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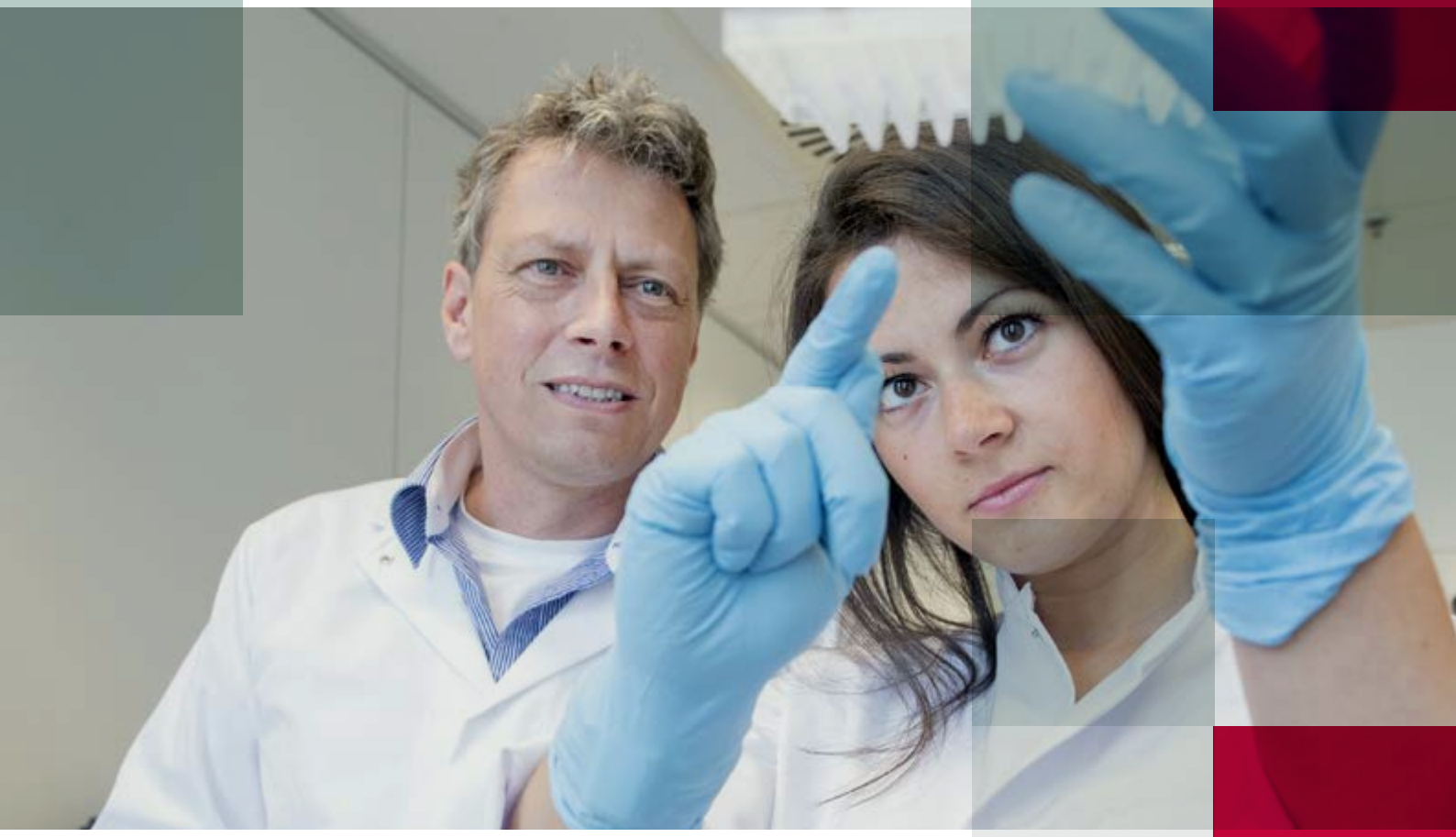

Guideline Quality assurance of research involving human subjects

Update September 2023

Preface

The Dutch UMCs are at the forefront of international biomedical and healthcare research. We are proud of the knowledge that we develop in the UMCs, together with many partners locally and abroad, concerning what is needed to live a longer and healthier life. Or what the best treatment is if we do become ill. An essential part of the wide spectrum of research activities in the UMCs is the medical-scientific research with human subjects. With this specific form of research, we gain knowledge about the functioning of the human body and obtain the latest insights into diagnostics and treatment.

Naturally, the safety of the participants in research and the quality of the research are paramount. Research involving human subjects must therefore meet strict requirements as set out in the *Guideline Quality assurance of research involving human subjects*. This guideline defines the minimum requirements that must be met by research involving human subjects in the UMCs. This primarily concerns the quality assurance of the research that falls within the scope of the *Medical research with Human Subjects Act* (WMO). The guideline also assists us in making clear quality agreements for research collaboration between UMCs, in the region or nationally.

The NFU presented the first edition of this guideline in 2012. In 2019 and 2020 it was revised to incorporate the latest insights, and this current version is the 2023 update. Every two years the *Working group Quality assurance of research involving human subjects* reviews the guideline. In case of substantial changes or new insights, the working group produces an update. In this way we contribute continuously to the quality and safety of research involving human subjects in the UMCs.

Dr. Bertine Lahuis
Chair of NFU

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Amendments compared to the previous version

General: all chapters have been textually and substantively revised.
The most important changes are described below by chapter.

Update September 2023 vs December 2020

- **Abbreviations and glossary:** Some additions and corrections;
- **Ch.2 Training:** Training for research personnel of participating sites added;
- **Ch.3 Quality management:** Clarification of what a quality system involves;
- **Ch.4 Risk management:** Clarification of process risk management;
- **Ch.5 Monitoring:** Clarification of remote monitoring and various aspects of the table for monitoring adjusted (Appendix 2);
- **Ch.6 Auditing:** Clarification about the process of following up on audit findings;
- **Ch.7 Contracts and liability:** Explanation about liability added;
- **Ch.8 Data and Safety Monitoring Board:** Text shortened;
- **Ch.9 Data management:** Clarification about setting up DMP and archiving eCRF;
- **Ch.10 Management and Archiving:** Clarification about storage of data in monocentre studies and about replacement of paper source documents by digital copies.

Abbreviations and Terminology

Abbreviation	Term	Meaning
AE	Adverse Event	Any untoward medical occurrence in a research subject that does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a (investigational) product, whether or not related to the (investigational) product..
AVG/GDPR	The General Data Protection Regulation/ Algemene Verordening Gegevensbescherming	European privacy legislation in force since 25 May 2018. In the Netherlands it is known as 'privacywet Algemene Verordening Gegevensbescherming' (AVG).
BoD	Board of Directors, Executive Board, Raad van Bestuur (RvB)	In this guideline Board of Directors/Executive Board of a UMC.
BROK®	Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers/ Basic course on Regulations and Organisation for ClinicalInvestigators	Mandatory course for clinical investigators required by the NFU. It covers the organisation as well as legislation and regulations of research involving human subjects. Furthermore it also contains centre specific information for each UMC.
CAPA	Corrective Action and Preventive Action Plan	A plan that Includes both corrective and preventive measures, for example, in case of audit findings.
CCMO	Central Committee on research involving human subjects	The CCMO ensures the protection of research subjects involved in medical scientific research, by reviewing the research protocol based on the relevant legal stipulations and taking into account the importance of progress in medical science.
CTA	Clinical Trial Agreement	An agreement transparently covering all rights, obligations and agreements of the parties involved in research involving human subjects.
CTR	Clinical Trial Regulation	Legislation governing research involving medicinal products in the European Union.
DMP	Data Management Plan	Document detailing how the data management of a study is arranged.
DPIA	Data Protection Impact Assessment	Process that analyses the risks to the privacy of research subjects and describes measures to reduce those risks.
DSMB	Data and Safety Monitoring Board	Independent committee that monitors the safety of research subjects during a study.
(e)CRF	(electronic) Case Report Form	Form used to record the study data of each research subject.
EDC system	Electronic Data Capture system	The system that stores data entered via eCRFs or electronic questionnaires.
-	Essential documents	Documents that separately and collectively enable evaluation of the conduct of a clinical trial and the quality of the data obtained (ICH-GCP).

Abbreviation	Term	Meaning
-	For-cause audit	An audit to examine a specific quality disruption or process deviation and/or to prepare for a legally required inspection.
-	Certified copy	A copy (originating from any medium, including photocopies/scans) of the verified (i.e. through a dated signature or prepared by a validated process, for example a validated scanning tunnel) original data point(s) containing the same information as the original, including data that describe the context, content and structure of the original.
HANDS	Handbook for Adequate Natural Data Stewardship	Handbook describing good data stewardship for investigators. Commissioned by the NFU.
IC	Informed Consent	A procedure to ensure that research subjects voluntarily confirm their willingness to participate in a particular study, after having been informed about all aspects of the study that are relevant for the research subject's decision to participate. Informed consent is documented with a completed, signed and dated informed consent form.
ICF	Informed Consent Form	Consent form for research subjects for participation in medical scientific research.
ICH-GCP	Guideline Good Clinical Practice of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 (R2).	GCP is an international ethical and scientific quality norm for designing, conducting, recording and reporting medical studies that involve the participation of human subjects. Compliance with this norm ensures that the rights, safety and well-being of research subjects are protected, in agreement with the Declaration of Helsinki, and that the data obtained from the medical studies are reliable.
IGJ	Health and Youth Care Inspectorate	Regulatory authority supervising the safety and quality of the care and compliance with the rules for medical studies.
ISF	Investigator Site File	Research file that must be managed and archived on site by the investigators in the participating centres.
ISO 14155	ISO 14155:2020	International standard with good clinical practice guidelines for clinical research with medical devices for human use.
IVDR	In-Vitro Diagnostics Regulation	Legislation governing performance studies of medical devices for in-vitro diagnostics (IVDs).
Low intervention clinical trial	Study involving medicinal products with limited intervention	A clinical trial (medical study) that fulfils all of the following conditions: • the investigational medicinal products, except for placebos, have marketing authorisation, and • according to the protocol of the clinical trial, - the investigational medicinal products are used in accordance with the terms of the marketing authorisation, or - the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned, and • the additional diagnostic or monitoring procedures do not pose more than minimal additional burden or risk to the research subjects' safety, compared with the normal clinical practice in any Member State concerned.

Abbreviation	Term	Meaning
MREC	Medical Research Ethics Committee	Independent accredited committee of experts that reviews medical scientific research prior to and during its conduct. A clinical study may not be started without the approval of this committee.
MDR	Medical Device Regulation	Legislation concerning clinical research into medical devices.
NFU	Netherlands Federation of University Medical Centres	The NFU represents the seven collaborating UMCs in the Netherlands, as advocate and employer of around 80,000 people.
O&O	Onderwijs & Onderzoek; Education & Research	NFU steering committee responsible for education and research.
PDCA	Plan-Do-Check-Act	Model to guide the continuous improvement and renewal in an organisation.
PI	Principal Investigator	(Local) Principal investigator responsible for conducting the clinical study (ICH-GCP).
-	Process audit	An audit that identifies the risks of a process.
RMP	Risk Management Plan	Document detailing identification, assessment, management and evaluation of risks.
-	Root-cause analysis	Analysis aimed at identifying (underlying) causes.
SAE	Serious Adverse Event	Any untoward medical occurrence experienced by a research subject which does not necessarily have a causal relation with the investigation and that: • is fatal, and/or • is life-threatening, and/or • necessitates hospital admission or extension of the hospital stay, and/or • causes permanent or significant invalidity, and/or • manifests itself in a congenital anomaly or malformation, and/or • in the opinion of the investigator of the study, without intervention/ treatment could have developed into a serious undesired medical event.
SDR	Source Document Review	An evaluation of the source documentation to check the quality of the source, compliance with the protocol and safeguarding of critical processes.
SDV	Source Document Verification	Comparing source data with (e)CRF data.
SOP	Standard Operating Procedure	Written operating instructions specifying in detail how a process or a specific task must be executed, with the aim to create uniformity in the implementation and thus in the end result.
SUSAR	Suspected Unexpected Serious Adverse Reaction	Suspicion of an unexpected severe side effect.
-	Tracer audit	An audit that takes one case as a model, like one research subject, clinical pathway or process and follows it over time. This type of audit is intended for healthcare, but can also be applied in research.
TMF	Trial Master File	Research file that must be managed and archived by the sponsor.

Abbreviation	Term	Meaning
UMC	University Medical Centre	Academic hospital with the core tasks of care, research and education/ training. It also acts as a faculty associated with a university.
-	Vendor audit	An audit of an external party carrying out tasks for the clinical study as delegated by the sponsor.
-	Sponsor (in Dutch: verrichter)	The commissioning party in the sense of the WMO and ICH-GCP.
UNL	Universities of the Netherlands	Association in which the 14 Dutch universities collaborate on e.g. common ambitions concerning scientific education and research.
WMO	Medical Research Involving Human Subjects Act	Scientific research involving human subjects falls under the WMO if it concerns medical-scientific research and participants are subjected to interventions or required to follow rules of conduct.

Chapter 1. Introduction

This guideline was drafted to safeguard the quality of research subject to the WMO in the Dutch UMCs. In the sections below, the context and importance of quality assurance are explained in more detail.

1.1 Quality assurance of research involving human subjects

The Dutch UMCs attach great importance to developing new medical insights, products and applications derived from scientific research, in addition to providing highly specialised patient care. The UMCs are pre-eminently the centres of excellence for conducting research involving human subjects given their extensive experience, expertise and infrastructure. They also have a good national and international reputation and image.

Optimal quality assurance of research in the UMCs is first and foremost concerned with the safety of the research subject. The risks and burden for the research subject must be minimised and be acceptably proportional to the expected outcomes and benefits of the research (to be assessed by the Medical Research Ethics Committee, MREC). Second, the scientific quality is important, resulting from the design of the study, method of implementation, documentation of data, analysis of the results and the reporting. Both aspects are primarily the sponsor's responsibility. Support can be offered by, for example, a scientific committee and research-facilitating departments.

1.1.1 Commission

To safeguard the quality of research involving human subjects in the UMCs, the *Education & Research* steering committee (*Onderwijs & Onderzoek*, O&O) adopted an advisory report in 2010 that was drafted by experts from various UMCs. This resulted in the first edition of the brochure titled *Quality assurance of research involving human subjects*, a request of the Health and Youth Care Inspectorate (IGJ). Since then, the guideline has undergone several revisions due to changes in legislation. It has been written for investigators, coordinators and managers who are responsible for the quality assurance of human-related research and covers the minimum requirements that must be met by research involving human subjects in the Dutch UMCs. The norms for quality assurance of research involving human subjects are documented in the following legislation: the Dutch *Medical Research Involving Human Subjects Act* (WMO), the European *Medical Device Regulation* (MDR), the European *Clinical Trial Regulation* (CTR), the European *In Vitro Diagnostics Regulation* (IVDR), the European *General Data Protection Regulation* (AVG) and the Dutch *Medical Treatment Contracts Act* (WGBO)[1]. The guideline follows the recommendations of the *Health and Youth Care Inspectorate* (IGJ), the *Central Committee on Research Involving Human Subjects* (CCMO), as well as the *Good Clinical Practice Guideline*

1 Legal framework for medical scientific research | Investigators | The Central Committee on Research Involving Human Subjects (ccmo.nl)

of the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use E6 R2 (ICH-GCP)[2] and *ISO 14155:2020* (ISO 14155)[3].

1.1.2 Scope

In the Netherlands, medical scientific research involving human subjects is legally regulated in the WMO[4]. The *Guideline Quality assurance of research involving human subjects* is applicable to all the investigator-initiated research subject to the WMO that is conducted in the UMCs, and for which the BoD of an UMC is the sponsor (commissioning party), or in which the UMC is participating as a research site. If the BoD is formally the sponsor, it has final responsibility for the research. As the sponsor, the BoD can delegate tasks and duties to, for example, a principal investigator, department head or division head (see Figure 1). The WMO applies to all medical scientific research in which humans are subject to interventions or required to follow a particular code of conduct. Types of WMO research include clinical studies involving medicinal products, investigations involving medical devices, studies involving surgical interventions, experimental therapies, and studies involving nutritional supplements. Research in which the subjects are not actively involved falls outside the scope of the WMO. Examples of research not subject to the WMO include patient record studies and research with human tissue left over after surgery (so-called 'secondary use'). The BoD can be the sponsor of research initiated by an investigator or research financed by industry. The requirements specified in the chapters below apply to both monocentre and multicentre research. The sponsor's responsibility also includes supervising the conduct of research involving human subjects at the participating research sites.

1.1.3 Working group Quality assurance

The guideline has been prepared through a structural and substantial revision by the *NFU Working group Quality assurance of research involving human subjects* (see Colophon). The NFU remains vigilant for relevant changes in the legislation and updates this online guideline on a regular basis.

2 GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)
3 NEN-EN-ISO 14155:2020 en
4 https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not

1.2 Research Code

When conducting research involving human subjects in the UMCs, various parties are involved, such as healthy research subjects, patients, scientific institutes, companies and governments. Investigators who want to conduct research in compliance with the law and guidelines can be faced with important choices when the interests of the stakeholders conflict, for example, when their roles as scientists are combined with that of practitioner. In that situation, the investigator is not only responsible for the quality of the study, but also holds a treatment relationship with the research subjects. In those cases, the rights, safety and well-being of the research subjects must prevail over the interests of science and society.

UMCs and investigators have a mutual duty to protect the integrity of the scientific research in such situations of tension. Acting with scientific integrity in research involving human subjects means closely following the principles and guidelines of ethical and socially responsible research. The *Dutch Code of Conduct for Scientific Integrity 2018 was endorsed by the Universities of the Netherlands* (UNL) and the NFU. This code specifies that an institute must ensure a work environment in which good research practices are promoted and safeguarded[5]. The UMCs have also formulated principles of integrity and good conduct in UMC-specific Research Codes. The Research Code makes transparent for both investigators and internal and external parties which starting points are considered fundamental.

1.3 Quality assurance in the research process

The BoD of each UMC is responsible for implementing and maintaining the systems and procedures for quality assurance, which allow quality to be assured at all stages of the research process. This is intended to ensure that the research is prepared, conducted and concluded in compliance with the protocol and the relevant national and international legal requirements. The safety of the research subjects and the quality of the data are key.

Monitoring and safeguarding the quality of a study should be done across the different phases of research (see Figure 1). Quality assurance within a research institute is a continuous process.

5 Wetenschappelijkeintegriteit (universiteitenvannederland.nl)

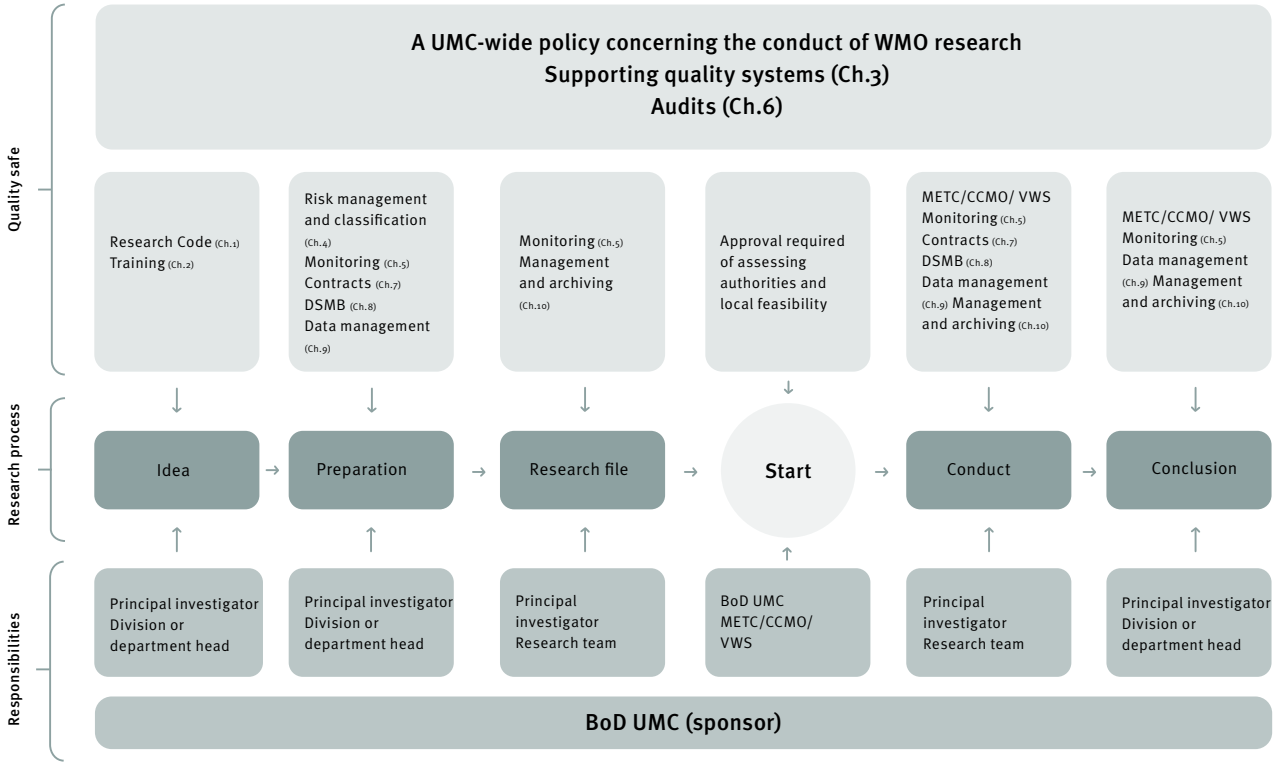


Figure 1: Schematic presentation of Quality assurance of research involving human subjects.

Chapter 2. Training

The quality of research depends to a great extent on the expertise of the investigators and other research personnel. Training contributes extensively to this. The required level of training depends on the role of the research staff and the tasks carried out. Each team member must be qualified by education, training and experience to carry out their specific task(s). The training covers legislation as well as protocol and study-specific training.

2.1 Training for research personnel

The foundation for training investigators is provided by the Education and examination regulations (in Dutch: OER) for the *Basic course on Regulations and Organisation for Clinical Investigators* (BROK®)[6]. For research that falls under the CTR, MDR or the IVDR, it is recommended to take the eBROK® advance modules 'Research with medicinal products' and 'Research with medical devices'.

For other research staff such as research coordinators and research nurses, a GCP-WMO training is sufficient, possibly including the national GCP-WMO exam. If applicable, this should be supplemented with relevant training (e.g. on MDR, CTR or IVDR). A GCP-WMO certificate is valid for 3 years.

For research staff (including scientific interns) with a single or a few restricted or specific tasks or procedures in a clinical study (such as recruiting research subjects, conducting measurements, processing samples, and entering, processing or analysing data), a suitable training in the relevant legislation topics is sufficient.

Alongside training in legislation, study personnel are trained in specific vocational skills associated with their role. This is recorded in their CV and/or training records/induction programme.

2.2 Training for research personnel of participating sites (other than UMCs) in multicentre research

The local principal investigator must be BROK® or GCP-WMO certified, in line with the local institute requirements. If applicable, this training can be supplemented with relevant courses on MDR, CTR and IVDR. Training of other research personnel is the responsibility of the local principal investigator, taking the local requirements into account. Along with training in legislation, the research personnel must be trained in specific vocational skills associated with their role. This must be evident from their CV or training records/induction programme.

6 BROK Opleidings-en examenreglement OER eBROK 2022 (nfu.nl)

2.3 Training for monitors and auditors

Along with a BROK® or WMO-GCP training course, appropriate and relevant training is required for this monitors and auditors. When training monitors, the DCRF test matrix for basic Clinical Research Associate[7] can be used. Requirements for training auditors and monitors should be determined by the UMCs as they depend partly on the audit system employed by the UMC.

7 Toetsmatrices: Handige links en documenten - Dutch Clinical Research Foundation (dcrfonline.nl) See under "Scholing"

Chapter 3. Quality management

The BoD of the UMC is responsible for implementing and maintaining the systems and procedures for quality assurance and quality control. This forms part of the UMC-wide quality management of research involving human subjects and is meant to ensure that research is prepared, conducted and completed in agreement with the protocol, relevant national and international legislation and established standards. The focus here lies on the safety of the research subjects and the quality of the data.

UMC-wide quality management describes the established quality policy in accordance with this guideline and offers advice and support to investigators, research staff and research support services. At very least, it covers: a quality management system, a registration system and centralised support.

Part of quality management is checking compliance with institutional policy and legislation through monitoring and auditing. According to the PDCA-cycle model, there should be a procedure for the continuous improvement of the UMC's policy on quality assurance.

3.1 Quality management system

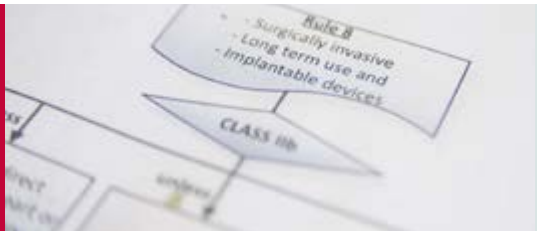
The quality management system should preferably be electronic and contain the published policy for the research process (from design to archiving). It also contains descriptions of the roles and responsibilities of the various internal and external parties involved in the research, and UMC-specific (and if applicable, also department-specific) policy is published there. Description and support of the research process takes place, among other things, through Standard Operating Procedures (SOPs). The SOPs are linked to instructions, standard forms, checklists, etc. to be used.

The system should at a minimum contain the following components:

- Version control
- Audit trail
- Document administrator/owner
- Periodic review of the documents

3.2 Registration system

The BoD has final responsibility for the research conducted in the institute. In the context of 'Sponsor's oversight', the BoD requires access to certain management information. The UMC has a registration database for scientific research involving human subjects, which contains information required by the BoD. UMCs define the minimum dataset required for mandatory registration of research projects. ▸ Appendix 1 contains a table with the minimum dataset, which can be used as a guideline for preparing the UMC-specific dataset.



3.3 Centralised support

Centralised support includes an audit programme, centrally facilitated monitoring, instructions regarding the use of services by external parties (vendor management), methodological and statistical support, data management support and a central helpdesk. The concrete implementation of research support is arranged by each UMC individually.

Chapter 4. Risk management

Risk management in research is primarily the sponsor's responsibility and involves the identification of risks that could manifest at the different levels of a study and taking mitigation measures prior to and during the course of the study. The risk management process consists of various parts: risk identification, risk assessment, risk mitigation and risk evaluation (see figure 2). The aim of risk management is to identify and manage aspects that could threaten the quality and integrity of the research and ethical aspects regarding the rights, safety and well-being of the research subjects.

Identifiying risks, risk assessment, associated mitigation measures, and risk evaluation should be documented in writing, for example in a Risk Management Plan (RMP). In a UMC mandatory templates can be available for documenting risk identification and associated mitigation measures.

Process risk management

4.1 Risk identification:	**4.2 Risk assessment:**	**4.3 Risk mitigation:**	**4.4 Risk evaluation:**
Takes place during the process of protocol writing on different levels: • System/site • Study design • Research subject • Participating centres • Vendors • Other	Assess possibility and extent of damage of each identified risk and classify. **Risk Classification** • Negligible • Moderate • High	Describe risk mitigation: accepting, limiting, sharing or avoiding. Document in for example: • Monitoring plan • Contract • DMP • DSMB charter • Other measurements: RMP	Evaluate risks periodically. If necessary adjust risk mitigation and identify possible new risks (go back to step 4.1).

This process could be documented in a Risk Management Plan (RMP).
In a UMC mandatory templates can be available for this.

Figure 2: Overview of the risk management process

4.1 Risk identification

Risk management can have an impact on the design of specific research processes. That is why risk identification should take place during the process of protocol writing, preferably by a multidisciplinary team.

Risk identification should be done at different levels, such as:

- System/site: for example, availability of SOPs, automated systems, personnel, logistics, finances, privacy measures.
- Study design: for example, complexity of protocol, multicentre/international study, research product, anticipated adverse events, informed consent process, data collection.
- Research subject: for example, study population, additional physical and psychological risks of the research.
- Participating centres: for example, experience and composition of the research team.
- Use of services by external parties in the conduct of the study (vendors).
- Quality of the data.
- Other: for example, social, societal, publicity.

Risks to the safety of participants in scientific research cannot always be avoided, but must be justified by the added value of the knowledge generated by the research. When identifying risks to the safety of the research subjects, the focus must be on the added risks in addition to the existing risks associated with undergoing the standard treatment. The extent to which a research subject runs an additional risk by participating in research depends on a number of aspects: for example, the likelihood that damage will occur, the severity of any damage occurring, whether the damage can be treated and reversed, and how uncertain these matters are. This is explicitly not restricted to potential physical risks, such as damage to the body, pain or discomfort. Research subjects can also run added risks at a psychological level (anxiety, stress) or a social level (privacy, stigmatisation, insurability).

When identifying risks to the quality of the data, attention should be paid to the complexity of the protocol, the method of data collection and analysis, parties involved in conducting the study, and additional aspects that could affect the reliability and integrity of the research data.

4.2 Risk assessment and risk classification

The magnitude/severity of each identified risk needs to be assessed, with preferably an overall risk per study (e.g. if the majority of the risks are negligible, the study as a whole can be considered as having a negligible risk). A risk classification is assigned to determine the extent of monitoring. Aspects should be included that could affect the safety of the research subjects and the quality of the data. The risk matrix in Table 1 can be used for this purpose.

Possibility/ Extent of damage	Slight damage	Moderate damage	Severe damage
Small chance	Negligible risk	Negligible risk	Moderate risk
Moderate chance	Negligible risk	Moderate risk	High risk
Large chance	Moderate risk	High risk	High risk

Table 1: Risk Matrix

Tools to determine the risk class of a study are available in every UMC. When assessing the study, certain considerations can result in the study being assigned to a higher risk class.

4.3 Risk mitigation

For identified and assessed risks, mitigation should be documented in (e.g. in an RMP). Mitigation entails accepting, limiting, sharing or avoiding of identified risks. Risk mitigation is incorporated in all aspects of quality assurance of the study, for example, the monitoring plan, contract, Data Management Plan, and DSMB charter.

4.4 Periodic evaluation of risks

Over the course of the study, risks should be periodically evaluated to ascertain whether changes in (potential) risks have occurred. Risk identification and assessment (incl. risk classification for monitoring purposes) should also be repeated at important timepoints in a study. For instance, in case of amendments to the study or unexpected events, such as slow inclusion, (temporary or permanent) inclusion or study stop due to an unexpected severe adverse event, or a pandemic. These events can lead to a revision of the risk mitigation measures. This, in turn, may have consequences for the extent and method of monitoring, research processes, and protocol. The periodic evaluation of risks should be documented (e.g. in an RMP).

Chapter 5. Monitoring

Monitoring is an essential instrument for the quality assurance of research subject to the WMO. It serves to verify that the research subjects' rights and well-being are protected, that the study data are recorded accurately and fully verifiably in source documents, and that the conduct of the study is in accordance with the approved protocol (including amendments) and the relevant legal requirements.

For all research subject to the WMO, the intensity of monitoring should be aligned with the degree of risk (see ▸ Appendix 2). Regardless of the risk classification associated with the study, monitoring activities should be carried out by qualified monitors. It is important that the monitor is not involved in the conduct of the research (i.e. independent party), as they must be able to objectively verify the proper conduct and associated documentation of the research.

5.1 Monitoring within UMCs

The NFU demands monitoring for all research falling under the scope of the WMO. Monitoring is the sponsor's responsibility, who must ensure that the study is monitored adequately by qualified monitors. In addition, a study-specific monitoring plan must be prepared, preferably in consultation with the monitor. This monitoring plan forms the basis for monitoring of all participating centres. If relevant changes occur in the course of the study, the monitoring plan should be adjusted accordingly (e.g. because of a protocol amendment or changes in the identified risks/risk analysis). Monitoring and reporting should adhere to the established monitoring policy. Frequency and intensity of monitoring depend on risk assessment of the study. ▸ Appendix 2 outlines for each risk classification which aspects must be checked during monitoring visits. Substantiated deviations are possible. The amount of attention each topic deserves needs to be assessed, and whether the number of visits is essential or sufficient. This could involve, for example, the use of deferred consent, conduct by experienced or inexperienced research teams, rapid or slow inclusion, etc. In case of phase 1 or multicentre research, more monitoring visits may be required, whereas in low intervention clinical trials or healthcare evaluation research subject to the WMO (*Veldnorm Toetsing en Kwaliteitsborging WMO-plichtige Zorgevaluaties -ZE&GG*[8]), fewer monitoring visits based on the identified risks may suffice.

8 Veldnorm — ZE&GG (zorgevaluatiegepastgebruik.nl)

5.2 Types of monitoring

The term monitoring is usually taken to mean the classic on-site monitoring visit. In recent years it has become apparent that more effective monitoring can involve other types of monitoring. Remote monitoring can be a sound choice. In the study-specific monitoring plan, a particular type of monitoring is chosen and substantiated on the basis of the identified risks.

5.2.1 On-site monitoring

In case of on-site monitoring the research site is visited by the monitor, who checks the accuracy of the conduct of the study and the associated documentation.

5.2.2 Remote monitoring

In case of remote monitoring the research location is not physically visited, and the conduct of the study is verified in another way. The monitor approaches the research team of a study site by telephone, video calling or e-mail to check remotely (in a secure environment) how the study is being conducted. For example, monitors can ask questions about the inclusion rate and about SAEs, protocol deviations and changes in personnel that may have occurred. Monitors can request documentation to check certain processes, but never documents containing personal data. Remote monitoring cannot entirely replace on-site monitoring, as verification of the signing of paper informed consent forms, certain local procedures (e.g. storage of material) and source documents with traceable personal data cannot take place remotely.

The conduct can also be verified by analysing the collected data for trends, missing data, outliers and/or inliers. Using the analysis results, monitoring can be targeted better, for example when choosing which research site to monitor and/or which source documentation requires verification. Prompt entry of data in an eCRF is a precondition for this.

5.2.3 Types of monitoring visits

There are different types of monitoring visits:

- **Initiation visit/kick-off meeting (central):** Before a research site may start including research subjects, an initiation visit or kick-off meeting (central) must be held. During this visit/meeting, the protocol and study procedures can be questioned and explained further. A check is done of whether the essential documentation (required to be able to start the study) is present. In addition, the logistics of the study are reviewed, tasks and authorisations are discussed, and the associated qualifications of the study team members are verified. An initiation visit/kick-off meeting (central) can be conducted either on-site or remotely.
- **Monitoring visit:** The monitoring visits are scheduled regularly on-site and/or remotely, during which procedures and activities are carried out to check the quality of the study and the research subjects' safety. See ▸ Appendix 2 for recommendations concerning the frequency and content of monitoring.
- **Close-out visit:** The close-out visit takes place after the last research subject has undergone the last study procedure at the research site. The close-out visit can be combined with the

final monitoring visit. During this visit a check is done on completeness of the data collection, whether essential documents are filed, and whether all action points/findings from prior monitoring visits have been addressed. The research site is also informed about long-term archiving, possible inspections and other expectations. The close-out visit can be done either on-site or remotely. For example, a checklist can be sent to the research site, which refers to the above matters and must be signed by the research site's investigator to confirm that all conditions have been met.

5.3 Follow up of monitoring findings

For all of the types of monitoring mentioned above, it is necessary to record in a report which matters were checked. Findings are summarised, including suggested improvements and action points. This report is sent to the coordinating or principal investigator/sponsor. The principal investigator of the centre where the monitoring took place receives a summary of the visit, including findings, suggested improvements and action points. Upon request, the entire report can be forwarded. Depending on the nature and severity of the findings, corrective or improvement measures may be required. If the reported improvement and action points are not or not completely followed up, the sponsor's principal investigator can undertake action or, in case of multicentre research, the site in question can be contacted on behalf of the sponsor. If this does not lead to the desired result, an escalation procedure is instituted. This can be documented in the study-specific monitoring plan and/or UMC-specific policy.

Chapter 6. Auditing

To safeguard the quality of research subject to the WMO, each UMC must have an internal audit programme. The BoD is responsible for setting up an adequate audit programme, which enables audits to be performed randomly covering all research groups in the UMC.

6.1 Process

Auditing is a component of quality management that involves assessing the level of quality within an organisation. This includes checking the quality assurance process and assessing whether parties are properly carrying out their tasks and responsibilities. An audit is a systematic and independent verification of processes, activities and documents related to the research and is independent and distinct from routine monitoring. An audit examines whether the activities are being conducted in agreement with the protocol, SOPs, relevant legal requirements and local policy. Audits promote continuous learning and improvement and contribute to quality improvement.

An audit should be performed by a trained, independent auditor. Independent means that the auditor is not involved in the study or research group in any way. The frequency of audits must enable checks of critical points of the process and risks. Each UMC determines the manner in which audits and the audit programme as a whole are organised.

6.2 Types of audit

An audit programme can consist of different types of audit. Audits can be performed at the study level, or at a broader or narrower level. Examples include department/division audits, routine audits, for cause audits, process audits, tracer audits and audits of external parties (vendor audits).

6.3 Follow-up of audit findings

The outcomes of an audit are communicated to those involved, the sponsor and possibly a quality professional of the part of the organisation that was audited. This often takes the form of an audit report or a checklist with findings. The sponsor is responsible for an adequate and timely follow-up of the findings. The follow-up is initially assigned to the responsible party in the relevant study (principal investigator) or the part of the organisation that was audited. If applicable, a Root Cause Analysis needs to be conducted and a plan for improvement, such as a Corrective and Preventive Action (CAPA) plan drawn up. If this does not lead to the desired result, escalation will take place according to an escalation plan that forms part of the UMC-wide policy.

Audit findings can also lead to UMC-wide improvements or revision of existing policy. Follow-up is assigned to the person with final responsibility for research at the relevant UMC.

The BoD is informed annually about the audit programme's progress. If necessary, the BoD will be informed promptly.

Chapter 7. Contracts and liability

When carrying out research subject to the WMO, in many cases contracts need to be drawn up, e.g. to cover any possible financial and legal risks, and to record agreements with third parties. The investigator can contact the relevant (legal) department of the UMC for assistance.

7.1 Contracts

When the sponsor needs to engage external parties to conduct the research, contracts have to be drawn up. A contract is defined as a binding agreement among at least two parties in written form.

External parties, also referred to as 'third parties', are parties that do not form part of the sponsor's legal entity. This concerns participating institutes in multicentre research and external organisations or people who are engaged to carry out tasks or provide services in the context of research (e.g. a central laboratory, a CRO, a supplier of a data management system, and DSMB members). These third parties must receive a clear commission agreement.

Contracts are not concluded on behalf of the UMC by individual employees, but by the UMC as an organisation. Contracts cover at a minimum the responsibilities and tasks of the parties involved, the contract duration, any financial arrangements, liability, ownership of any results, coverage of risks and, if applicable, agreements about publication and the sharing of personal data and/or human tissue. When a third party obtains access to human tissue and/or personal data in order to analyse, store or combine them with other data, separate agreements are often needed to protect the privacy of the research subjects' data.

Contracts can take different formats, depending on the nature of the agreements. The contractual parties decide which type of contract should be used. Often national templates are available, such as Clinical Trial Agreements and Material/Data Transfer Agreements. In addition, UMCs may have UMC-specific templates. When preparing and reviewing contracts, specialised legal advisors in the UMC are involved, partly because pitfalls and risks are associated with the privacy legislation and liability. Contracts must be signed by someone who is officially authorised to do so on behalf of the UMC.

When supporting departments/divisions in the UMC provide services that benefit the research, it is similarly important to make sound internal agreements. Because the departments/divisions belong to the same legal entity, this is not formally considered a contract. Nevertheless, both the supporting service and the applicant/investigator must approve the agreements made and record them in writing.

7.2 Liability

Liability must be contractually documented. Important points to consider are agreements that maximise liability, exclude indirect damage from liability, and disclaimers. In addition, each UMC has taken out insurance policies, including ones for medical and legal liability risks. Insurance policies put limits on the coverage.

Chapter 8. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB; or independent Data Monitoring Committee) may be installed for a clinical study. A DSMB usually consists of a group of three to five members, with scientific expertise specifically relevant for the research. The members are independent of the clinical study in question, and thus have no conflict of interests regarding the research.

Clinical research often takes years to complete, during which period a growing amount of data/outcomes becomes available. It can be extremely important to evaluate the interim results with regard to safety and efficacy. For example, safety problems could arise that would render continuation of the trial unethical. Or, in case of convincing evidence that the investigational treatment is effective before the end of the study, it is justified to terminate the study and make the treatment available to all participants. It is important that interim analyses are performed independently under the supervision of a DSMB. This ensures that the course of the clinical study remains unaffected if it is recommended that the trial should continue according to the protocol.

8.1 Composition

A DSMB consists of clinical scientists and a statistician, who jointly prepare an advisory report for the sponsor based on a sound scientific evaluation. The DSMB statistician evaluates the analyses and the results. This requires specific statistical expertise due to the complexity of repeatedly evaluating the cumulative data during the clinical study. The DSMB statistician will not conduct these analyses him/herself, but can make suggestions for supplementary analyses to the research team. Depending on the type of analysis, this could include analyses for futility (inability of a trial to realise a certain objective), or analyses for a double-blind study could be conducted by a second, equally independent statistician supporting the DSMB. The DSMB chooses a suitable chair from among its members, or a candidate chair is approached who will recruit the remaining members of the DSMB. The chair must have previous experience with DSMBs (preferably extensive) and a proven ability to transform discussions impartially into a consensus.

8.2 Charter

A DSMB charter should at a minimum contain the following information: title and sponsor of the clinical study, including risk analysis of the clinical study; objectives of the clinical study and scope of the charter; DSMB composition (including names and signatures); the role and responsibility of the DSMB; and the dates/frequency and organisation of the DSMB meetings, including the method of preparation, progress, decision-making and reporting[9]. The principles on which the DSMB decision-making is based must also be documented, including any statistical termination rules. The charter is submitted to the MREC for assessment as part of the research file.

9 K5. DSMB charter template | Form | The Central Committee on Research Involving Human Subjects (ccmo.nl)

8.3 Recommendations

The DSMB issues recommendations to the sponsor or delegated principal investigator, without disclosing the interim results. These recommendations concern the research subjects' safety, that of subjects still to be recruited and the scientific added value of continuing with the clinical study. The DSMB also pays attention to the conduct of the clinical study, particularly those aspects that could affect the quality and integrity of the collected data. Along with adequate recruitment (speed and procedure), this generally concerns: being up-to-date with the data collection and data entry, ensuring that no serious or other adverse events ((S)AEs) are missed and that they are all recorded in the eCRF, and as complete a follow-up of research subjects as possible, even if they discontinued treatment. The DSMB expects to be kept informed by the research team of any relevant external developments (from another study or clinical practice).

A DSMB can issue various recommendations during the course of a clinical study:

- Continue the study in accordance with the study protocol.
- Continue the study with modifications (e.g. terminating one treatment arm, excluding a subgroup).
- Discontinue the study due to evident damage.
- Discontinue the study due to evident efficacy.
- Discontinue the study due to a lack of convincing evidence of efficacy ('futility').
- Discontinue the study because completing it is not feasible.

The DSMB issues recommendations; it is up to the sponsor or delegated principal investigator whether or not to act on them. It should be clear that a decision to deviate (partly or entirely) from a consequential recommendation should not be taken lightly, and should never be taken by the principal investigator alone, but also requires the sponsor's approval. In these cases the principal investigator, in consultation with the sponsor, is responsible for informing the MREC and the competent authority.

8.4 Reporting

It is the responsibility of the sponsor or the delegated principal investigator to ensure that the DSMB receives an interim summarised research report, with an overview of the recruitment, and (in case of a randomised study) tables and analyses comparing the groups in terms of important safety and efficacy outcomes. These reports should be prepared carefully. It is also important to take adequate measures to keep these reports independent of the investigators directly involved.

8.5 Types of research

For high-risk studies, a DSMB is almost always installed. If the additional risks are moderate, the decision whether to install a DSMB will be made for each study individually. The MREC assesses the composition, installing and procedures followed for a proposed DSMB. It can also determine that a DSMB must be installed. A complete, independent DSMB is normally not required or sensible for phase I studies involving medicinal products (in the presence of extra supervision or an internal safety committee) or for studies with negligible additional risks (or minimal exceedances thereof). See ▸ Appendix 3 for an overview of the responsibilities concerning the DSMB in investigator-initiated research.

Chapter 9. Data management

Research data form an essential part of a research project. The data must be collected and managed in a principled, verifiable and reproducible way. This applies during all phases of research, from collecting, processing and analysing to archiving and publishing the data. According to the GDPR, the privacy of research subjects must be protected. In addition, it must be possible to reuse the data and share them with other investigators. The NFU subscribes to broad application of the FAIR data management principles: data must be Findable, Accessible, Interoperable and Reusable. These principles are elaborated in this chapter and are in line with the requirements from legislation, ICH-GCP and ISO 14155, the *NFU Handbook for Adequate Natural Data Stewardship* (HANDS)[10] and leading grant providers.

9.1 Preparation of data collection

9.1.1 Data Management Plan

The way in which the data management of a study is arranged must be documented in a mandatory Data Management Plan (DMP). The DMP must be prepared by the sponsor at the start of a study and can be augmented during the course of the study. For a multicentre study, the local principal investigator is responsible for local data management. A DMP or a local addendum to the DMP provided by the sponsor can be useful when preparing for data management. The DMP must describe which existing data are to be reused and what new data will be collected during the study, how the data will be stored and managed during the study, and how the data will be archived and shared after the study. In addition, the DMP must describe how the privacy of research subjects will be protected. Most UMCs have a centre-specific DMP template, but grant providers may require the use of other DMP templates.

9.1.2 Data validation and statistical analysis

It is recommended that a data validation plan is drawn up before the start of data collection, which specifies the quality requirements the collection must meet. Good quality of data can be achieved by data validation, which involves checking the data for completeness, correctness and mutual consistency. This can be done with either programmed automatic checks or manual checks. The statistical analysis should be described in advance in the research protocol or in a statistical analysis plan (SAP).

10 Data stewardship handbook (HANDS) | Health-RI

9.2 Data collection

9.2.1 Reuse of existing data

A first step in data collection is ascertaining whether the necessary data are already available in public data archives or in patient records obtained in the healthcare context. When reusing data, the purpose of the reuse must correspond to the purpose to which the research subject initially consented. Always check when considering the reuse of existing data whether the research subject has been asked for consent or whether additional consent has to be requested, or if an exemption to obtaining consent applies.

9.2.2 Collection of new data

The data collection may only contain the research data specified in the study protocol (data minimisation). It is recommended to record data in a validated Electronic Data Capture (EDC) system, if possible. In an EDC system, data are entered by investigators via the eCRF or directly by research subjects via electronic questionnaires.

The collection of research data that fall under the scope of the WMO should be recorded in a validated EDC system with:

- An audit trail that automatically records changes to the data (who, what, when), without deleting the originally entered data.
- An audit trail that documents the reason for a change when data are revised (mandatory according to ICH-GCP and ISO 14155).
- Possibilities to apply access minimisation: preventing unauthorised access to the data by means of secure access, and restricting access in personal accounts to what is essential.
- Periodic and adequate back-ups.
- Protection of the blinding.
- Preferably an ISO 27001 or NEN 7511 certification.

At the start of the study, the sponsor provides an (e)CRF (and if applicable, also randomisation system) that has been demonstrably tested and provides instructions for use. Together with the principal investigator (in the case of a multicentre study, the local principal investigator), the sponsor is responsible for ensuring that the data can be collected in a complete, correct, consistent and demonstrably reliable manner. The (local) principal investigator is responsible for ensuring that the study data in the (e)CRF match the source documents; any discrepancies must be explained. The (local) principal investigator (or a delegated representative) should check each completed (e)CRF for each research subject and record this step in the (e)CRF. Research data should be reported to the sponsor in a timely manner so they are readily available for statistical analysis.

Wherever possible, standards should be employed in collection of the data. They must align with standards used in the relevant field of research. For example, recording the diagnosis according to ICD-10, conducting laboratory measurements according to the protocol or LOINC, other standards for medical terminology like SNOMED CT, MedDRA, CDISC, or using validated questionnaires. The DMP must record which standards are being used.

9.3 Privacy

Data from WMO research are almost never anonymous, it is rarely possible to say with certainty that no individual can be re-identified in a dataset. To ensure the privacy of research subjects, each UMC has an information security policy that must be complied with, and facilities to implement the policy. The UMC's Data Protection Officer (DPO) can advise on this topic. In the context of accountability, all research subject to the WMO must be registered in the processing register of the respective UMC. In addition, the sponsor determines at an early stage of each research project which technical and organisational measures must be taken to protect personal data (privacy by design). In case of an increased privacy risk, the sponsor is obliged to draft a Data Protection Impact Assessment (DPIA), in which the risks regarding the privacy of research subjects are analysed and measures to reduce those risks are described. This can include the use of two-factor authentication (2FA), access restriction, logging and monitoring, password policy, encrypting data on mobile devices, and safe methods to exchange data with third parties (e.g. via SURFfilesender). Record agreements about providing personal and/or research data or human tissue to an external party in a contract. If necessary, legal advisors or the DPO should be involved. Pseudonymisation is another measure that can be taken to protect personal data. With this method, directly identifiable data (name, address, patient number, date of birth) are not entered in the (e)CRF, but an (in itself meaningless) code is used instead. This pseudonym and the identifiable data are recorded in an identification list (key file). Pseudonymisation thereby allows the possibility of tracing data back to the individual research subject. The local principal investigator is responsible for ensuring that the sponsor receives pseudonymised data, with the associated identification list stored at the research site, separately from the pseudonymised data. Pseudonymisation can also be done by an independent third party.

9.4 Documentation concerning data

All research steps taken and procedures used to arrive from the raw data to the analysis data and results must be documented. The laboratory procedures should be recorded in a lab journal (paper or electronic). The cleaning of the data and the statistical analyses must be documented, to allow for reproduction; for example, the syntax used for cleaning and analysis and software used with version number. The data collection and the dataset must be accompanied by metadata, for example a good description of how the data collection was set up, well-written scripts/syntaxis, a codebook for the dataset (data dictionary), clear version management and contact details.

9.5 Data storage during the study

During all phases of the study, the data must be stored securely. Each UMC has its own procedures and facilities to realise this.

9.6 Closing the data collection

After the collected eCRF data have been declared complete and clean, the data must be locked in the EDC system. External data outside the eCRF can be locked by revoking in full the write permission of anyone who has access to the data. The sponsor orders the locking of the data and ensures that this step is documented. After the data are locked, the local principal investigator retains read permission for the entered data and receives an export of them.

9.7 Data publication and archiving

The underlying (raw) data, including the associated documentation, should be made available for new research, unless concrete agreements have been drawn up not to do so ("as open as possible, as closed as necessary"). The data must be deposited in a sustainable data archive or repository, in which the dataset can be cited and found. Data should preferably be made available before publication of the scientific article, so reference to the dataset can be made in the article.

It is the sponsor's responsibility to document the procedures and agreements for making data accessible in the DMP at an early stage. This may include control over the data, choosing a licence, drafting terms of use, ensuring privacy, the role of any Data Access Committee, and ensuring the research subjects have given informed consent for sharing the collected data. The long-term management of the data should be entrusted to a department head.

Chapter 10. Management and Archiving

This chapter describes the management and archiving of essential documents and data, jointly called the research file. Management refers to the storage and maintenance of essential documents and data during the design and conduct of a clinical study. Archiving refers to secure storage after the study has been completed. The research file serves as a source of information for research staff during the conduct of the study and supports future reuse of the data after completion of the study. It also ensures that the design and conduct of the study are verifiable for supervisory authorities. SOPs for the proper and uniform conduct of management and archiving must be available at the UMCs.

10.1 Research file

ICH-GCP Chapter 8 and ISO 14155 Annex E for research involving medicinal products and medical devices, respectively, provide an overview of essential documents that must be managed and archived during the preparation and conduct of the study, and after completion. A distinction is made between the research file that must be managed and archived as Trial Master File (TMF) by the study sponsor and the research file that must be managed and archived on site as the (Investigator) Site File (ISF) by the local principal investigator of a participating centre. For other types of research subject to the WMO, these overviews should be used as guidelines. If, due to the nature of the research, fewer documents need to be managed and archived, the sponsor must be able to justify this choice. If documents are to be stored elsewhere, reference to these locations must be made in the relevant TMF/ISF.

The content of the research file should be obvious for authorised third parties without requiring additional clarification from the sponsor or investigator. The file should comply with the following criteria[11]:

Accurate and complete: The file presents the complete, observed reality, and the content is not manipulated. Changes in the file's contents are traceable through version management and authorisation of documents.

Readable and enduring: The file is stored and archived in such a way that all of the documents and data remain fully readable throughout the entire storage period.

Original: The file contains the original documents (see also 10.1.2).

Available on demand: The research file is accessible and readily available to authorised persons (e.g. auditors, inspectors) once their authorisation has been verified.

10.1.1 Digitisation

A research file may consist of paper documents, digital documents or a combination thereof. A digital file meets the same requirements as a paper file throughout the entire storage period. Changes in the file can only be made by authorised individuals and are recorded in an audit trail.

11 Guideline on the content, management and archiving of the clinical trial master file (europa.eu)

10.1.2 Replacing paper documents

ICH-GCP and ISO 14155 permit original (paper) documents to be replaced by certified (digital) copies. A digital copy is required to be validated and authorised according to a detailed process. Simply scanning is not sufficient. There is no clear guideline that specifies when a copy is sufficiently validated to be accepted as a certified copy by the supervisory authorities. Therefore, the NFU advises investigators not to destroy the paper original of documents with a wet signature or other handwritten information.

It is permitted to make a work copy for the TMF/ISF of paper originals stored elsewhere, as long as it is clear that it is a copy and a reference is made to the location of the original.

10.2 Management

During the preparation and conduct of research, the research file must be findable and accessible to suitably authorised research staff and supervisory authorities, such as monitors appointed by the sponsor, auditors and inspectors. The research file must contain those documents needed to verify the conduct of the study and the quality of the data. This involves careful handling of information that can be traced back to individual research subjects, in such a way that this information is only accessible to persons who are authorised to have access. Directly identifiable data of research subjects (e.g. the identification list/key file and the Informed Consent Forms signed by the research subjects) should not be part of the pseudonymised study data. The sponsor's TMF may only contains data of research subjects that cannot be directly traced back to them (pseudonymised), while the (local) investigator's ISF also contains identifying data. If the TMF and ISF are combined in a monocentre study, the identifying data should be stored separately. This applies during the study and when archiving after the study has ended.

10.3 Storage location

Storage locations of both physical and digital documents and data are secure. This means that the sponsor and local principal investigators ensure that only authorised people have access and that any changes are recorded. The UMC is responsible for complying with the archiving obligation and providing an adequate infrastructure for management and archiving. The sponsor and the participating research institutes maintain a register of the location(s) where the research file is stored during and after completion of the study.

10.4 Archiving

The research file is stored for verification purposes (e.g. in case of inspections) after the study has been completed for the duration of the predetermined storage period.

10.4.1 Storage periods

The sponsor makes written agreements with the local investigator about the storage period of the research file. The storage period must be stated in the protocol and in the information for research subjects. If the file is to be stored for longer than the legally prescribed minimum storage period, this must be justified in the protocol. The CCMO has published extensive information about the storage periods on its website. For research falling within the scope of the CTR, MDR or IVDR, the storage period of the research file is stipulated by law. The WMO does not prescribe a fixed storage period. The CCMO indicates that it considers 15 years acceptable for research subject to the WMO that does not fall under the CTR, MDR or IVDR. The NFU recommends using this period unless there is a need to deviate from it.

During the study, research subjects may withdraw given consent for use of their personal data. This applies to the study and/or to the storage and use of study data for future research. The study data collected up to the moment of consent withdrawal remain part of the dataset to be analysed, to avoid methodological bias and are therefore also retained in the context of research quality assurance.

Once the predetermined storage period has expired, the sponsor commissions destruction of the data. Documents with directly identifying data are deleted irretrievably, so they can no longer be accessed. For purposes of data sharing (reuse), the sponsor may store the anonymised frozen dataset (including descriptive documentation), collected in the context of the study, for a longer period (see Ch.9 Data management for more information about reuse).

Appendix

Appendix 1
Minimum data set

Appendix 2
NFU Guideline for risk-based monitoring of research subject to the WMO

Appendix 3
Responsibilities concerning the DSMB in investigator-initiated research

Appendix 1: Minimum data set

This minimum dataset is a guideline for creating the UMC-specific data set.

Category	Main information	Sub-information
General	UMC study number	
	Title/acronym	
	Sponsor	
	Department	
	Mono-/Multicentre	
	Is/is not subject to WMO	
	NFU Risk classification	
	Type of study	Medicinal product, incl. phase
		Medical devices, incl. class
		Other
	(planned) Number of participants	
	(planned) Number of participants in UMC	
	ABR-number/CTIS-number	
	Principal investigator at UMC	
	Email of principal investigator at UMC	
	Status of research project	
	Financing	
	Contract is present/absent	
	Type of research subjects	Patients
		Volunteers
		Minors/legally incompetent
	WMO research subject insurance	
GDPR	Processor of data	
	Project does/does not collect, process or manage data (files), medical information or human material	
	Anonymous or encrypted	
	Biobank is /is not involved	
	Informed consent is present/absent	
Approvals	MREC number	
	Date of MREC approval	
	Date of BoD approval	
Data management	Validated eCRF/EDC system is/is not used	Specify
	Storage site of eCRF/EDC system	
	How are personal data and/or medical data (on paper) kept secure	Specify
	Data storage period	
Monitoring	Monitoring is/is not arranged	
	Who/which party is monitoring	

Table 2: Required information in minimum data set

Appendix 2: NFU Guideline for risk-based monitoring of research subject to the WMO

Topic	Negligible risk = Minimal monitoring		Moderate risk = Moderately intensive monitoring	High risk = Intensive monitoring
	Negligible risk: Other research	Negligible risk: Clinical studies involving medicinal products, medical devices and nutritional products		
Monitoring frequency	**Monocentre study:** Minimum[1] of one on-site visit during the study[2]. **Multicentre study:** Minimum of one on-site visit in the coordinating centre[3] during the study + one remote[4] monitoring per participating centre during the study[2]. Depending on the findings, on-site visits can also be planned at the other participating centres.	For each participating centre at least[1] one visit annually, with at least two on-site visits per participating centre during the study[2].	For each participating centre at least[1] two visits annually, with definitely one on-site visit annually[2].	For each participating centre at least[1] two visits annually, including at least one on-site visit annually[2].
Inclusion progress	Asking about inclusion rate and drop-out percentage, regardless of risk classification.			
Trial Master File / Investigator Site File	Check the accuracy and completeness of essential documents (at centres monitored on-site or centres with (in part) digital files).			
Informed Consent Form (ICF) present[5]	Confirm presence of at least 10% of the total number of included* research subjects or as many ICFs as possible at the time of the on-site visit.	Confirm presence of at least 10%, (preferably 100%) of the total number of included* research subjects per participating centre.	Confirm presence of at least 25% (preferably 100%) of the total number of included* research subjects per participating centre.	Confirm presence of at least 50% (preferably 100%) of the total number of included* research subjects per participating centre.
Informed Consent (IC) process and verification of implementation[5]	Enquire about IC process (also possible via remote[4] monitoring). Verification of the entire IC process of at least two (preferably more) of the total number of included* research subjects (per centre monitored on-site)[6].	Enquire about IC process. Verification of the entire IC process of at least 10% of the total number of included* research subjects per participating centre[6].	Enquire about IC process. Verification of the entire IC process of at least 25% of the total number of included* research subjects per participating centre[6].	Enquire about IC process. Verification of the entire IC process of at least 50% of the total number of included* research subjects per participating centre[6].
Inclusion/exclusion criteria[7]	Verification of at least two (preferably more) of the total number of included* research subjects (per centre monitored on-site).	Verification of at least 10% of the total number of included* research subjects per participating centre.	Verification of at least 25% of the total number of included* research subjects per participating centre.	Verification of at least 50% of the total number of included* research subjects per participating centre.

* included research subjects = Informed Consent signed.

1 It is important to determine whether the (minimum) number of described monitoring visits is sufficient for a study to uncover certain trends or whether that number should be increased. A trained monitor can aid in this assessment.
2 Depending on the inclusion rate, duration of the study, number of research subjects and previously observed deviations, a participating centre can be monitored more or less frequently, and the percentages per topic to be monitored can be justifiably adjusted.
3 If no research subjects are included in the coordinating centre, the monitor need only verify the conduct of the sponsor's tasks.
4 Monitoring of participating centres for 'Other research subject to the WMO with negligible risk' can be done remotely or on-site. The choice for remote or on-site depends on several factors and may differ from one institute to another. Check the UMC-specific policy for presence of additional criteria.
5 If ICFs are missing or if errors are identified in the IC process, the sample is increased appropriately, regardless of the level of intensity of the monitoring. The monitor is expected to continue to strive for the described percentage, but it is possible that at the time of the visit, the percentage cannot be achieved because the expected number to be included has not yet been realised. This is why the phrase "if possible" has been added.
6 If the IC process is/is not considered to contain risks, deviation from this percentage is permitted, and increased or decreased, respectively.
7 If research subjects have been erroneously included in the study (violation of inclusion and exclusion criteria in relation to safety is especially important), the sample size is increased appropriately, regardless of the intensity of monitoring.

Topic	Negligible risk = Minimal monitoring		Moderate risk = Moderately intensive monitoring	High risk = Intensive monitoring
	Negligible risk: Other research	Negligible risk: Clinical studies involving medicinal products, medical devices and nutritional products		
Source Data Review and Source Data Verification[8]	Verification of at least two included* (preferably more) research subjects (per centre monitored on-site). (Based on a defined list of variables, including the primary endpoint, that are clearly related to the safety and validity of the study)[9].	Verification of at least 10% of the total number of included* research subjects per participating centre. (Based on a defined list of variables, including the primary endpoint, that are clearly related to the safety and validity of the study)[9].	Verification of at least 25% of the total number of included* research subjects per participating centre. (Based on a defined list of variables, including the primary endpoint, that are clearly related to the safety and validity of the study) [9].	Verification of at least 50% of the total number of included* research subjects per participating centre. (Based on a defined list of variables, including the primary endpoint, that are clearly related to the safety and validity of the study)[9].
SAEs[10]	Research subjects who were randomly selected for the SDV/SDR, are checked for unreported SAEs (per centre monitored on-site). Followed by check of all reported SAEs at the time of the on-site visit.	Research subjects who were randomly selected for the SDV/SDR, are checked for unreported SAEs. Followed by check of 10% of the reported SAEs at the time of the on-site visit, with any SUSARs/DDs always being verified.	Research subjects who were randomly selected for the SDV/SDR, are checked for unreported SAEs. Followed by check of 25% of the reported SAEs at the time of the on-site visit, with any SUSARs/DDs always being verified.	Research subjects who were randomly selected for the SDV/SDR, are checked for unreported SAEs. Followed by check of 50% of the reported SAEs at the time of the on-site visit, with any SUSARs/DDs always being verified
Investigational product[11]	Not applicable	Check product accountability[12] of research subjects selected for SDV and which instructions they received (if applicable).	Check product accountability of research subjects selected for SDV and which instructions they received (if applicable).	Check product accountability of research subjects selected for SDV and which instructions they received (if applicable).
Research procedures (e.g. randomisation, deblinding, data management and privacy)	Check whether instructions for carrying out research procedures are present and whether the study personnel are trained in carrying out the research procedures.			
Equipment	Verify whether the equipment used, if involved in determining the primary endpoint, have been included in a quality assurance system/programme.			
Support departments including Laboratory & Pharmacy[13]	Check whether written agreements have been made, if applicable. If a pharmacy, for example, prepares and supplies the investigational products, or is involved in the randomisation or deblinding, etc., verify procedures (e.g. training, manuals, stock management, preparation, temperature, etc.) based on the risk of the study. If a laboratory is involved in determining the primary endpoint, verify laboratory procedures (e.g. training, manuals, storage, temperature, etc.), except when the determination is carried out by an accredited laboratory that does not deviate from standard routine determinations.			

8 Source Data Verification (SDV) involves comparison of source data with (e)CRF data. Source Data Review (SDR) is an evaluation of the source documentation to check the quality of the source or compliance with protocols, and safeguard critical processes (source: TransCelerate), and an assessment of whether a source is present for the collected data (medical status).

9 The aim is to check as much as possible during the on-site visit and take this aim into account when planning the on-site visit. This also means that it is not always feasible to check all desired data, for example because not all research subjects have achieved the primary endpoint or no SAEs have occurred thus far. Take this into account when preparing the study-specific monitoring plan.

10 If the reporting and/or appropriate notification of severe adverse events is incomplete or incorrect, the sample is increased appropriately, regardless of the intensity of monitoring. If these irregularities concern SUSARs, the sample should be increased to 100%.

11 Product accountability can be checked at the level of the research subjects, department and/or pharmacy level (storage of products, expiry date, arrival in the pharmacy, issuing by the pharmacy/issuing to the research subject, dosage, return/destruction, etc.), depending on the product and study risk.

12 For low-intervention clinical trials, no separate product accountability record is required; product accountability need only be checked at the level of the research subject.

13 NB: checking written agreements also applies to other supporting departments involved in the study. An external pharmacy or central laboratory which is enrolled in the UMCs vendor management programme shall not be monitored separately.

Appendix 3: Responsibilities concerning the DSMB in investigator-initiated research

The table below describes the responsibilities of different parties when setting up a DSMB in investigator-initiated research (Table 3).

Action	Medical Department head (delegated by BoD)*	Principal investigator	DSMB members	Independent second statistician
Establishing DSMB	A	R	C	I
Periodic reporting to DSMB	I	A	I/C	R
DSMB decision-making	I	I	A/R	I
Interim recommendation report about the study to the sponsor via the principal investigator	I	I	A/R	I
Following up recommendation DSMB, or notification of not following up	A	R	I	I

Table 3: Responsibilities in case of investigator-initiated research

- R: Responsible: person carrying out task.
- A: Accountable: person ultimately responsible ('final responsibility').
- C: Consulted: person consulted about the task.
- I: Informed: person informed.

* Or another responsible manager, depending on the organisation in the UMC.

Colophon

This guideline is issued by the *Netherlands Federation of University Medical Centres* (NFU).
For more information, please contact the NFU at nfu@nfu.nl.

Authors:

NFU Working group Quality assurance of research involving human subjects:

- Dannie van den Brink, PhD, Senior Research Consultant (Radboud University Medical Center),
- Jacqueline van Dalen, PhD, Senior Clinical Research Associate (Clinical Monitoring Center, Amsterdam UMC),
- Marian Janson, Advisor Quality of Research (Leiden University Medical Center),
- Liesbeth Knaepen, PhD, Manager General Research Compliance (Maastricht UMC+/Clinical Trial Center Maastricht),
- Denise Mailly, MSc, Senior Research Consultant (Service Desk Clinical Research Office, UMC Groningen),
- Eugenie Ram, Research Staff Advisor (UMC Utrecht),
- Engelien Septer-Bijleveld, BSc, Senior Project Manager (Julius Clinical),
- Petra Westveer, MSc, Research Policy Advisor (Erasmus MC).

Review and input:

- NFU Platform Clinical Research,
- NFU Working group Data management,
- Legal Affairs Department, UMC Utrecht.

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Editorial board

Members of *NFU Working group Quality assurance of research involving human subjects*

Images

- CTCM B.V.
- Erasmus MC
- NFU

NFU Netherlands Federation of University Medical Centres

Physical address

Oudlaan 4
NL-3515 GA Utrecht

Postal address

PO Box 9696
NL-3506 GR Utrecht

T +31 30 273 98 80
nfu@nfu.nl
www.nfu.nl

NFU-23.01365