progress and CHaRT encourages trials to issue newsletters and a lay summary of results to the trial participants when available. The sponsor and/or the REC should be consulted as to whether such correspondence requires approval before distribution.

6.15.2 Long-term follow-up
In some trials, long-term follow-up would not be appropriate, for example, short-term interventions with no perceived safety or effectiveness issues in the long-term.

Some CHaRT trials will seek to obtain funding to collect long-term follow-up data. Long-term follow-up is potentially for many years or decades after the participant has reached the primary study outcome – for example, a trial of knee replacement may have its primary outcome as quality of life at two years post-operation but it may look at the device failure at 10 years post-operation. Long-term follow-up is usefully differentiated between that which requires further patient contact (whether by post, telephone, clinic or home visit) and that which can be completed solely by record linkage (remote capture of further participant data from natural registries, hospital, GP databases, and so on). Long-term follow-up that involves further patient contact is usually more expensive and requires considerable organisation. Whatever the nature of the follow-up, the following three requirements are key:

- REC favourable opinion for the long term follow-up, specifying the nature and frequency of participant contact, must be obtained, and it is strongly advised to obtain these permissions, and the consent of the participant, at the beginning of their involvement i.e. on the original consent form (prior to randomisation).
- Adequate funding needs to be secured to guarantee the viability of the follow-up and quality of data captured.
- The project needs to be set up and documented on the assumption that the long-term follow-up will not be carried out by the original study team. It should be assumed that no-one will be available with direct knowledge of the original conduct of the trial. It is therefore the responsibility of the original team to specify the long-term follow-up protocol in such a way that this critical knowledge is passed on, in so far as possible, in writing.

6.16 The role of the Chief Investigator (CI)

The Chief Investigator has overall responsibility for the trial. The responsibilities of the CI are documented in the delegation of responsibilities appended to the sponsorship/Co-sponsorship agreement.

6.16.1 CI absence
If the CI is temporarily absent (e.g. on short periods of annual or sick leave), a suitably qualified delegate should be identified to provide cover for any essential tasks.

For absences which are known or expected to be longer (e.g. sabbatical or maternity leave), consideration should be given that an acting or new CI is appointed. The sponsor and/or funder should be consulted for advice on the most appropriate approach. If a new CI is appointed, a substantial amendment will be required.
6.16.2 CI leaves or retires
If the CI is leaving to work at another institution either a new CI would be appointed or the existing CI would continue in this role, subject to the approval of the funder, sponsor and the old and new employing institutions. This would involve significant consultation and agreement of the sponsor(s) and funder.
If the CI is retiring a new CI would usually need to be appointed, though there may be exceptions to this. This would involve significant consultation and agreement of the sponsor(s) and funder, and a formal appointment process may be required. A change of CI would constitute a substantial amendment.

For locally sponsored CTIMP studies, please refer to the SOP-QA-24 for further details on managing a change in CI.

6.17 The role of the Principal Investigator (PI)

The Principal Investigator has overall responsibility for the trial at site. The responsibilities of the PI are documented in the site delegation log and the site agreement.

6.17.1 PI absence
If the PI is temporarily absent (e.g. on short periods of annual leave or sick leave), a suitably qualified delegate should be identified to provide cover for any essential tasks. R&D offices at NHS sites should be notified about cover arrangements for absent PIs.

For absences which are known or expected to be longer (e.g. sabbatical or maternity leave), consideration should be given that an acting or new PI is appointed. The sponsor and/or relevant R&D department should be consulted for advice on the most appropriate approach. In a CTIMP, if a new PI is appointed, a substantial amendment will be required.

CROSS REFERENCE
Chapter 5: Trial initiation
Chapter 10: Data management
Chapter 16: CHaRT Staff Training

VERSION HISTORY

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<td>03</td>
<td>Total revision and re-ordering of this chapter; particularly to sections 6.6 and 6.7.</td>
<td>Jan 2012</td>
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<tr>
<td>04</td>
<td>Substantial changes to section 6.4, 6.5, 6.6, 6.8, 6.15 and new Section 6.16: the role of the Chief Investigator (CI); including updates to relevant web links.</td>
<td>Aug 2015</td>
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<td>05</td>
<td>Updates to sections 6.4, 6.8, 6.10; and 6.15.1 Addition of new section 6.7 on urgent safety measures; and 6.17 on the role of the PI. Essential documentation moved to Chapter 5, Section 5.7.</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Minor clarification to sections 6.15 and 6.16.2. Addition of GRP and removal of reference to Declaration of Helsinki (6.1); update to the</td>
<td>Mar 2020</td>
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<td>UoA’s Research Governance Handbook (6.3); clarification that substantial amendment may require updating RSI, addition of text around MedDRA coding (6.4); removal of reference to internal safety reporting policies and link to HR guidance added (6.5); addition of text about reporting data breaches (6.6); clarification of process for USMs in CTIMPs (6.7); text updated to include information regarding the new amendment tool being used for all project based research, clarification of text around RSI in CTIMP, and amendments to CRFs (6.8); addition of text regarding personal identifiable information that should not be redacted (6.9); clarification of process for CI absence (6.16.1) and PI absence (6.17.1).</td>
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CHAPTER 7: TRIAL CLOSE-OUT
[v06.0700.06]

LEAD AUTHOR
Senior and deputy senior trials managers.

BACKGROUND
All clinical trials will end at some point, either having reached their scheduled milestones and finished at the expected time, or unexpectedly due to safety concerns, for overwhelming evidence of benefit sooner than expected, or for other reasons (e.g. it is futile to continue, or other competing trials make it impossible to continue). The end of a trial must be anticipated and planned for accordingly from its start.

PURPOSE
To document CHaRT processes for the management of trial close-out.

APPLICABILITY
- Essential reading for all CHaRT staff involved in the close-out phase of a trial.

TRIAL CLOSE-OUT
7.1 Close-out procedures [v06.0701.06]
Usually a close-out is scheduled. Procedures for a scheduled close-out should be discussed and documented by the trial team prior to close-out beginning. Information on trial close-out procedures can be found at: www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/. A close out checklist for end of study or early termination of study and a site close-out form are available on Q-Pulse. It is the ultimate responsibility of the sponsor (may be delegated to Chief Investigator (CI)) to ensure that proper procedures are in place, and are then undertaken (please refer to the SOP-QA-31 for details on the procedure for formally closing a trial for locally sponsored studies).

Although undertaken as an ongoing process, it is essential that the TMF is checked for completeness and any personal identifiable information from questionnaires or interviews have been checked for anonymity (when appropriate). Any outstanding errors and inconsistencies should be resolved and, if they cannot be resolved, the reasons for this are documented (for example in a file note or within the study website).

In a scheduled close-out, there is sometimes the opportunity to close-out in a staggered timetable. The trial manager will develop centre specific plans for close-out which will include:

- The date of closure of the randomisation system. Confirmation of the date of closure should be documented.
- Timing of the closure of emergency unblinding, if relevant, should be agreed in advance. Closure of any unblinding process will often post-date closure of randomisation and/or the active treatment period.
- Resolution of any outstanding data queries.
- Organisation of transmission of appropriate data, either electronic or paper, using secure measures where appropriate to CHaRT.
Chapter 7: Trial close-out

- Confirmation of which records are to be archived, and for how long (refer to original IRAS, protocol and site agreements).
- Return of all equipment (e.g. computers, clinical kit), as appropriate and arrangements for closing down dedicated office space, removal of publicity material, decommissioning dedicated phone lines, closing study web portals and so on.
- Completion of all contractual issues with a centre, including final payments for services.

On occasion, a trial may be terminated early (see section 7.3) or suspended for a short period. In such cases the plan for close-out or suspension should be discussed, documented, and updated as the situation develops. Prior to a decision to terminate early or suspend a trial, the Sponsor, Funder, TSC and/or DMC should be consulted. They should be involved in ongoing discussions and planning.

7.2 Timelines for notifying stakeholders of scheduled study termination  [v06.0702.03]

- **For CTIMPs:** the competent authority (in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA)), the Research Ethics Committee (REC) and the sponsor(s) should be notified of the end of trial within a specific time (currently 90 days) of the end of trial as defined by the protocol by completing a Declaration of the End of Trial form (found at [www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/](http://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/)) and submitting this through the Common European Submission Portal ([cespportal.hma.eu/Account/Login?ReturnUrl=%2f](https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f)). A copy should also be sent to the local R&D office(s) if they have requested a copy. The appropriate final trial report should be submitted to the REC within 12 months of end of the trial. The clinical trial summary results should also be posted to EudraCT within six or 12 months depending on the type of study.

- **For non-CTIMP trials:** the trial manager should ensure that the end of trial notification is made to the appropriate REC and sponsor within 90 days using the necessary form (found at [www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/](http://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/)). A copy should also be sent to the local R&D office(s) if they have requested a copy. The final study report should be submitted to the main REC within 12 months of the end of trial as defined in the protocol.

The trial manager should ensure that all pertinent study reports are issued (see section 8.1 for further details), participants are notified of the results (if applicable) and financial procedures have been completed. In addition, all relevant registers (see Section 5.2) should be updated as appropriate. For locally sponsored studies, please refer to [SOP-QA-31](#).

7.3 Early termination of study  [v06.0703.04]

If the study is still in the recruitment phase and early termination is required, the randomisation system must be closed and staff at recruitment sites informed of this by adding information to the randomisation line and/or the randomisation section of the study website. In the event that participants are still “on treatment” (e.g. still taking study medication, undergoing surgery, or part way through a behavioural intervention), a comprehensive plan is required detailing what actions need to be taken in terms of ceasing (or continuing) treatment and how this is communicated to participants and investigators. If the study is being terminated early due to safety issues and participants are still ‘on treatment’, immediate action must be taken in terms of ceasing (or continuing) treatment.

Once this is achieved, the plan for the scheduled close-out should then be exacted.
• **For CTIMPs**: the MHRA, sponsor(s), and REC should be notified within 15 days of an early termination of a trial using the EudraCT ‘Declaration of End of Trial form’ found at ec.europa.eu/health/files/eudralex/vol-10/declaration_end_trial_form.doc. One of the sections of this form records the reasons for ending the trial early. Local R&D office(s) should also be informed.

• **For non-CTIMPs**, the sponsor(s) and REC, should be notified within 15 days of an early termination by completing the NRES ‘Declaration of End of Study form’ which can be found at www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/. Local R&D office(s) should also be informed.

7.4 **Temporary suspension of a trial**  [v06.0704.03]
Possible reasons for a temporary suspension include to investigate a Suspected Unexpected Serious Adverse Reaction (SUSAR), because there is a product recall, or it might be that a sponsor suspends the study to deal with funding or insurance issues. In such circumstances, it may be necessary to suspend the randomisation system temporarily with the intention to restart once the issues have been resolved. If dealing with a temporary suspension, please refer to CHaRT’s guidance for significant major study events on Q-Pulse.

• **For CTIMPs**, the MHRA, sponsor(s), funder and REC should be informed within 15 days from when the study is temporarily suspended. This should be made as a substantial amendment, using the notification of amendment form and clearly explain what has been halted (e.g. stopping recruitment and/or interrupting treatment of participants already included) and the reasons for the temporary halt www.gov.uk/guidanceclinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#suspend-or-terminate-a-trial. Depending on the reason for the suspension, it may also be appropriate to inform the TSC and DMC.

• **For non-CTIMPs**, apart from the MHRA notification process, all other relevant notifications and procedures as for CTIMPs apply.

To restart a trial that has been temporarily halted, the request is made to the MHRA (for CTIMPs), sponsor and the REC as a substantial amendment using the notification of amendment form and providing evidence that it is safe to restart the trial. If the decision is taken not to restart a study that has been temporarily halted, the MHRA, sponsor and REC should be notified within 15 days of this decision, using either the ‘Declaration of End of Trial form’ or the ‘Declaration of End of Study form’ as appropriate and the procedures for early termination should be followed as described in Section 7.3.

7.5 **Archiving**  [v06.0705.04]
The sponsor’s named archivist is ultimately responsible for ensuring that the TMF and all trial data is archived appropriately. CHaRT ensures that the TMF is complete, properly labelled and securely archived. Most documentation within the TMF will not be identifiable; however, there are exceptions to this (e.g. consent forms, prescriptions and associated documentation, letters from participants).

Unless otherwise agreed and documented, CHaRT also ensures that the final database on which the analysis and publication is based is complete, properly labelled and securely archived.
Chapter 7: Trial close-out

The sponsor and/or funder will advise on the retention period for the TMF and trial data at the outset of the study. This is usually documented in the protocol, the Integrated Research Application System (IRAS) application and site agreements. It is a requirement that trial documentation can be accessed by appropriate senior CHaRT staff and therefore archived data must be retrievable within a reasonable timeframe. The University of Aberdeen has an archiving policy (see SOP-QA-32 for details relating to archiving for locally sponsored studies). The trial manager should ensure that, for studies sponsored outwith University of Aberdeen/NHS Grampian, archiving arrangements and procedures are clearly documented in the protocol, IRAS, site agreements or elsewhere in the TMF.

If the CI leaves or retires during the period that data is in archive, arrangements must be made to ensure its ongoing safekeeping and security.

CROSS REFERENCE
Section 5.1 Trial authorisations
Section 5.2 Trial registration
Section 5.8 Essential Documentation
Section 8.1 Trial publications and dissemination

VERSION HISTORY

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<td>03</td>
<td>More clarification to procedures for trial close-out and two new sections: 7.2 Timelines for notifying stakeholders of study termination and 7.4: Temporary suspension of a trial.</td>
<td>Jan 2012</td>
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<tr>
<td>04</td>
<td>More detail added to Section 7.1, 7.2, 7.3 and 7.4 including updates to relevant web links.</td>
<td>Apr 2015</td>
</tr>
<tr>
<td>05</td>
<td>Updates to all sections.</td>
<td>Apr 2018</td>
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<tr>
<td>06</td>
<td>Minor update to section 7.1 around procedures for a scheduled close-out, plus additional text to clarify the processes for early termination and trial suspension (7.1); clarification around identifiable information and archiving of database (7.5).</td>
<td>Mar 2020</td>
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BACKGROUND
There is an obligation to full and open publication of trial results, whatever the findings. Trials with null results, trials which failed to recruit to target and trials which were unexpectedly terminated, all need to be reported. In so far as possible, trials should be reported to their planned intentions. Moreover, trials need to be reported as soon as is practicable.

PURPOSE
To describe CHaRT’s policies for ensuring trials are properly reported in a timely fashion.

APPLICABILITY
- Essential reading for all CHaRT staff involved in publishing trial findings.
- Useful background reading for all CHaRT staff with research interests.

TRIAL PUBLICATION(S) AND DISSEMINATION
8.1 Trial publication(s) and dissemination
It is the responsibility of the CI, in conjunction with the CHaRT lead, where appropriate, to be aware of the requirements of the stakeholders in the trial (the funder, the sponsor, ethics, regulatory, consumer groups, and so on) in respect of final study publication(s) and dissemination, and to ensure that these are delivered in a timely and appropriate manner (see Section 7.2 for more details). Please refer to the SOP-QA-33 for further information for locally sponsored studies on drafting publications and dissemination.

8.2 Publication
All studies managed by CHaRT have a commitment to publish the findings of the research.

8.2.1 Minimum requirements
It is mandatory that the results of every trial appear in the public domain in a timely fashion. For the majority of CHaRT trials, it is anticipated that there will be a results paper published in a peer-reviewed medical/scientific journal. Particular attention should be paid in ensuring it is followed for trials which failed to meet their objectives either in terms of failing to recruit; terminating early due to safety issues, or futility concerns; or failing to demonstrate a clinically worthwhile treatment effect. If the study is a CTIMP, there is an obligation to register the findings on the EudraCT website.

In addition, many trials also publish a design and/or baseline characteristics paper in a peer-reviewed journal (ideally any design paper should be accepted for publication before final database lock).
8.2.2 Authorship
The protocol should include a clear statement of authorship. Authorship should include all individuals who have made a substantial academic contribution according to the guidance and recommendations of the International Committee of Medical Journal Editors (ICMJE). Where possible the CHaRT authorship policy, which can be found on Q-Pulse, should be used, but in certain instances CIs based elsewhere may use their host institution’s authorship policy.

All individuals who have made a substantial contribution to the research project without fulfilling the authorship criteria should be clearly acknowledged, usually in an ‘Acknowledgments’ section, detailing their contributions.

8.2.3 Dissemination
It is important that as well as a commitment to peer reviewed medical/scientific publication, study results and methodology are disseminated to an appropriate level at scientific meetings (e.g. Society for Clinical Trials Conference, workshops, invited lectures). There should also be a commitment to disseminate material from the study internally within CHaRT/HSRU in lunchtime research meetings, study days and so on, and to professional and lay publications when appropriate.

As detailed in the HRA guidance, which can be found at www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project, participants should be informed of the final study results as detailed in the protocol and in the Integrated Research Application System (IRAS) application (see section 5.1 for more detail).

8.3 Conflicts of interest
The key CHaRT policy with regard to actual or potential conflict of interest is open disclosure. It is very seldom, if ever, that a potential conflict would stop participation in an activity, or preclude a major journal from publishing. Identified conflicts of interest are discussed at the project management group (PMG: see section 5.10.1) level on a case-by-case basis. If the perceived conflict is openly disclosed, it can usually be discounted when weighed against the researcher’s reputation and track record. Likewise, institutional conflicts of interest (for example, the source of CHaRT funding) can be dealt with similarly by open disclosure.

It should be noted that, in general, to maintain their strict independence, independent members of the Trial Steering Committee and Data Monitoring Committee should not gain any academic credit by being a co-author on study publications. Their role should be gratefully acknowledged and their agreement to this should be obtained before accepting this role (see section 5.10.1 for further details).

CROSS REFERENCE
Section 5.4: Trial protocol
Section 6.3: Governance arrangements
## VERSION HISTORY

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<th>Version</th>
<th>Significant changes from previous version</th>
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<td>Renaming of Chapter from “Trial Reporting” to “Final Reporting and Publication” and further information in sections 8.1 and 8.3.</td>
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<td>04</td>
<td>Renaming chapter from 'Final Reporting and Publication' to 'Trial Publications and dissemination'; Changes to sections 8.1 and 8.2.</td>
<td>Jun 2015</td>
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<td>05</td>
<td>Minor wording amendments.</td>
<td>April 2018</td>
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<td>Minor change to section 8.1 to remove the word ‘grantholder’ as CHaRT lead would be a grantholder and deletion of CTIMP specific text as SOP-QA-33 is now relevant to all studies. Update to section 8.2.2 to clarify that CIs based elsewhere may use a different authorship policy.</td>
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BACKGROUND
IT Infrastructure forms the backbone of CHaRT’s online data management websites and applications that support clinical trials. Many different pieces of hardware and software are used by the Programming Team but are managed by the University of Aberdeen’s (UoA) IT Services. There is a constant interface between UoA IT Services and CHaRT’s Programming Team and CHaRT in general. All CHaRT users will have desktop PCs that are the property of and fully maintained by IT Services. The Programming Team also interface with many servers and services owned and operated by IT Services.

PURPOSE
To describe CHaRT’s policies and procedures for IT infrastructure.

APPLICABILITY
- Essential reading for all CHaRT technical staff (including programmers, IT professionals, and statisticians) and all CHaRT staff using the information systems (including trial managers, data co-ordinators and HSRU general office secretaries).
- Desirable background reading for all other CHaRT staff, particularly those who interact with CHaRT IT systems.

IT INFRASTRUCTURE
9.1 Receipt and Installation of new Hardware and Software [v06.0901.02]
New hardware and software are installed and configured by the UoA’s computer services unit, hereafter called IT Services, who are responsible for the management, operation and support of the University’s networks, server infrastructure, software and hardware. Pre-approved software is available from the System Centre Configuration Manager (SCCM) Software Centre and can be installed by any user. The user reviews and accepts the new system. Programmers have elevated privileges that allows them to install some software without getting permissions from IT services.

9.2 Modification to existing hardware and software [v06.0902.02]
Requests for modification to hardware or software can be made by the Senior IT development manager to IT Services if the upgrade is to improve performance or functionality. IT Services will make the modifications if they have the resource to support them.

Requests for modification to CHaRT software are made via email to support.chart@abdn.ac.uk or directly logged in the support section by users via the trial website. Requests may require completion of a Change Request Form (see Section 10.2.3).

9.3 Description of Redundancy Features [v06.0903.01]
Redundancy features for the CHaRT’s critical systems are managed by IT Services.
Chapter 9: IT infrastructure

9.4 System decommissioning  [v06.0904.01]
Hardware and software decommissioning will be handled by IT Services.

9.5 System and data back-up  [v06.0905.01]
Routine server and individual PC backup are managed by IT Services.

9.6 Preventative Maintenance  [v06.0906.01]
Hardware and software maintenance are handled by IT Services. They will arrange warranties and support at the time of purchase.

9.7 System or Application Patch Installation  [v06.0907.01]
Notification of new patches will be received from IT Services. New patches will be installed remotely if considered necessary.

9.8 Servers: start up and shut down  [v06.0908.01]
All server start-ups and close-downs will be managed by IT Services.

9.9 System monitoring: capacity management  [v06.0909.01]
System space capacity will be monitored by IT Services. If additional space is required for a particular system, new space will be purchased or will be extended by expanding system volume space.

9.10 Support desk and problem resolution  [v06.0910.02]
IT Services will provide a first line support service. Requests for support will be via email (servicedesk@abdn.ac.uk). Support requests are tracked until resolved and accepted by the user.

Support requests for CHaRT software will be made via the relevant study website (where appropriate) or by email to support.chart@abdn.ac.uk.

9.11 System failure register  [v06.0911.01]
IT Services will document such problems as server shut-downs, disk space issues which have resulted in a loss or reduction of service, serious system problems flagged via internal support requests, web service attacks and virus infections. CHaRT will document any randomisation service downtime.

9.12 Third party networks: interfacing of local networks to wide area networks  [v06.0912.01]
Network topology diagrams will be documented by IT Services. Copies of server details used by CHaRT are available in the server diagrams document on Q-Pulse.

9.13 Distribution of software upgrades  [v06.0913.01]
IT Services will manage software upgrades if they provide additional functionality that may be of use, or the upgrade includes error fixes required to ensure system integrity or the current version becomes obsolete.
9.14 Maintenance of virus protection and handling of virus alerts and infections [v06.0914.01]
IT Services will manage virus protection software upgrades. If a virus is suspected, then IT Services should be notified immediately (servicedesk@abdn.ac.uk).

9.15 Security management – user account management, passwords and access rights [v06.0915.02]
IT Services will ensure that users will be assigned a unique username and will be allocated to a staff group. Usernames will be deleted when they are no longer required. IT Services will provide guidance about passwords (see www.abdn.ac.uk/staffnet/working-here/passwords.php) which must be kept confidential. Passwords should not be written down. Normal practice is an annual update, however all programmers and some statisticians are forced to change passwords every 90 days.

Usernames and passwords to log in to study websites will be requested by the trial manager or data co-ordinator and then will be actioned by the CHaRT programming team. Usernames for CHaRT websites consist of the first initial followed by the surname (all lower case). If this username already exists for someone else, then an integer will be appended to the name. Passwords will be at least 8 characters, using a mix of upper and lower case and numerical values. On first login to the trial website users will be prompted to change the password to something more memorable. CHaRT use their in-house system called SPoT (Single Point of Trust) to issue logins and passwords for study websites. A user will have a single login and will be given access rights for studies as appropriate. Once a trial user (including both CHaRT trial staff and trial site staff) leaves, all access to the study website will be removed accordingly.

Programmers will run a monthly report on users not accessing the system for longer than 6 months. Trial managers will then review the reports and will then utilise the user account management system to remove permissions and accounts where required (see the monthly users’ review document available on Q-Pulse).

9.16 Network security [v06.0916.01]
Network security and the physical security of the network are managed by IT Services.

9.17 Calibration and environmental monitoring [v06.0917.01]
IT Services is responsible for monitoring the environment where servers are housed to prevent overheating of equipment.

CROSS REFERENCE

VERSION HISTORY

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<tr>
<td>05</td>
<td>New chapter.</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Minor updates to Background and sections 9.1, 9.2, 9.10, 9.15.</td>
<td>Sep 2019</td>
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CHAPTER 10: DATA MANAGEMENT

LEAD AUTHOR
Senior IT development manager.

BACKGROUND
High quality data (usually defined by completeness and accuracy) are of fundamental importance to the scientific integrity of any clinical trial. Trial data are expensive to collect, so it is imperative that there are tried and trusted processes for the collection, storing, back-up, and archiving of study data. Trial data are often confidential and potentially sensitive, so data security is essential. Staff need to be trained in the safe and efficient use of IT systems.

PURPOSE
To describe CHaRT’s policies and procedures for handling trial data.

APPLICABILITY
- Essential reading for all CHaRT technical staff (including programmers and IT professionals, and statisticians) and all CHaRT staff using the information systems (including trial managers, data co-ordinators, and HSRU general office secretaries).
- Desirable background reading for all other CHaRT staff, particularly those who interact with CHaRT IT systems.

DATA MANAGEMENT

10.1 Data Management Plans
A Data Management Plan (DMP) describes and defines all data management activities for a study. A DMP should consider the following requirements:

- Map of file server arrangements.
- Details of study personnel involved with the study and data access roles assigned to each.
- A complete set of finalised case report forms (CRF).
- Database design
  - Software, hardware and database location.
  - Detailed description of database structure (data dictionary).
  - Detailed description of data entry system.
- Data entry procedures
  - Type of data entry - double or single data entry with checking (entry and verification).
  - Data preparation before entry onto electronic system.
- Data query rules
  - Automated checks should be specified in enough detail to enable set up of data entry screens and validation programs. Checks that can be done automatically during or after data entry should be clearly identified.
  - Data flow and tracking to ensure optimal data completion and to facilitate reporting.
- Query handling
  - How queries will be tracked.
  - Expected resolution time for data queries.
  - Who is responsible for making required changes to the data.
Chapter 10: Data management

- Who is responsible for ensuring all queries are resolved before data is locked for analysis.
  - Quality Assurance plan should include:
    - Audit trail checks.
    - Sample checks of critical data.
  - Data review checks to ensure monitoring has been performed consistently.
  - Training plan and log for data entry systems if required.
  - Electronic data transfer rules.
  - Back-up and recovery procedures.
  - Archiving and security arrangements.
  - Reporting progress.

It is the responsibility of the senior IT development manager to ensure that the DMP is in place before the first randomisation to the study. These tasks may be delegated to the CHaRT study specific trial manager and applications programmer to produce, from standard templates.

The DMP for each trial does not exist as a single document. The various constituent parts of the DMP can be found across multiple files. Some are standard documents that apply to all, for example, the server diagram, and some are trial specific, for example, CRFs. All of the required information can be found within the trial specific shared folder areas in use by the CHaRT programming team.

10.2 Programming standards

All programmers will be competent in the development of web applications for clinical studies and work to CHaRT guidelines for software development and will receive on the job training to achieve at least this competence.

In-house software which is resident on a secure server is developed according to a quality framework which encompasses the following:

- Controlled access.
- Full audit trails and traceability.
- Modular structure with re-usable elements to maximise portability and maintainability.
- In-built logical and consistency checks where appropriate.
- Testing using test data before system goes live.
- Automatic back-up of data.
- Study specific user guides.

10.2.1 Software design

Requirements will be discussed with relevant parties in the research team, including end users of the software solutions. The CRFs will form part of the specification together with the protocol and data flow diagram (see section 5.5).

During development a review of progress will be undertaken at appropriate stages. This will include review of design, source code and testing. Validation will include user testing and acceptance. Testing will include comparison of the software requirements against the software developed and component testing to ensure correctness. Change Management will be in accordance with section 10.2.3.
A trial service definition (TSD) document available on Q-Pulse will be completed by the trial team, this will detail all requirements for the secure area of the trial website. This document will be used as reference during development and through to testing.

A project website initiation (PWI) document available on Q-Pulse will be completed by the trial team, this will detail all requirements for the public area of the trial website. This document will be used as reference during development and through to testing.

10.2.2 Software testing
Testing will be performed in accordance with the software validation plan and test plans which will describe the actions to be taken, the expected results and the observed results. Wherever possible, test data should be used when testing components of a program. Test data will contain typical values, extreme but realistic values, boundary values and invalid values. Testing must not be performed by the original developer. The results of tests should be documented and summarised as being acceptable, or not, listing any anomalies that are outstanding. Where errors are identified an action plan for correction must be drawn up and the task assigned to a developer, this procedure is repeated until no errors remain.

Internal testing is performed against the TSD. Any changes to requirements as a result of testing is reflected in the TSD document by the application programmer.

In some circumstances e.g. trial set-up, the software will be supplied provisionally to trial staff who are required to perform live testing against original requirements. This is referred to as User Acceptance Testing (UAT). UAT documentation is provided to trial staff which, in turn, is passed back to the application Programmer to review and make further amendments as required. In the example of trial set-up, completion of the UAT is documented by way of the website green light form. This form can be found on Q-Pulse. UATs may also be required for software involving complex design or where dynamic requirements exist. The final user acceptance tests must be signed off by a senior programmer or senior IT development manager.

10.2.3 Change management
Changes made during the initial development of a trial website will not require a formal change request. Any change to CRFs or patient questionnaires that either requires ethical approval or will require a change to the database in terms of new forms or updated fieldsets after first version release will be documented and will require completion of a change request form. This form can be found on Q-Pulse. First version release of any data collection form is defined as active participant data being entered for that form and any change request should be discussed with the Project Management Group (PMG) and be signed off by two members of the CHaRT Senior Management Team. Only in exceptional circumstances (e.g. to amend safety procedures) can a change request be submitted without the approval of the PMG. If authorisation for a change is not approved, then the reason must be documented.

It is the responsibility of the research team to ensure that any corresponding paperwork updates have the appropriate approval as described in section 6.8.

Throughout the life of a trial, the Programming Team will receive requests for trial related technical assistance. Any requests for assistance, termed ‘Support requests’, are made through the trial website via a ticket system and often made by the trial manager or person with delegated authority, though a support request can be submitted by any trial staff who has a website login.
Authorisation may be sought by a member of the programming team prior to work being undertaken. Questions related to determining the content for a future support request or urgent enquiries can be directed to the Programming team’s shared mailbox, support.chart@abdn.ac.uk.

10.2.4 Database design
Database creation will be reviewed by senior programming staff. The CRFs and questionnaires will form part of the TSD together with the protocol and the data dictionary. The database name, database structure and data formats will be documented, including:

- Table name
- Variable name
- Variable type
- Variable format
- Stored procedures
- Views
- User defined functions
- Study specific jobs

Internal naming conventions will be adhered to. The CHaRT coding standards can be found on Q-Pulse. The table and column extended properties will be used to describe question text and response coding in order to create the data dictionary and facilitate software development.

10.2.5 Database testing
Databases will be tested prior to release in conjunction with software testing (see section 10.2.2). Examples of testing procedures are:

- Checking test data entered against data stored in the database
- Checking test data is validated correctly against system validation plan.

Test results will be documented and signed off by senior programming staff.

Prior to the trial software being made available for general use, audit logs are installed to capture any changes to data and the database must have all test data removed. This is verified by a Senior Programmer. The website green light form which is available on Q-Pulse is used to capture this information. The database authorisation will then be signed off by the Trial manager and Senior IT development manager on go live.

10.2.6 Database locking and data archival
For each interim DMC report, a copy of the database will be taken and preserved so that the report may be re-produced if required at a later date. Any data cleaning performed on the copy must be reflected in the live database. Live databases may continue to be used after final analyses if the study then enters long-term follow-up.

If a study terminates with no other planned follow up, the database must be archived to a secure network drive with adequate back-up procedures in place for the length of time stipulated by the funder.

The trial manager will complete the project and website archiving (PWA) form (available on Q-Pulse). Upon receipt of the completed PWA, the programming team will ensure all electronic
data relating to that trial website and associate programming files is zipped up and archived securely in a restricted archive area. The database is detached from the database server (MS SQL Server), and the trial website is decommissioned from the web server and replaced with a simple holding page. The archived elements include the database, trial website, trial source code and trial documentation. Only the senior IT development manager and senior programmers will have access to the archive area, permissions can be granted to other programmers on request.

Databases must be archived in a format such that they may be recreated if necessary. It is the policy of the University that database software in production use is version N – 1, as such the database software will be upgraded incrementally as required to do so. To ensure compatibility with historic database archives, tests will be performed to ensure a database can be restored on the new software version as it is introduced. In the cases where restoration fails, an upgrade method will be identified and documented.

10.3 Data transfer [v06.1003.05]

10.3.1 Data issued from CHaRT

Electronic data transferred to an external location should be anonymised if possible and the data only identified by a unique study number. If this is not practical (e.g. for data linkage to such institutions as Information Services Division) then the data should be encrypted, and password protected. The transfer should be made by the University secure transfer service; ZendTo which is available at zendto.abdn.ac.uk/.

All data transfers should be approved by the PMG using the data request form found on Q-Pulse. Once approved, the data transfer form should be completed and signed by the CHaRT staff member transferring the data. The data transfer form should be countersigned by the recipient and then returned to CHaRT. Further details of the data transfer procedures and required form can be found on Q-Pulse.

Please refer to the NHS Information Governance Toolkit (www.igt.hscic.gov.uk/about.aspx) for further information regarding the handling of information.

10.3.2 Data received from the NHS

Strict guidelines have been issued by NHS digital (NHSD) that specify requirements for the secure storage and management of NHS data. These guidelines can be found in the NHS digital data management document, a copy of which can be obtained from the University of Aberdeen IT relationship management team – please refer to following web page for current contact details: www.abdn.ac.uk/it/services/relationship-management.php. NHS data must be kept secure and tightly controlled so requests for access and deletion can be completed in the appropriate manner.

Access to the data and requests for deletion, are under the control of the NHSD gateway manager and the Gateway Manager deputy. Contact details, areas of responsibility, and details of the processes involved can be found in the NHS digital data management document. These processes are important to prevent misuse of NHS data and must be adhered to whenever personal or sensitive patient related data is provided by the NHS for research purposes.
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10.4 Information security  [v06.1004.02]
Information security management provides an enabling mechanism for information sharing, which ensures the protection of information and computing assets. Information security management has three basic components:

1) Confidentiality - protecting sensitive information from unauthorised disclosure.
2) Integrity - safeguarding the accuracy and completeness of information and computer software.
3) Availability - ensuring that information and vital services are available to authorised users when required.

The University security policy applies to all staff and students of the University, and hence CHaRT, and covers the operation and uses of all IT systems and facilities administered by the University. It has been developed with reference to the University Colleges and Information Systems Association (UCISA) Information Security Toolkit. The information security policy can be viewed at:

www.abdn.ac.uk/staffnet/governance/policies-procedures-plans-and-guidlines-399.php

Any serious incidents resulting from non-compliance with Information Security Policies will be dealt with by Human Resources and may result in disciplinary action. The CHaRT security policy builds on the University of Aberdeen’s policy and includes specific clinical trial issues/processes.

Access to information on University computers is controlled by allocating all staff and students a unique username and password. This is done by IT Services. Access to websites set up for randomised trials is controlled by allocating a unique username and password to all staff and users who require access to the sites. This is done by the CHaRT programming team. These usernames and passwords are not the same as the ones managed by IT Services and apply only to the Trial websites each person is allowed to access. Passwords must be kept confidential and must not be written down.

10.5 Data Protection Act  [v06.1005.03]
Personal information (including patient and staff information) relating to living individuals held on a computer or manual system is safeguarded by the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, which replaces the Data Protection Act 1998, both of which came into effect on 25 May 2018. This places obligations on those who record or use information, while at the same time giving specified rights to people about what information is held. Data Protection protects the right of the individual about what information is obtained, shared, processed or supplied whether via a computer or manual paper records.
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All data handling processes carried out by CHaRT must conform to the current legislation and all personnel are made aware of this document as part of their induction checklist by reading and signing the Health Services Research Unit’s protecting information policy which can be found on Q-Pulse.

Any breach of the current legislation may result in the University, as the registered ‘Data Controller’, being liable in law for the consequences of the breach. This liability may extend to the individual processing the data and their Head of School under certain circumstances (see www.abdn.ac.uk/staffnet/governance/policies-proceedures-plans-and-guidlines-399.php).

10.6 Back up [v06.1006.01]
The security and safety of electronic study data is a primary concern. Procedures exist which ensure that the data will be safe and intact if anything goes wrong with any element of the database system. Procedures fit in with corporate policies implemented by the IT services and are not a CHaRT-specific responsibility.

All data is stored on the University of Aberdeen’s storage area in a password protected secure area. Access both physically and electronically is restricted.

10.7 Business continuity / disaster recovery [v06.1007.02]
The University of Aberdeen has drawn up a business continuity plan (www.abdn.ac.uk/staffnet/governance/business-continuity-352.php#panel5528). The contact details of the CHaRT director and senior IT development manager are included in the plan. The document outlines the response to a partial or complete loss of the building, including IT and communication systems. Central IT recovery solutions have been implemented to ensure business continuity within specified timescales.

The IT recovery schedule for central resources states:
• Emergency web communication will be enabled in less than four hours.
• Emergency email capability will be enabled within four hours.
• The CHaRT randomisation service will be operational within 24 hours and the service will be diverted to a mobile or different extension number initially.
• Up to 24 hours of data may be lost (since the last backup).

Since most trial data entry systems are now web-based there may be some delay in restoring these systems but essential correspondence between the study office and sites or participants should be enabled within four hours of a critical incident. Access to a PC connected to a central server, a telephone and a recovered dataset will be the only immediate requirements.

The CHaRT randomisation service will provide all users with a suggested alternative randomisation plan for use in the event of a critical incident. The senior IT development manager is responsible for holding a list of all customer details that is kept off-site along with paper copies of randomisation details for emergency randomisation. Customers will also be instructed how to perform a local randomisation if no contact can be made with the study office.
10.8 Encryption

There are basically three levels of encryption for electronic data, these are:

**Level one:** Routine e-mail correspondence, with non-confidential attachments (e.g. study meeting minutes) – no encryption required.

**Level two:** Confidential or sensitive information (e.g. documents containing results: slides, meeting papers, draft publications etc.) - encrypted using the resident ‘encryption’ in the package being used e.g. password protection in Word, Excel, earlier version of WinZip etc.

**Level three:** This is reserved for highly confidential and/or sensitive information (e.g. randomisation codes, patient identifiable data, data monitoring reports) - staff MUST use the University File Transfer Service, ZendTo which is available at zendto.abdn.ac.uk/. If it is not possible or appropriate to use ZendTo, please use an appropriate alternative. Please contact the CHaRT Senior IT Development Manager or senior Trials Managers if you need advice or need to encrypt any data.

Currently approved algorithms for the encryption are 3DES, AES (FIPS197), Blowfish and should be used at a recommended 256-bit strength (please refer to the Good Practice Guidelines on “Encryption of data and management of removable media” for further details: digital.nhs.uk/binaries/content/assets/legacy/pdf/n/j/encryption_-_good_practice_guide_230517.pdf).

These are readily available within a range of commercially available off-the-shelf products and services (e.g. WinZip 9.0 or later).

The use of freeware or shareware that does not benefit from independent security evaluation or fails to comply with these standards is NOT permitted.

CROSS REFERENCE

Chapter 5: Trial initiation
Chapter 6: Trial conduct and management
Section 7.5: Archiving
SOP-QA-20: Data Management for Clinical Trials

**VERSION HISTORY**

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<td>03</td>
<td>Further information and revisions to sections 9.2.2, 9.3, 9.7 and 9.9.8.</td>
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<tr>
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<td>Minor changes and updates to sections 9.1, 9.2, 9.3, 9.4 (username and passwords to access trial websites).</td>
<td>Jul 2015</td>
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<td>05</td>
<td>Update to DMP information in 10.1, new information about NHS digital in 10.3; additions made to paragraphs 10.2 programming standards; 10.2.2 Software testing; 10.2.3 Change management;</td>
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CHAPTER 11: RANDOMISATION

LEAD AUTHOR
Senior IT development manager

BACKGROUND
Randomisation is the process used for assigning subjects in a clinical trial to intervention groups without introducing human bias due to external factors. Random allocation ensures that any differences between the groups at trial entry are due to chance alone and that each individual has the same chance (after considering intervention ratios) of receiving each intervention.

PURPOSE
To describe CHaRT's policies and procedures for handling randomisation, blinding in clinical trials and to describe the documentation of these procedures.

APPLICABILITY
• Essential reading for all CHaRT technical staff (including programmers and IT professionals; and statisticians)
• Desirable background reading for all other CHaRT staff; particularly those who interact with CHaRT IT systems.

RANDOMISATION
11.1 Responsibilities
The grantholder statistician will discuss the randomisation specification with the senior statistician and senior IT development manager, Chief Investigator and possibly other senior staff (e.g. the CHaRT director, the senior trials manager, or other CHaRT/HSRU staff that are grantholders).

The senior IT development manager will advise the applications programmer of the specification for a randomisation system. It is the responsibility of the trial manager to ensure that all study personnel who are authorised to randomise participants are properly trained in the use of the randomisation system.

11.2 Specification
The specification of the randomisation design is the responsibility of the grantholder or senior statistician or the senior IT development manager. The type of randomisation method used will be trial specific and must attempt to reduce the chance of imbalance between treatment groups (e.g. simple, block, minimisation).

The randomisation methods and parameters of the randomisation process (e.g. stratification variables, inclusion and exclusion criteria) should be described fully in the protocol and entered into the TSD.

For non-CHaRT trials, anyone who approaches the programming team to request a randomisation service will communicate this specification in writing by completing a randomisation service request form which can be found on Q-Pulse.
Chapter 11: Randomisation

11.3 Implementation [v06.1103.01]
The applications programmer will be responsible for operationalising the randomisation specification.

11.4 Testing and simulations [v06.1104.02]
The applications programmer will be responsible for producing test runs and completing the randomisation simulations verification (RSV) document (available on Q-Pulse). The number of simulations will be based on target recruitment across target centres.

The senior statistician for the trial will then check the RSV and sign off after checking the simulation results.

Supporting documentation for all simulations should be held in the programming common drive for the trial.

11.5 Non-CHaRT trials [v06.1105.02]
As well as being used for all CHaRT trials, the randomisation service is made available on a selective basis as a discrete consultancy level service. This is paid for by the client. Similar processes are followed as in section 11.2. The senior IT development manager will send details of all new external randomisation systems to the relevant University of Aberdeen Research and Innovation Business Development Officer so that Service Level Agreements can be issued before randomisation commences.

A formal assessment by the client's statistician as to the methodological appropriateness of the proposed randomisation scheme should be done before they provide it to us.

11.6 Unblinding [v06.1106.02]
The trial statistician, programmer and DMC may have access to unblinded data during the course of the study. These staff members must not be involved in any other aspects of trial conduct. The rest of the research team will only have access to unblinded data after the end of the study when final analyses have been completed (also refer to section 12.5: Unblinding).

If emergency unblinding of individual participants data due to safety concerns is required, then a study specific 'Unblinding Procedure' will be drawn up. Emergency unblinding may be offered through the Telephone Randomisation Service or Web-based unblinding function where logging of such events is automated and alerts will be automatically sent to the appropriate people (which may include Chief Investigator, trial manager, manufacturer and sponsor). Please see SOP-QA-35 for further details on unblinding procedures for locally sponsored studies.

11.7 Quality Assurance [v06.1107.02]
- As indicated, a study randomisation solution will be prospectively tested before going live (see section 11.4).

- Once the system is live, the properties of the study randomisation solution will be checked at 20% and 50% of the randomisation recruitment target, and also at the end of the trial, by the trial statistician (or another suitable qualified person, independent from the CHaRT programming team). Please refer to SOP-QA-18 for further information on randomisation and blinding for locally sponsored studies.
Chapter 11: Randomisation

11.8 Training  
Randomisation applications will be used routinely by non-CHaRT personnel, usually study coordinators, research nurses, and clinicians engaged as study staff. Although the randomisation applications are inherently simple, and have been designed to be user friendly and easy to operate, nevertheless it is of paramount importance that all staff involved in the randomisation process (a) understand that process and (b) are trained in the facilitation of those processes – for example, in how to successfully complete a randomisation using the study randomisation application. Every study will have a section “Randomisation Procedures” in their study guidance (see Section 5.4.1)

It is the responsibility of the study trial manager to ensure that all study personnel who are authorised to randomise participants are properly trained in the use of the randomisation system. Multicentre studies can vary considerably in the number of authorised users of the randomisation application, from a handful at a few sites, to perhaps several hundred across dozens or more sites. The length of time a recruitment application is live for also varies considerably, from as little as a few weeks to several years. As a result, training needs to be flexible in terms of both content and mode of delivery. Flexibility in content is required because users will be from many different backgrounds and have none to extensive experience of randomisation. Flexibility in delivery is required because over a long recruitment window in dozens of sites, there will usually be significant turnover in authorised randomisation staff. CHaRT have therefore developed as standard:

- Randomisation procedures in study guidance (available on study portal).
- Instructor-led demonstration of randomisation system at study training day(s) at start of study and as required.
- Remote one-on-one training (via phone or video link).
- All users should be given the opportunity to complete a successful ‘dummy’ randomisation prior to full authorisation.
- Telephone User Guide for telephone randomisation systems.

11.9 Failures and unexpected occurrences  
The CHaRT randomisation system is automated, and so relies on either telephone or internet access being available. It therefore could potentially happen that a randomisation cannot be made via the telephone or web-based randomisation system. When the service is denied to all users (in all trials) by a breakdown in Aberdeen, all users will be notified as soon as possible and will be given a mobile telephone number to contact. In general, randomisations will be done manually by contacting Aberdeen staff until the automated service is resumed. If this is inconvenient (e.g. time zones for international studies) local randomisation may be permitted. Full details of specific arrangements will be documented for each trial in the randomisation service operations manual and held with the programming team. The same procedure will operate when the denial of service is caused by a local problem at the site (i.e. not a systems failure in Aberdeen). All extraordinary randomisations will be documented, and communicated to CHaRT (via the study trial manager or senior IT development manager for non-CHaRT studies) at the earliest opportunity.

The systems are designed in such a way that if a transaction fails midstream, the transaction is cancelled. It is only at the point a randomisation ID and/or treatment assignment is issued that the transaction is considered complete.
11.10 Misuse & unauthorised use

If an authorised user attempts to randomise the same person twice the application issues a warning. This is usually when the user believes that the initial randomisation has failed, and immediately attempts to randomise the participant again. (Note: This only happens if the study identifier is collected at time of randomisation. In other cases, double randomisations may not be readily identified).

As with all our secure web systems, unauthorised users are denied access through the use of access control via user ID management and passwords.

If a user attempts to access the web system and fails to use the correct user ID/password they are locked out after three failures. Users will be alerted on screen that they have been locked out and they will have to email the support desk (support.chart@abdn.ac.uk) to have their account unlocked.

CROSS REFERENCE
Section 12.4: Randomisation (Statistics)
Section 12.5: Unblinding

VERSION HISTORY

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<td>05</td>
<td>New chapter; this Chapter used to be a sub section of Chapter 10: Data Management, and is now a stand-alone chapter; and reverted to version 01, e.g. [v05.11ss.01].</td>
<td>Apr 2018</td>
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<tr>
<td>06</td>
<td>Background text updated, minor updates and clarifications to sections 11.2, 11.4, 11.5, 11.6, and 11.9, particularly with respect to the role of the statistician. More detail provided regarding when the properties of the study randomisation solution will be checked (11.7).</td>
<td>Oct 2019</td>
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CHAPTER 12: STATISTICS  
[v06.1200.06]

LEAD AUTHOR  
Senior statistician.

BACKGROUND  
The application of rigorous statistical principles to every stage of the clinical trial – from optimal design, to pre-specification of analysis plans, to informative progress reporting of maturing data to Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) in collaboration with the Trial team, to timely and accurate analysis and interpretation of the final data – is of fundamental importance to delivering a high quality trial that will provide reliable evidence.

PURPOSE  
To document requirements for all statistical aspects of CHaRT’s trials.

APPLICABILITY  
• Essential reading for CHaRT statisticians, and any statistician involved in a CHaRT trial.  
• Useful reading for any staff interacting with statistical staff.

STATISTICS

12.1 Methodology [v06.1201.01]  
CHaRT is committed to designing and delivering trials that are methodologically sound.

12.2 Statistical analysis plans [v06.1202.04]  
All CHaRT trials will have a statistical analysis plan (SAP; see SOP-QA-23 for further details on the purpose and content of a SAP for locally sponsored studies). This document will specify the statistical analyses for the trial. It will be a comprehensive statement of the study hypotheses, and the methodology to be employed in addressing these hypotheses. It will be largely drafted early in the study, will evolve reflecting any study design amendments and generally be finalised towards the study end before any unblinded information has been seen (except by the DMC). Although at present the SAP is not usually formally published, it would be expected to be available (for example, on the study website) to interested researchers and may be required at submission of a paper on related work to a journal. It is authored by the trial statistician and approved by the Chief Investigator (CI) on behalf of the TSC (and grant holders) and the senior statistician. The DMC would usually be invited to comment on a draft.

12.3 Pilot / feasibility studies [v06.1203.01]  
Increasingly, definitive trials of complex interventions, as well as drug trials, need to demonstrate feasibility (in terms of theory-based interventions, and measurable outcomes), an ability to recruit sufficient participants from interested centres, as well as demonstrate that adequate resource has been requested to complete the trial on time. Therefore, many studies require comprehensive pilot and/or feasibility work to be undertaken.

From a statistical perspective, such preliminary studies are often challenging, since by definition they face increased uncertainties, the resolution of which is the object of the study. The design,
conduct and analysis of such pilot and feasibility studies requires commensurate attention and commitment from the statistical team.

### 12.4 Randomisation (statistics) [v06.1204.02]
Randomisation is of fundamental importance in a randomised controlled trial (RCT). All CHaRT RCTs utilise a proven, automated, centralised randomisation application. This is accessed by telephone or via the internet, e.g. through a desktop workstation, a handheld computing device or a mobile phone. The randomisation application is capable of employing a variety of designs, usually incorporating a minimisation algorithm, or stratification, or a mixture of the two. The randomisation procedure is tested for robustness prior to randomising the first participant (see section 11.4). A check should be made that the randomisation method is what is specified in the protocol. Checks should be made that the correct minimisation or stratification variables have been used and that the correct levels have been specified. The simulations should be examined to confirm that randomisation is balanced for these variables. The randomisation sequence for each centre should also be inspected and any unusual allocation sequences investigated. Ad hoc monitoring of the randomisation procedure should be undertaken (such as during interim reports).

### 12.5 Unblinding [v06.1205.03]
For open trial designs of non-drug, complex interventions conducted by CHaRT it is usually not useful to insist on blinding the trial statistician or the DMC to allocation during study analyses (since it is obvious from the data reported which intervention arm a participant is in). In trials where there is some element of blinding, consideration will be given as to whether it is appropriate for the trial statistician to be blinded to treatment allocation. There are mechanisms of dummy coding treatment allocations resolved by another statistician in the Unit (but not on the study team) should the DMC team feel the need to know. Throughout the conduct of the trial no persons except the trial statistician, the CHaRT programmer and the DMC will have access to unblinded data. At trial analysis, the data will be unblinded to the rest of the research team only when final analyses have been formally conducted in accordance with the agreed SAP. Please see SOP-QA-35 for further details on unblinding procedures for locally sponsored studies.

### 12.6 Statistical reports [v06.1206.02]
The trial statistician has overall responsibility for the production of all statistical reports for a trial, though it will usually involve liaison with a number of trial personnel such as trial manager, data coordinator or programmer.

#### 12.6.1 Blinded/aggregate reports
Blinded or aggregate reports are usually made available for PMG or TSC meetings and will typically involve a description of current recruitment rates, questionnaire response rates and missing data items in key variables.

#### 12.6.2 Unblinded reports
Unblinded reports are only written for DMC meetings and only the trial statistician and programmer will author and have access to the report(s).
12.6.3 Final study reports
The trial statistician is responsible for the execution and reporting the agreed SAP for the final study reports. (See Chapter 8 for details on trial publications and dissemination).

12.7 Statistical programming [v06.1207.01]
There is no single prescribed statistical package for CHaRT trials, rather there is an expectation that the package should be proven and fit for purpose (e.g. should a Bayesian decision model form part of the trial analysis, an appropriate Bayesian package such as WinBugs would be used). SPSS, SAS, Stata and WinBugs are the most commonly used packages. Irrespective of the package used, a common file structure is advocated for the management of the statistical analyses in the SAP.

12.8 Statistical quality control [v06.1208.02]
Quality control of statistical aspects of CHaRT trials is highly important. All CHaRT trials will have at least two statisticians involved in the trial – a senior statistician to take overall management responsibility for the statistical aspects of the trial and a second statistician (called the trial statistician in this documentation) to be responsible for the day-to-day performance of all statistical aspects. The analysis of the primary outcome(s) will always be verified by a second statistician. To facilitate the handover of statistical analyses to other CHaRT statisticians due to any unforeseen staff changes (such as illness or staff retention) or for replication of the primary result, a common file structure is advocated. All CHaRT statisticians must undergo appropriate Good Clinical Practice (GCP)/ Good Research Practice (GRP) training (see section 6.1).

12.9 International Conference on Harmonisation (ICH) statistical principles [v06.1209.01]
All statisticians working on CHaRT trials are expected to read the ICH Tripartite Guideline Statistical Principles for Clinical Trials E9 (see: database.ich.org/sites/default/files/E9_Guideline.pdf). Whilst recognising that the majority of CHaRT trials are non-drug or complex intervention studies that are not directly covered by this document, the document provides useful guidance on good statistical practice in trials. CHaRT does not, however, advocate an uncritical application of all the principles in the document.

12.10 Partnerships with external statisticians [v06.1210.01]
For CHaRT trials there is an expectation during the development of a trial proposal that an HSRU senior CHaRT statistician will be involved in the process and whenever possible the statistical aspects will be conducted by statisticians within CHaRT. However, it is recognised that, dependent upon the proposed design of the study and the trial subject area, an external statistician may be more appropriate to maintain levels of academic rigour. In such circumstances, the external statistician will liaise with a senior CHaRT statistician throughout the trial design, conduct and analysis and will be expected to apply the appropriate CHaRT statistical SOPs.

12.11 Interaction with Data Monitoring Committee [v06.1211.03]
The trial statistician will have responsibility for creating the reports to the DMC. Generation of the report will involve liaising with the trial programmer. Occasionally the trial statistician may not be the statistician who attends the DMC meeting and answers statistical queries in the interpretation of the data. In such circumstances this will be documented in the meeting papers, minutes and may be specified in the DMC Charter.
Chapter 12: Statistics

CROSS REFERENCE
Section 5.5: Case report form (CRF) design
Section 6.1: Good Clinical Practice
Chapter 10: Data management
SOP-QA-18: Randomisation & Blinding for Randomised, Controlled Trials

VERSION HISTORY

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<td>03</td>
<td>Revision to section 10.11 in line with DMC Charter and addition of link to SOP-QA on Statistical Analysis Plans in section 10.1.</td>
<td>Jan 2012</td>
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<td>04</td>
<td>Changes to wording of sections 10.2 and 10.8.</td>
<td>Jun 2015</td>
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<tr>
<td>05</td>
<td>Update to section 12.5 and minor wording amendments.</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Minor wording changes to Background text and section 12.2. More detail added to section 12.4 to describe the randomisation method checks in line with section 11.6. Updates to sections 12.5 and 12.11 to reflect current practice regarding blinding and implications for a closed DMC meeting.</td>
<td>Mar 2020</td>
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Chapter 13: Health economics

CHAPTER 13: HEALTH ECONOMICS
[v06.1300.04]

LEAD AUTHOR
Senior health economist.

BACKGROUND
Health economics plays a critical role in bringing together information on the effectiveness and resource implications of health care interventions within clinical trials. This chapter covers the generic issues in the conduct of an economic evaluation.

PURPOSE
To document generic issues for health economists involved in CHaRT trials.

APPLICABILITY
• Essential reading for all health economists involved in CHaRT trials.
• Useful background for all staff that interact with health economists.

HEALTH ECONOMICS

13.1 Methodology [v06.1301.02]
CHaRT is committed to designing and delivering trials that are methodologically sound.

The economic evaluations conducted as part of such trials should as a minimum conform to guidelines for the design, conduct and reporting of economic evaluations.¹,²

On some occasions, cross-cutting methodological work will arise from the conduct of a trial. Such work should be agreed with the project management group (PMG) and Trial Steering Committee (TSC) and it is the economist’s responsibility that all necessary permissions and ethical approvals are obtained to use the trial data for a methodological purpose. Some form of written independent peer review should be obtained prior to the commencement of the methodological work.

13.2 Development of care pathways [v06.1302.01]
It is good practice for every economic evaluation to formally consider the care pathway that would be followed by patients receiving the trial interventions. The care pathway, as described in Table 13.1, should describe the care and events that may be expected to occur following randomisation. The care pathway informs decisions about what data are required for the economic evaluation, how it might be collected and valued.
### Table 13.1 Constructing a care pathway for an economic evaluation

<table>
<thead>
<tr>
<th>Care pathway</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Clinical event</td>
<td>Stroke</td>
</tr>
<tr>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Clinical event management + subsequent clinical events</td>
<td>Acute care and rehabilitation + sequelae and complications of treatment</td>
</tr>
<tr>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Resources used to manage events and outcomes of events</td>
<td>Length of hospital stay, intensity of rehabilitation therapy, management of sequelae and complications (e.g. bleeding from secondary prophylaxis) and health outcomes associated with each stage</td>
</tr>
<tr>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Cost of resources used and utilities of outcomes</td>
<td>Valuation of resources using health care (and other) pay and prices and valuation of outcomes using quality adjusted life years (QALYs)/willingness to pay (WTP)</td>
</tr>
</tbody>
</table>

#### 13.3 Economic analysis plans

All CHaRT trials, where the health economics is being led from the University of Aberdeen, should have a health economics analysis plan (HEAP). This document will specify the economic analyses for the trial, including any modelling that might be conducted to extrapolate results or place the results of the trial within the wider body of evidence.

The HEAP is a comprehensive statement of the study hypotheses, and the methodology to be employed in addressing these hypotheses. It will be developed as the study proceeds based on the plans recorded in the protocol, and in conjunction with the development of the CRFs and other instruments for data collection. It will generally be finalised towards the end of study before analysis of the data commences. It will specify the importance of the questions (e.g. primary, secondary or tertiary outcomes), and the nature of the hypothesis (confirmatory or exploratory). It will pre-specify what, if any, subgroup analyses will be undertaken. A set of ‘dummy tables’ (these are *a priori* agreed tables illustrating how the final trial results will be reported) is expected to be included. The economic analysis plan is likely to be closely related to the statistical analysis plan (SAP: see [section 12.2](#)) and should as far as possible follow the procedures set out in that analysis plan for natural and clinical outcomes. Where the economic analysis plan deviates from the statistical analysis plan this should be documented, and a rationale provided.

It is expected that the HEAP should be available to interested researchers (for example, on the study website). It is authored by the trial economist, and approved by the Chief Investigator (CI) on behalf of the TSC (and grantholders) and the senior economist.
13.4 Pilot studies and pre-trial modelling [v06.1304.01]
Data collection tools should always be piloted before use within trials. Consideration should also be given to the development of a model prior to the start of the trial, should resources allow, to identify information needs and key areas for further data collection within the trial. Such a model should be conducted following the principles of good practice for modelling studies.

13.5 Economic reports [v06.1305.01]
The trial economist has overall responsibility for the production of all economic reports, though it will usually involve liaison with a number of trial personnel such as trial manager, data coordinator or programmer. Due to the nature of an economic analysis, which requires interventions to be costed, all reports will be unblinded and only prepared for the final study report.

13.6 Economic programming [v06.1306.02]
There is no single prescribed package for economic evaluation alongside CHaRT trials, rather there is an expectation that the package should be proven and fit for purpose (e.g. should a decision model form part of the trial analysis, an appropriate package such as Treeage, Excel or WinBugs would be used).

For within trial analyses STATA is currently the most commonly used package. The within trial economic analysis should follow the guidance set out for the statistical analysis plan (SAP) and statistical programming (sections 12.2 & 12.7) respectively.

13.7 Economics quality control [v06.1307.01]
Quality control of economic aspects of CHaRT trials is highly important. All CHaRT trials will normally have two economists involved in the trial – a senior economist to take overall management responsibility for the economic aspects of the trial and a second economist responsible for the day-to-day performance of all economic aspects and who will draft the analysis plan. All economists involved in CHaRT trials must undergo appropriate Good Clinical Practice (GCP)/ Good Research Practice (GRP) training (see section 6.1).

13.8 Partnerships with external economists [v06.1308.01]
For CHaRT trials involving an economic evaluation, a senior economist will be involved in the development of a trial proposal and, whenever possible the economic aspects will be conducted by a more junior economist allocated to the trial. However, it is recognised that, dependent upon the proposed design of the study and the trial subject area, an external economist may be more appropriate. In such circumstances, the external economist will be expected to apply the appropriate CHaRT SOPs including those relating to the production of an economic analysis plan (Section 13.3), the piloting of trial instruments (Section 13.4), the production of economic reports (Section 13.5), and the quality control of economic data collection and analyses (Section 13.7).

CROSS REFERENCE
Section 5.5: Case report form (CRF) design
Chapter 8: Trial Publication(s) and dissemination
Chapter 10: Data Management
Chapter 13: Health economics

References:


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<td>03</td>
<td>Clarification of peer review requirements prior to the commencement of methodological work.</td>
<td>Jan 2012</td>
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<tr>
<td>04</td>
<td>Minor update to section 11.8: further clarification on the expectations of external economists</td>
<td>Jun 2015</td>
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<td>05</td>
<td>Modification to text in paragraph 13.3 (economic analysis plans) to accommodate the need for a separate economic analysis plan where and when required.</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Update to section 13.3: more detail regarding the Health Economics Analysis Plan (HEAP) and minor changes to section 13.6 to update economic programming packages used.</td>
<td>Feb 2020</td>
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Chapter 14: Embedded qualitative evaluations

CHAPTER 14: EMBEDDED QUALITATIVE EVALUATIONS [v06.1400.02]

LEAD AUTHOR
HCA programme director

BACKGROUND
The aim of embedded qualitative research is to identify any challenges during the internal pilot relating to design or conduct that can then be addressed and modified before progression to the full trial. This may include changes to the way the trial information is presented, recruitment consultations are framed or requirements for staff training.

PURPOSE
To document generic issues for qualitative researchers involved in CHaRT trials.

APPLICABILITY
• Essential reading for all qualitative researchers involved in CHaRT trials.
• Useful background for all staff that interact with qualitative researchers.

EMBEDDED QUALITATIVE EVALUATIONS
14.1 Methodology [v06.1401.02]
CHaRT is committed to designing and delivering trials that are methodologically sound.

It is likely that embedded qualitative evaluations are more appropriate in some trials than others (e.g. those with very different interventions, surgery vs medical management) and the extent of the work planned may also vary across trials depending on the perceived challenges. However, each trial approaching CHaRT will be assessed by the CHaRT director and research managers (and further with the CHaRT Advisory Group), prior to consultation with the CHaRT Qualitative Lead before a judgement is made about inclusion of qualitative evaluation. If appropriate, a bespoke package of work will be developed accordingly and written up in a protocol as an appendix to the main trial protocol.

Qualitative researchers will be involved in all meetings and discussions regarding trial work up. The work required will be costed accordingly into any proposed grant application.

14.2 Qualitative analysis plans [v06.1402.01]
The analysis for the proposed qualitative work will be specified within the trial protocol. Established pragmatic approaches to analysis will be taken in order to support delivery of the trial.

14.3 Qualitative reports [v06.1403.01]
Data from the embedded qualitative evaluations will be developed into reports and fed back to the trial team and specific sites as appropriate. Reports will focus on indicators such as recruitment, retention, and cross-overs. Explanatory data that facilitates fuller understanding of the process of these indicators will be presented at key points in trial delivery.
Chapter 14: Embedded qualitative evaluations

14.4 Partnerships with external qualitative researchers

For CHaRT trials involving an embedded qualitative evaluation, a senior qualitative researcher will be involved in the development of a trial proposal and, whenever possible the qualitative aspects will be conducted by a Research Fellow allocated to the trial. However, it is recognised that, dependent upon the proposed design of the study and the trial subject area, an external qualitative researcher may be more appropriate.

CROSS REFERENCE

Chapter 5: Trial initiation
Chapter 6: Trial conduct and management

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<td>05</td>
<td>New Chapter</td>
<td>Apr 2018</td>
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<td>06</td>
<td>Update to the methodological process in sections 14.1 and 14.4.</td>
<td>Feb 2020</td>
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CHAPTER 15: PATIENT AND PUBLIC INVOLVEMENT

[Version 06.1500.05]

LEAD AUTHOR
HCA programme director/PPIE coordinator

BACKGROUND
Patient and Public Involvement (PPI) is used as a wider term to cover a range of interactions that patients and the public have with the NHS, in service improvement, service delivery and feedback. When thinking about PPI in research, INVOLVE (www.invo.org.uk) defines public involvement in research as research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them. This includes, for example, having patients and the members of the public working with research funders to prioritise research, offering advice as members of a project steering group, commenting on and developing research materials, or undertaking interviews with research participants. The importance of involving patients and the public in this way as PPI partners in guiding the design and conduct of research (including trials) has been recognised in the literature and is widely accepted as best practice. PPI may take various forms, from the sharing of information and opinion to joint decision-making power and responsibility. CHaRT has an unambiguous commitment to the involvement of PPI partners in as many of its trial processes as possible.

PURPOSE
To detail the type, level and timing of PPI in CHaRT trials.

APPLICABILITY
Essential reading for all CHaRT staff

PATIENT AND PUBLIC INVOLVEMENT (PPI)
The HSRU Patient and Public Involvement and Engagement (PPIE) coordinator should be the primary contact point for any queries relating to patient and public involvement (PPI) in research studies, including CHaRT trials. A Unit level Public Partners Group made up of local members of the public is available, through the PPIE coordinator, to provide additional input and feedback on general or specific elements of the research process and also give strategic input to the PPI activities for the Unit.

15.1 Who should I involve? [Version 06.1501.02]
In the context of CHaRT, we identify “PPI partners” as people with personal experience of the health condition being studied (e.g. as a patient, family member or carer), or interested members of the public. This is distinct from those individuals who are professionally engaged with the research process – in CHaRT’s case, the design and conduct of randomised controlled trials. Examples of the type of people who might provide PPI input to the design and delivery of CHaRT trials could therefore include:

- Members of organisations that represent people who have a lived experience of the condition under study (e.g. a disease specific patient support group).
- Individuals with a personal experience of the condition under study (or similar) either as a patient, family member or carer.
- Members of the public.
It is helpful to draft a PPI plan of who will be identified (patients, carers, public), how many PPI partners are likely to be involved and how they will contribute during the research cycle (e.g. within an advisory group, project management group, trial steering committee, one-off consultation, questionnaire survey). This can be reviewed regularly during the trial by the trial team and the PPI partners.

15.2 Identifying appropriate PPI partners [v06.1502.04]
When identifying PPI partners it is helpful to consider the likely location of any face to face meetings and how the PPI partners will be involved. It is not always straightforward to identify appropriate PPI partners. There are often dedicated support organisations for patients who may be able to facilitate identifying potential PPI partners (see for example www.invo.org.uk/communities/invodirect/). Individual patients may be identified through direct contacts with the sites involved in the trial. There are also a number of national organisations/resources dedicated to the involvement of PPI partners in research who can provide advice on appropriate PPI, for example:

- INVOLVE (www.invo.org.uk) which is a national advisory group set up to support the promotion of PPI in the UK
- The UK Directory of Self Help Groups (www.selfhelp.org.uk/) which is a free directory that lists self-help groups, support group and charities in the UK.
- People in research, where opportunities can be advertised nationally (www.peopleinresearch.org/)
- Additionally, the Unit Public Partners Group may be contacted through the Unit PPIE lead to give additional input and/or feedback on relevant stages of the research process.

Additional opportunities to identify PPI Partners also exist through less traditional routes.
- Scottish Health Research Register (SHARE) - note that there may be a cost attached to this.
- Volunteer organisations (e.g. Volunteer Aberdeen www.acvo.org.uk) – which may be appropriate if a more generic health experience/perspective is required, or to help with advertising.
- Social media (e.g. Facebook, Twitter, etc).

When identifying PPI Partners through established patient groups, it is important for the trial team to identify any funding source for the group and judge whether there could be any potential conflicts of interest depending on the nature of that funding, e.g. pharmaceutical companies. It may be important to explicitly clarify any potential conflicts with the trial funder.

It is often helpful to develop an advert (see the advert for TSC PPI partner example on Q-Pulse) and a role descriptor (please see the PPI Role Descriptor document on Q-Pulse) to advertise or provide information about potential opportunities for PPI partners. It may also be helpful to clarify the mutual expectations of researchers and PPI partners.

15.3 Range of input from PPI partners [v06.1503.04]
PPI partners can contribute to the design and delivery of a randomised controlled trial in numerous ways.

For CHaRT trials, involvement of PPI Partners includes activities across the life of a trial, from design stage to publication. These include but are not limited to:
- Advising on the appropriateness of the trial question and proposed trial outcomes (see section 5.4)
Chapter 15: Patient and public involvement

- Commenting on the research protocol (see section 5.4).
- Commenting on written information materials e.g. patient information leaflets (PIL) and consent forms (see section 5.6).
- Commenting on (and testing) the questionnaires to be used to collect patient outcomes.
- Advising on how best to conduct the consent process (see section 5.6).
- Serving as a member of trial governance committees (see section 6.3).
- Contributing to scientific output – authorship/review (see section 8.2).
- Advising on appropriate engagement with participants, patients and the public (e.g. via social media, newsletter, email etc.)
- Contributing to dissemination e.g. conference presentation, lectures, workshops at patient support groups, dissemination to patients and the public (see section 8.2.3).

If the PPI partners identify any training or support needs across these objectives, these will be addressed accordingly. PPI Partners may also serve as full co-applicants on the research proposal. In this case a helpful introductory document is role descriptor for PPI on the research proposal available on Q-Pulse.

15.4 Remuneration of PPI partners [v06.1504.03]

It is widely acknowledged that PPI partners should be remunerated for their time and contribution to research. For CHaRT trials, we adhere to the principles laid out in the INVOLVE guidance (www.invo.org.uk/posttypeorgpub/involve-policy-on-payments-and-expenses-for-members-of-the-public/) and ensure appropriate costs (e.g. out of pocket expenses and honorariums) for PPI involvement into grant applications. There may be processes required to set up such payments depending on the sponsoring organisation.

15.5 Support for PPI partners [v06.1505.01]

It is best practice for the trial to identify a trial team PPI lead who will be the named contact for any PPI partners. This ensures a clear communication pathway for PPI partners. It should be noted that contact details (including email) for PPI partners should not be shared within the trial team without prior consent of the PPI partner. When emailing, PPI Partners should be blind copied (Bcc) whenever possible.

Prior to the first meeting it is helpful to have a one to one phone call or meeting with new PPI partners so they can ask any questions about the trial and their role. Summary documents about the trial, e.g. the plain language summary, study website, PIL and the CHaRT document How does the research proposal process work? (available on Q-Pulse) may all be helpful resources. At intervals through the trial, PPI partners may require additional support to understand the research process and their role within it. A template PPI feedback form is available on Q-Pulse to help identify these needs. It is also helpful to consider the needs of any partners in the research when planning patient and public involvement - for example location, access requirements, vision, hearing, dietary, carers, timing of meetings, IT access, native language, any needs relating to the health condition being studied. Should PPI partners want support outside of the research team they can be directed to the PPIE co-ordinator who may be able to facilitate this.
Chapter 15: Patient and public involvement

15.6 Documenting PPI

There is an expectation that PPI will be clearly documented throughout the lifetime of the trial. Documentation of PPI may be included within the trial protocol, trial authorisations, trial registration, funder documents, PILs, newsletters, publications and other dissemination activities; see Chapter 5 and Chapter 8.

CROSS REFERENCE
Section 5.5: Case report form (CRF) design
Section 5.11: Patient and Public involvement
Chapter 8: Trial Publication(s) and dissemination

Further reading and resources:


Tarpey M. Public involvement in research applications to the National Research Ethics Service. INVOLVE, Eastleigh, 2011

VERSION HISTORY

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<td>03</td>
<td>New section added: 13.4 – Remuneration of consumers</td>
<td>Jan 2012</td>
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<td>04</td>
<td>Change from ‘Consumer issues’ to ‘Patient and Public involvement’; more detail added to ‘Background’ and section 13.4</td>
<td>Jun 2015</td>
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<tr>
<td>05</td>
<td>Updates to 15.2, 15.3 and 15.4, in particular addition of information on identifying PPI Partners Applicability amended to ensure that the chapter is ‘Essential reading for all CHaRT staff’</td>
<td>Apr 2018</td>
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<td>Updates to all sections to reflect changes in CHaRT processes and links to new templates available on Q-Pulse (15.1 – 15.4); addition of two new sections to provide information on Supporting PPI partners and the best methods for documenting PPI (15.5 and 15.6).</td>
<td>Feb 2020</td>
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CHAPTER 16: CHaRT STAFF TRAINING

LEAD AUTHOR
Senior trials manager/QA manager

BACKGROUND
The successful delivery of high quality trials over a sustained period requires highly trained staff following tried and tested processes. Relevant and timely training of staff is a key component of CHaRT’s ability to deliver these high quality trials.

PURPOSE
To document the expectations for CHaRT staff in terms of requirements for, receipt of, and documentation of training needs and solutions. These may be gained from training courses, workshop, attendance at conferences etc.

APPLICABILITY
- Essential reading for all CHaRT staff.

CHaRT STAFF TRAINING

16.1 General
CHaRT staff are required by their job specifications to possess the appropriate experience and qualifications for their responsibilities. On appointment, all staff are assigned an appropriate buddy and given an induction pack, which includes the HSRU staff handbook, as a basis for familiarisation and initial training. Part of this induction process includes a general SOP overview training session (see section 1.7). In addition, further training will be provided or offered: for example, an external course on a specific statistical technique for a statistician analysing a clinical trial; or a University internal course on time management for a trial manager; or a professional development course on team management.

Each member of the CHaRT staff has their training needs discussed regularly and at least once a year during their annual review. Training needs are identified according to the person’s experience and responsibilities and solutions to those needs (e.g. on-the-job training and mentoring from CHaRT colleagues; internal training on the University staff development courses; and external training on courses or at conference workshops) identified.

16.2 Good Clinical Practice
It is a minimal requirement that all CHaRT staff – including trialists, trial managers, statisticians, IT programmers, secretaries, data co-ordinators, research managers, health economists, qualitative researchers, clinicians, clerical staff – have appropriate up to date GCP (or GRP) training (see also Section 6.1). For locally sponsored studies, refer to the SOP-QA-34 on GCP training requirements.

16.3 Training records
It is the responsibility of all staff to document their training by keeping their dedicated staff development manual, or equivalent, up to date and accurate (see section 3.4). This would, for example, include a copy of their current CV, current job description, CHaRT organogram, any promotion/regrading/contribution award application(s), annual review objectives, copies of certificates of attendance if available, outline of course content (e.g. hand-outs and agendas) etc.
Chapter 16: CHaRT Staff Training

as evidence of appropriate training and a cumulative training log to maintain an ongoing record of all internal and external training. The training log template can be found on Q-Pulse (for locally sponsored studies refer to the SOP-QA-2).

Training records should be available for any annual reviews, audits, monitoring visits and inspections. When a study finishes or when a staff member leaves, a copy of their essential training documents (e.g. CV, GCP certificates) should be retained in the Unit within the appropriate Trial Master File (TMF) for the trial they were working on.

16.4 Training feedback [v06.1604.02]
Training is expensive and time consuming, and there are limited training options available, particularly in the external market. CHaRT staff should proactively feedback on training experiences they have had. Feedback, if appropriate, should be directed to the Senior CHaRT management group.

CROSS REFERENCE
Section 1.7: SOP training
Section 6.1: Good Clinical Practice

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<td>06</td>
<td>Removal of text about centralised training records (16.1); minor addition of reference to GRP (16.2); and further detail of what to file in training records regarding award applications (16.3).</td>
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