Risk Assessment of Studies for Inclusion in the GCP Annual Audit Plan

NJRO-QA-SOP-005

Contents

1. Background/Introduction

The UK Policy Framework for Health & Social Care Research 2017 requires all organisations ensure that legislation applicable to research is followed for sponsored and hosted research projects where care is provided to research participants. The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH FT) uses the annual audit cycle of research projects to help meet this responsibility. The purpose of a Good Clinical Practice (GCP) research audit is to assess compliance with:

- UK policy framework for health and social care research (November 2017)
- Medicines for Human Use (Clinical Trials) Regulation 2004 (SI:1031) incorporating amendments on GCP (SI:1928)
- Medicines Act 1968
- ICH-GCP (International Conference on Harmonisation Good Clinical Practice) E6 (R2) November 2016
- HRA Guidance
- Good Practice Quality Guidelines (GxP)
- Data Protection Act 2018
- General Data Protection Regulation 2016/679
- Joint Protocol Between Newcastle University and Newcastle upon Tyne Hospitals NHS Trust
- Newcastle Joint Research Office (NJRO) SOPs
- NuTH FT Standard Operating Procedures (SOPs), policies and procedures
- Research and Development/ Research Governance Policy
- Research Passport Policy
- Research Sponsorship Policy
- Study protocol

Audit helps to:

- Ensure participant and staff safety
- Assist research teams with meeting their responsibilities under the necessary frameworks and regulations
- Identify trends for further education
- Prepare researchers for audit/inspection by external organisations

The GCP QA team select studies for audit based on risk as recommended by ICH GCP E6 (R2) and the MHRA Good Clinical Practice Guide

ICH GCP E6 (R2) section 5.0 states “The quality management system should use a risk-based approach… The methods used to assure the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected”

MHRA Good Clinical Practice Guide Section 14.4 observes “It is recommended that the frequency and approach to QA activities are proportionate to the nature and scope of the clinical trial activities performed by the organisation. A risk-based approach maybe appropriate providing that the organisation is able to provide a sound rationale.”

The audit of research activity involving human tissue, under the Human Tissue Act (2004) is described in NJRO-TISS-SOP-004 Internal Auditing Procedure for Research Tissue Banks

2. Purpose

The purpose of this SOP is to describe the process of risk assessment of studies which are sponsored or hosted by NuTH FT, to be included in NuTH FT Research and Development (R&D) GCP Annual Audit Plan.

The audit of research activity involving human tissue is subject to a separate annual audit plan.

3. Scope of Document

The SOP describes the risk assessment process for the selection of studies for audit and links closely with the NJRO-QA-SOP-001 GCP Auditing of Research Studies.

The risk assessment of research activity involving human tissue, under the Human Tissue Act (2004) is described in NJRO-TISS-SOP-009 Human Tissue Act (2004) Risk Assessments

4. Definitions

AQAM	Assistant Quality Assurance Manager
ATIMP	Advanced Therapy Investigational Medicinal Product
CTIMP	Clinical Trials Investigational Medicinal Product
GCP	Good Clinical Practice
LPMS	Local Portfolio Management System
NCTU	Newcastle Clinical Trials Unit
NJRO	Newcastle Joint Research Office
QA	Quality Assurance
QAM	Quality Assurance Manager
RCT	Regulatory Compliance Team
RGT	Research Governance Team

Hazard: any source of potential damage, harm or adverse event.

Risk in a clinical trial: the likelihood of a potential hazard occurring and causing harm to the trial participant and/or an organisation, or detrimentally affecting the reliability of the trial results.

Risk assessment: a process of identifying the potential hazards associated with a trial and assessing the likelihood of those hazards occurring and resulting in harm.

Risk rationale: The explanation of the reasons for the study being included in the audit.

5. Roles & Responsibilities

It is the responsibility of the GCP Quality Assurance Manager (QAM) or their delegate to risk assess the studies to be included in the annual audit plan.

The RCT also undertake risk assessment for High Risk, NuTH FT Sponsored Trials as described in NJRO-REG-SOP-004 as part of their Sponsorship responsibilities.

6. Procedures

6.1 Selection of Studies

- To generate the GCP annual audit plan, using the Local Portfolio Management System, reports will be run to identify those projects which:
    - Received NuTH FT R&D approval in the previous appropriate twelve-month period
    - Those projects that closed or completed within the previous two years
    - Those projects which have been running for > 2 years
    - CTIMP and ATIMP projects
    - Intelligence is also gathered from the Regulatory Compliance, Research Governance, Information teams and Research Matron regarding areas of concern

- On the basis of risk, priority will be given to the following NuTH FT sponsored trials:
    - All Clinical Trials of an Investigational Medicinal Product (CTIMP)
    - All Advanced Therapy Investigational Medicinal Product (ATIMP) trials
    - All randomised surgical trials
    - All medical device trials of non-CE marked devices or CE marked devices that are being used outside the intended use(s) covered by the CE marking

However, the GCP annual audit plan reflects the breadth of the research portfolio across NuTH FT and Newcastle University therefore it also includes a selection of:

- Commercially sponsored, high risk CTIMP/ATIMP trials
- Trials closed and in follow-up
- Trials completed
- Self-assessment audits
- Vendor audits (internal and external)
- Sponsorship and hosting activities
- Low risk studies e.g., Registry, Questionnaire and PhD projects

Audits undertaken by Clinical Trials Units (CTUs), Trust Tissue and University Biobanks are taken into consideration in facilitating coverage of the research landscape.

The following studies are excluded from the audit plan:

- Studies which received local approval < 3 months prior to date of LPMS report generated as basis for the Audit Plan and which are yet to recruit (with the exception of NuTH FT sponsored automatically eligible studies or 'For Cause' audits as raised by Compliance, Governance, Informatics or Delivery teams)
- Studies that have been audited/inspected within the previous 12 months unless explicitly required as part of a previously agreed/identified action plan.
- Studies where NuTH FT is a Patient Identification Centre (PIC) only

Where service providers particularly, have demonstrated high levels of GCP compliance the frequency of auditing may be reduced.

If a study is audited at the beginning of its lifecycle, depending on the risk assessment and initial audit outcome it may be added to a future audit schedule for revisiting.

6.2 Assessment of the risk

ICH GCP 5.0.2 “states “Risks should be considered at both the system level (e.g., SOPs, computerised systems and personnel) and clinical trial level (e.g., trial design, data collection, informed consent process)”

Other factors taken into account in assessing the risks are:

- Status: e.g., ctIMP, ATIMP, Device

- Study design: an uncommon study design could potentially be a higher risk than an established design
- Speciality/Team: specialities or teams new to research activity or who perform higher risk research infrequently possibly pose a higher risk than those who are regularly involved in the delivery of studies
- Service providers: while all new providers are subject to assessment prior to engagement it is conceivable that service provision does not meet expectations
- The outcome of the risk assessment undertaken by RCT and RGT

6.2.1 Risk Analysis

ICH GCP 5.0.3 notes that "The Sponsor should evaluate the identified risks, against existing risk controls by considering:

a) The likelihood of errors occurring
b) The extent to which such errors would be detectable
c) The impact of such error on human subject protection and reliability of trial results

The GCP QA Manager or Delegate will use the Impact Scoring Matrix (NJRO-QA-SOP-005 Appendix 1, Figure 1), to assess the current risk and the impact of that risk occurring. Considering the cause of the risk, the likelihood or frequency of the of the risk arising is also included. Both the Impact and Likelihood of the risk are awarded a numerical score from 1 to 5

6.2.2 Risk Evaluation

Using the Risk Evaluation Matrix (NJRO-QA-SOP-005 Appendix 1, Figure 2) The risk score is calculated by multiplying the IMPACT score by the LIKELIHOOD score (Risk Score = Impact Score x Likelihood Score)

The numerical score will fall as shown within the range below:

Very Low 1-5	Low 6-10	Moderate 12-16	High 20-25

The evaluation score will inform the type and scope of the audit undertaken.

The completed risk assessment will be independently reviewed by another member of the QA team or RCT.

Once confirmed the assessment will be documented on the annual audit plan with the risk rationale and the risk evaluation score.

The risk assessment of the annual audit schedule will not usually be repeated throughout the lifecycle of the plan. The plan is subject to continuous review, at a minimum every two weeks, as part of workload planning and oversight. If there were a significant number of high risk, for cause audits required the plan would be revised and the risk assessment amended as required.

7. References

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7.3 United Kingdom. United Kingdom Parliament.(2006) 2006 No.1928 The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [Available from: http://www.legislation.gov.uk/uksi/2006/1928/pdfs/uksi_20061928_en.pdf]

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7.5 United Kingdom. United Kingdom Parliament.(2008) 2008 No.941 The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 [Available from: http://www.legislation.gov.uk/uksi/2008/941/pdfs/uksi_20080941_en.pdf]

7.6 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6(R2) November 2016. [Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf]

7.7 The MHRA Good Clinical Practice Guide, 6th Edition, The Stationary Office, 2016

7.8 SOP GCP Auditing of Research Studies (NJRO-QA-SOP-001). [Available from: https://www.newcastlejro.com/resources]

7.9 SOP Clinical Trial Risk Assessment for High Risk, NuTH FT Sponsored Trials (NJRO-REG-SOP-004). [Available from: https://www.newcastlejro.com/resources]

7.10 SOP Human Tissue Act (2004) Risk Assessments (NJRO-TISS-SOP-009) [Available from: https://www.newcastlejro.com/resources]

7.11 Internal Auditing Procedure for Research Tissue Banks (NJRO-TISS-SOP-004 SOP) [Available from: https://www.newcastlejro.com/resources]

8. Appendices

Appendix 1: Impact Scoring Matrix and Risk Evaluation Matrix

Appendix 1:

Figure 1: Impact Scoring Matrix:

Impact		**Likelihood of Hazard**		
1	Insignificant	1	Rare	May only occur in exceptional circumstances
2	Minor	2	Unlikely	Not expected but may occur infrequently
3	Moderate	3	Possible	May/will occur at some time
4	Major	4	Likely	Will probably occur but not a persistent issue
5	Catastrophic	5	Almost certain	Likely to occur on many occasions, persistent issue.

Figure 2: Risk Evaluation Matrix

Likelihood	**Impact**				
	1. Insignificant	2. Minor	3. Moderate	4. Major	5. Catastrophic
1. Rare	1	2	3	4	5
2. Unlikely	2	4	6	8	10
3. Possible	3	6	9	12	15
4. Likely	4	8	12	16	20
5. Almost Certain	5	10	15	20	25