



NETHERLANDS FEDERATION OF
UNIVERSITY MEDICAL CENTRES



Guideline Quality assurance of research involving human subjects

Update December 2020

Preface

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

Naturally, the safety of the participants in the research and the quality of the research are paramount. Research involving human subjects must therefore meet strict requirements 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 research that falls within the scope of the *Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met mensen; WMO)*. The guideline also assists us in making clear quality agreements in research cooperation between UMCs, in the region or beyond.

The NFU presented this guideline for the first time in 2012. In 2019, a substantial revision followed, incorporating the latest insights. The current version is the 2020 update. In principle, we intend to release annual updates, unless no substantial changes have occurred. In this way we contribute continuously to the quality and safety of research involving human subjects in the UMCs, for tomorrow's life.

Prof. Margriet Schneider, MD
Chair of NFU

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Amendments to earlier versions

Update December 2020 compared to version 2019

Abbreviations and Terms glossary: some additions and corrections; Monitoring: clarification of remote and statistical monitoring and following up findings (Ch.5); Appendix 3: NFU guideline for on-site monitoring in relation to the estimated risk involved in the study: modifications, clarification, expansion of monitoring frequency negligible for other WMO research. Data management (Ch.9): minimal adjustments; clarification and reference to HANDS.

Version 2019 compared to version 2.0

Updated as a result of changed legislation (WMO, ICH-GCP, GDPR) and findings from IGJ inspections. Version 2019 is only available digitally. Changes to the content: Training: training for monitors and auditors added (Ch.2); Quality system: new chapter and combined with former Ch.9 'Reporting to the Sponsor' (Ch.3); Risk management and risk classification: risk management added and risk classification expanded with more weighting factors (Ch.4); Monitoring: more room for risk-based monitoring including centralised monitoring (Ch.5); Auditing: more attention paid to following up audit findings (Ch.6); Contracts, agreements and liability: new chapter (Ch.7); DSMB: more detailed information about setting up and implementation (Ch.8); Data management: new chapter (Ch.9); Management and archiving: updated storage periods (Ch.10).

Abbreviations and Terms

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 ¹ .
AVG/GDPR	Algemene Verordening Gegevensbescherming/ General Data Protection Regulation	The General Data Protection Regulation (GDPR) is the European privacy legislation in force since 25 May 2018.
BROK®	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers/ Basic course on Regulations and Organisation for clinical investigators	Mandatory course for clinical investigators required by the NFU that covers legislation as well as knowledge about supporting departments that enables the research to be carried out.
CAPA	Corrective Action and Preventive Action Plan	A plan that includes both corrective and preventive measures for e.g. an audit finding.
CCMO	Centrale Commissie Mensgebonden Onderzoek/ 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 that transparently covers all rights, duties and agreements of the parties involved in research involving human subjects.
DMP	Data management plan	Document specifying the manner in which the data management of a clinical study is arranged.
DPIA	Data Protection Impact Assessment	Process that analyses the risks regarding the privacy of research subjects and that describes measures to reduce those risks.
DSMB	Data and Safety Monitoring Board	Independent committee that monitors the safety of the research subjects during the 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 which individually and collectively permit evaluation of the conduct of a clinical study and the quality of the data produced (see ch. 8. ICH GCP).
-	For cause audit	An audit to examine a specific quality disruption or process deviation and/or prepare for a legal inspection.

¹ See https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Abbreviation	Term	Meaning
-	Certified copy	A copy (originating from any conceivable medium, including photocopies/scans) of the verified original data point(s) (i.e. by a dated signature or prepared in a validated process, such as a certified scanner) 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 <i>good data stewardship</i> for investigators. Commissioned by the NFU.
IC	Informed Consent	A process by which a research subject voluntarily confirms his or her willingness to participate in a particular clinical study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by a completed, signed and dated informed consent form ¹ .
ICF	Informed Consent Form	Informed consent form for research subjects for participation in medical scientific research.
ICH-GCP	Good Clinical Practice Guideline of the International Council on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.	GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting medical studies that involve the participation of human subjects. Compliance with this standard ensures that the rights, safety and well-being of research subjects are protected, in agreement with the Declaration of Helsinki.
IGJ	Inspectie Gezondheidszorg en Jeugd/ Health and Youth Care Inspectorate	Regulatory authority supervising healthcare and youth care services in the Netherlands.
ISF	Investigator Site File	Research file that must be managed and archived on site by the investigators of the participating centres.
METC	Medisch Ethische Toetsings Commissie/Medical Research Ethics Committee	Independent accredited committee of experts that reviews clinical research prior to and during its conduct. A clinical study may not be started without the approval of this committee.
NFU	Nederlandse Federatie van Universitair Medische Centra/ Netherlands Federation of University Medical Centres	The NFU represents the eight collaborating UMCs in the Netherlands, as advocate for and employer of over 65,000 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 of processes in an organisation.
PI	Principal Investigator	Investigator responsible for conducting the clinical study at a research site (ICH-GCP).
-	Process audit	An audit that identifies the risks of a process.
RvB	Raad van Bestuur/Executive Board	In this guideline, the RvB of a University Medical Centre.
-	Root-cause analysis	Analysis aimed at identifying the (underlying) causes.
SADE	Serious Adverse Device Effect	Severe side effect of a medical device.

Abbreviation	Term	Meaning
SAE	Serious Adverse Event	Any untoward medical occurrence in a research subject, that: <ul style="list-style-type: none"> ▪ Results in death, ▪ Is life-threatening, ▪ Requires hospital admission or prolongation of existing hospitalization, ▪ Results in persistent or significant disability/incapacity, Or <ul style="list-style-type: none"> ▪ Is a congenital anomaly/ birth defect².
SDR	Source Document Review	An evaluation of the source documentation to check the quality of the source and compliance with protocols, safeguard critical processes and check whether a source is present for the collected data (medical status).
SDV	Source Document Verification	Comparison of source data with (e)CRF data.
SOP	Standard Operating Procedure	Written operating instructions that describe in detail how a certain task must be executed, with the aim to create uniformity in the conduct of the task and thus in the final 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 patient, research subject, care track or process, and follows it over time. This audit form is designed for care, but can also be applied to research.
TMF	Trial Master File	Research file that must be managed and archived by the sponsor of the clinical study.
UMC	University Medical Centre	Academic hospital with the core tasks of care, research and education/training. Also linked to a university as a faculty.
USADE	Unanticipated Serious Adverse Device Effect	Unexpected severe side effect of a medical device.
-	Vendor audit	An audit at an external party that carries out delegated tasks (of the sponsor) for a clinical trial.
-	Sponsor	The commissioning party in the sense of the WMO (in Dutch: verrichter).
VSNU	Vereniging van Universiteiten/ Association of Universities in the Netherlands	Association in which the 14 Dutch universities collaborate on e.g. common ambitions concerning scientific education and research.
VWS	Ministerie van Volksgezondheid, Welzijn en Sport/Ministry of Health, Welfare and Sport	In research involving medicinal products, the Ministry of VWS, just like the CCMO, can act as competent authority (2nd assessing authority, along with the MEC or CCMO).
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen/ Medical Research Involving Human Subjects Act	Scientific research involving human subjects falls under the WMO if it concerns medical scientific research and participants are subject to procedures or are required to follow rules of conduct.

² See <https://english.ccmo.nl/investigators/during-and-after-the-research/saes-susars-and-sades>

1. Introduction

This guideline was drafted to safeguard the quality of research subject to the WMO in the Dutch UMCs. The background and importance of quality assurance are further explained in the sections below.

1.1 QUALITY ASSURANCE OF RESEARCH INVOLVING HUMAN SUBJECTS

Within the Dutch UMCs, in addition to providing highly specialised patient care, great importance is attached to developing new medical insights, products and applications by means of scientific research. The UMCs are pre-eminently the centres of excellence where research involving human subjects can be conducted, because of 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 related to the safety of the research subject. The risks and burden for the research subject must be minimised and be in acceptable proportion to the expected outcome and benefits of the research (to be assessed by the Medical Research Ethics Committee, MREC). Secondly, the scientific quality is important, which is the result of the study design, method of implementation, documentation of data, analysis of results and reporting. Both aspects are primarily the responsibility of the sponsor. 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 *Quality assurance of research involving human subjects*, a request by the *Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd, IGJ)*. In the summer of 2011, the NFU commissioned the same work group to carry out an evaluation and incorporate any changes in a new version of the advisory report, resulting in the *Guideline Quality assurance of research involving human subjects 2.0*. In 2018 O&O commissioned the *Quality assurance work group* to revise version 2.0 in line with the changed legislation (including the revised WMO, ICH-GCP Addendum R2, the *General Data Protection Regulation (GDPR/AVG)*). This current version December 2020 is an update of the guideline. Page 5 lists an overview of changes with respect to previous versions.

The guideline is written for investigators, coordinators and managers who are responsible for the quality assurance of human-related research and covers the minimal requirements that research involving human subjects in the Dutch UMCs must meet. The guideline is in line with recommendations made by the IGJ, *Central Committee on Research Involving Human Subjects (CCMO)* and the *Good Clinical Practice guideline of the International Council on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH-GCP)*.



1.1.2 SCOPE

In the Netherlands, medical scientific research involving human subjects is legally regulated in the WMO³. The *Guideline Quality assurance of research involving human subjects* has been specifically formulated for all **investigator-initiated** research subject to the **WMO** that is conducted in the UMCs, and for which the RvB of a UMC is the sponsor (commissioning party) or in which the UMC participates as a research site. If the RvB is formally the sponsor, it is ultimately responsible for the research. As the sponsor, the RvB can delegate 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 subjected to procedures or are 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, diagnostic studies and studies involving nutritional supplements. Research in which 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 RvB can be a sponsor of research that is initiated by an investigator and of research that is financed by industry. The criteria specified in the chapters below apply to both monocentre and multicentre research. The sponsor's responsibility also includes the supervision of the conduct of research involving human subjects at the participating research sites.

1.1.3 QUALITY ASSURANCE WORK GROUP

The guideline is created as a result of a structural and substantive revision by the *NFU Quality assurance work group* (see Colophon). The NFU remains vigilant of relevant changes in legislation and updates this guideline on a regular basis.

³ See <https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/wmo-protection-human-subjects-central>

1.2 RESEARCH CODE

When conducting research involving human subjects in the UMCs, various parties are involved, such as healthy research subjects, patients, scientific institutions, companies and governments. An investigator who wants to carry out research that complies with the law and guidelines can face important choices when interests of the stakeholders conflict, for example, when an investigator combines his/her role of scientist with that of practitioner. In that situation, s/he is not only responsible for the quality of the research, but also has a treatment relationship with the research subjects. Therefore, the research subject's rights, safety and welfare must prevail over the interests of science and society.

UMCs and investigators have a joint duty to protect the integrity of scientific research in such areas of tension. Acting with scientific integrity in research involving human subjects means complying with the principles and guidelines of ethical and socially responsible research. The *Dutch code of conduct for scientific integrity 2018* is endorsed by the *Association of Universities in the Netherlands* (VSNU) and the NFU. This code specifies that an institution must ensure a work environment in which good research practices are promoted and safeguarded⁴. The UMCs have also formulated specific principles of integrity and good conduct in their *Research Codes*. The *Research Code* aims to make it transparent for both investigators and internal and external parties which starting points are considered fundamental. Each UMC has its own *Research Code* in which these starting points are documented.

1.3 QUALITY ASSURANCE IN THE RESEARCH PROCESS

The RvB of each UMC is responsible for implementing and maintaining systems and procedures for quality assurance, which allow quality to be controlled at all stages of the research process. This is meant to ensure that the research is prepared, conducted and concluded in compliance with the protocol, WMO/GCP/ISO14155, and other relevant national and international legal requirements. The focus lies on the research subject's safety and quality of the data.

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

⁴ See https://vsnu.nl/en_GB/research-integrity

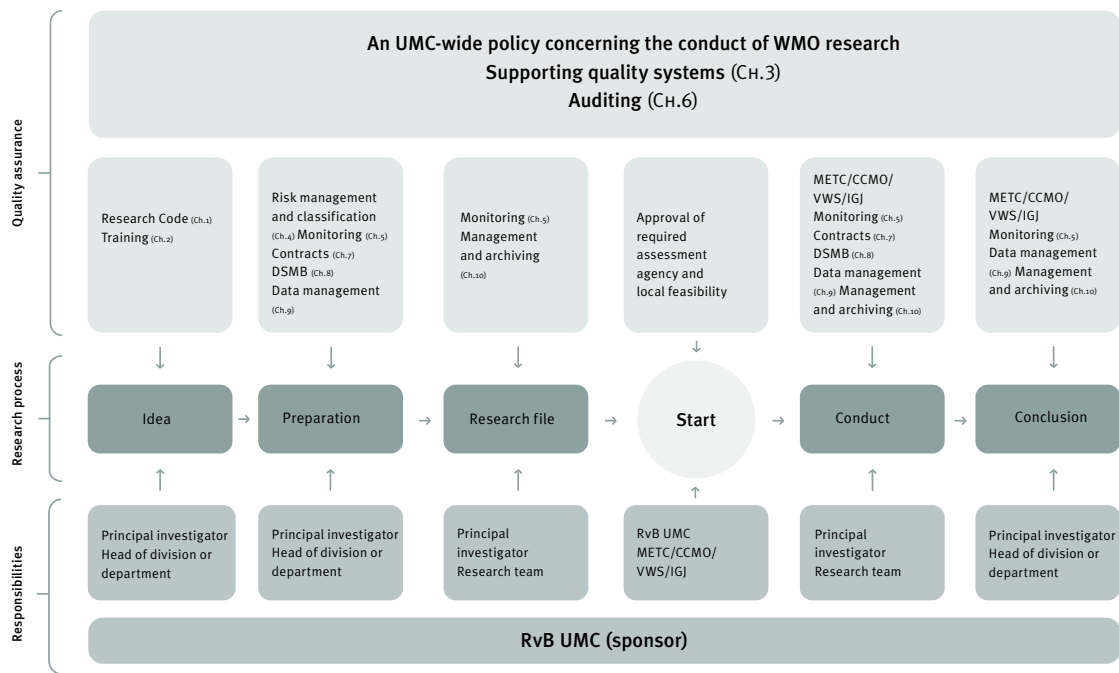


Figure 1: Schematic presentation of Quality assurance of research involving human subjects.

Training

The quality of research depends to a great extent on the expertise of the investigators and other research team personnel and the available facilities. Training greatly benefits the former. The necessary level of training depends on the role of the research team members and the tasks carried out. Every team member must be qualified through education, research-specific training, and experience to be able to carry out his or her respective task(s) in line with legislation and the protocol.

2.1 TRAINING FOR RESEARCH PERSONNEL

The RvB's have made it mandatory for **all** clinical investigators setting up and/or conducting and/or concluding research subject to WMO to be BROK®-certified, or become certified within 6 months after the start of the clinical study.

With regard to this obligation the following applies⁵:

- The obligation applies to all clinical investigators executing research procedures involving research subjects.
- The obligation applies not only to the *Principal Investigator* (PI) or the investigator submitting the MREC application, but to all researchers involved, including department heads.
- The obligation also applies to investigators who are not in direct contact with research subjects, e.g. a research team member writing the protocol or submitting the MREC application.
- The obligation applies both to medical doctors and clinical investigators who do not have a medical degree (e.g. pharmacists, psychologists, movement researchers).

Staff members with a coordinating role in the conduct of a clinical study, e.g. research coordinators and research nurses, require a WMO/GCP training, preferably including the national GCP exam.

Research personnel with a restricted or single, specific task or procedure in a clinical study, like recruiting research subjects, conducting measurements, processing samples, and entering, processing or analysing data, require a suitable WMO/GCP training in the topics relevant to them.

Scientific interns and research personnel working in a clinical study for less than 6 months and working under supervision need to follow a suitable WMO/GCP training in the topics relevant to them.

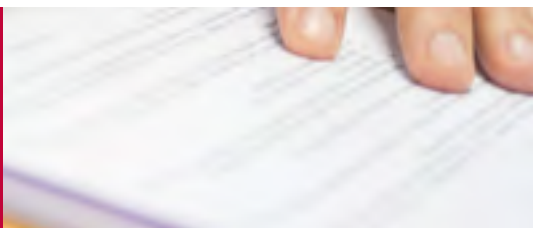
⁵ Training and Examination Regulations (OER) for the Basic course on Regulations and Organisation for clinical investigators (BROK®). Available in English at the NFU.
See <https://www.nfu.nl/themas/randvoorwaarden-wetenschappelijk-onderzoek/brokr>



2.2 TRAINING OF MONITORS AND AUDITORS

Along with a BROK[®] or WMO/GCP training course, appropriate and relevant training is required for monitors and auditors. When training monitors, the DCRF test matrix for basic monitoring can be used⁶. Required training for auditors should be determined by the UMCs themselves as it depends on the audit system employed by the UMC.

⁶ See https://dcrfonline.nl/wp-content/uploads/sites/12/2016/11/NVFG-Toetsmatrix-Competentiegebieden-basis-CRA-final_24Oct2016.pdf



3. Quality system

The RvB of each UMC is responsible for implementing and maintaining systems and procedures for quality assurance and quality control. An essential component of quality assurance is the availability of a UMC-wide quality system for research involving human subjects. This is meant to ensure that research is prepared, conducted and concluded in agreement with the protocol, WMO/GCP/ISO14155, and other relevant national and international legal requirements. The focus lies on the research subject's safety and the quality of the data.

A UMC-wide quality system offers advice and support to investigators and contains at a minimum: a quality management system, a registration system and centralised support, e.g. helpdesk with qualified personnel, monitoring and auditing (see also 3.3). A UMC-wide quality system should incorporate a PDCA cycle. The PDCA cycle is a management method to drive the continuous improvement and renewal of processes in an organisation.

3.1 QUALITY MANAGEMENT SYSTEM

The quality management system should be an electronic system describing the research process from design to reporting. Description and support of this research process takes place by means of SOPs. The SOPs are linked to instructions, forms, checklists and templates that can be used directly. Part of the quality management system involves recording the responsibilities and the roles of the various (internal and external) parties involved in research. In addition, UMC-specific policy is included in the quality management system.

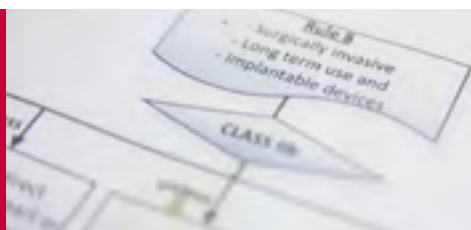
The electronic system should contain at least the following components:

- Version management
- Audit trail
- Document management/ownership
- Periodical review of the documents

3.2 REGISTRATION SYSTEM

To be able to take final responsibility with regard to research being conducted within its institution, the RvB requires access to management information. This information is collected in the registration component of the UMC quality system. This registration should preferably take place in a central system instead of in various decentralised systems.

UMCs compile the minimum data set required for the mandatory registration of research projects. This minimum data set should be documented in a SOP/procedure. Appendix 1 contains two tables with minimum data sets, which can be used as a guideline for preparing a UMC-specific data set.



3.3 CENTRALISED SUPPORT

Centralised support includes an audit programme, a central monitoring policy, vendor management, methodology, statistical support and data management support. Concrete implementation of this support is arranged by each UMC individually.

4. Risk and research

In the sections below, the areas of attention with regard to risks in research that is subject to WMO and therefore involves human subjects are described.

4.1 RISK MANAGEMENT

Risk management was added to chapter 5 of the ICH-GCP as the sponsor's responsibility and is part of the first article on quality management systems. How risk management and the implementation of ICH-GCP R2 are dealt with can differ between UMCs.

Clinical research has two areas of attention concerning risks and risk management:

- The ethical aspects referring to the rights, safety and welfare of research subjects. This includes safety aspects, the right to decide for yourself and privacy rights.
- The quality and integrity of the research data. This includes data collection and processing.

Risk identification in the context of risk management should take place during the process of protocol writing, by a multidisciplinary team consisting of a treating physician, investigator, methodologist/statistician, monitor, etc. Preferably in a meeting, this multidisciplinary team should identify the processes and required data that are essential to ensure the protection of the research subjects and the reliability of the research results. Risks should be considered at the system level (e.g. SOPs, automated systems, personnel, logistics, privacy) and at the clinical study level (e.g. protocol design, study population, data collection, informed consent procedure, adverse effects). Finally, risks at site level should also be considered (e.g. experience, size and composition of the research team).

The conclusion of risk identification should be recorded in writing and periodically evaluated to ascertain whether any changes in the risks (real or potential) have occurred. This periodic review should be documented.

4.2 RISK CLASSIFICATION

Risks regarding the safety of research subjects in research subject to WMO cannot always be avoided, but must be justified by the added value of the knowledge generated by the clinical study. The extent of the risk is independent of the justification for conducting the clinical study itself. The investigator must take both aspects into consideration. The MREC/competent authority(ies) independently assess the justification for conducting the research, based in part on the investigator's assessment.

When identifying risks, the focus needs to be on the **added risks** that research subjects are exposed to, in addition to the existing risks associated with undergoing standard treatment. A comparison with the standard treatment that the research subject would undergo outside the research context is therefore always important. For example: a physician determines that orthopaedic surgery is indicated for a patient. This patient is asked to participate in a clinical study which requires sampling a small amount of bone marrow during surgery. The risk of this study does not include the risks associated with the surgery, but the added risk of the bone marrow biopsy.

A number of aspects are important for estimating risks concerning research procedures. First, the nature of the risks must be considered broadly. To classify the added risks regarding the participant's safety within the study, the following aspects and characteristics must be taken into account:

- Physical (damage to the body)
- Psychological (e.g. anxiety or stress)
- Social (problems with participating in daily life)
- Societal (e.g. stigmatisation, societal support)
- Privacy (risk of GDPR violation)
- Financial (e.g. risk of loss of income due to participation in study)
- Publicity (e.g. negative publicity)
- Characteristics of the study design
- Characteristics of the investigational product/intervention
- Characteristics of the study population

Second, there can be large differences in the available knowledge about the risks of a procedure, intervention or medicinal product. Some medicinal products have already been on the market for a while and are prescribed for large groups of people. In these cases, knowledge about the risks of these products is considerable. Other substances are at the start of the development process towards becoming a product with marketing authorisation. Knowledge about the reactions of the human body to these substances is still limited. The same applies to the quality of an investigational product, for example in research involving nutritional supplements or medical devices. When classifying risks, it is important to pay attention to these aspects.

To support the determination of a risk classification, the *Risk classification Checklist* (Appendix 2) has been compiled, which lists the relevant characteristics, aspects and factors for classifying research into risk categories. The *Risk classification Checklist* can be made UMC-specific. It is referred to a checklist as it aims to help researchers substantiate the risk estimate. In some cases, certain aspects can be omitted or can be weighed more heavily than others. One example is the vulnerability of the study population. For each identified added risk, consult Table 1. The extent to which a research subject is exposed to an added risk depends on the possibility that damage occurs set against the severity of the damage.

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

Based on Table 1 and the *Risk classification Checklist* the investigator should make a broad inventory the added risks and ultimately arrive at an estimate in one overall risk classification in one of the following categories:

- Negligible risk
- Moderate risk
- High risk

The most important and first factor in risk classification is the added risk of research procedures for the participant's safety. It must then be examined whether there are other risks that result in the study being classified in a higher risk class. An investigator, MREC or RvB can decide to place a (certain type of) research in a higher risk class based on societal grounds.

5. Monitoring

Monitoring is part of a broader quality control system and an essential instrument for the quality assurance of research that is subject to WMO. It serves to verify that the rights and wellbeing of the research subjects are protected, that the study data are reported accurately and are fully verifiable in source documents, and that the conduct of the study is in accordance with the approved protocol/amendment(s), with ICH-GCP and with the relevant legal requirements.

For all research subject to WMO, the intensity of monitoring should be aligned with the degree of risk (see Appendix 3). Regardless of the study's risk classification, monitoring activities should be carried out by qualified monitors (see Ch.2 Training), who have an independent role in relation to the study.

The monitor's independence is important because s/he must be able to objectively verify the correct conduct and associated documentation of the study.

5.1 MONITORING WITHIN UMCS

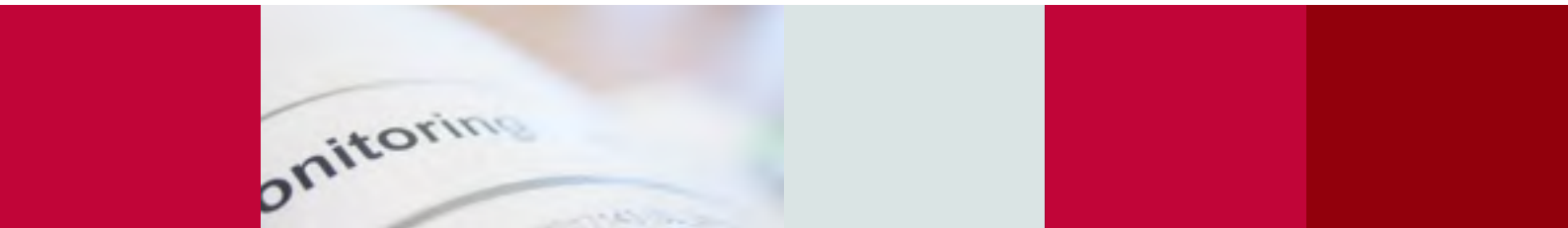
The NFU makes monitoring mandatory for all research that falls under the scope of the WMO. Monitoring is the responsibility of the sponsor. The sponsor is therefore responsible for setting up a study-specific *Monitoring Plan*, possibly together with the monitor, and contracting a qualified monitor or monitoring organisation. Monitoring and reporting should be carried out on the basis of a *Monitoring SOP* and the study-specific *Monitoring Plan*. The frequency and intensity of monitoring depend on the study's risk assessment (see Ch.4 Risk and research). Appendix 3 contains guidelines outlining what must be checked during monitoring visits specified for each risk class.

5.2 FORMS OF MONITORING

The term monitoring is usually taken to mean the classic form of on-site monitoring. In recent years, however, it has become clear that monitoring can be made more efficient by employing other forms of monitoring. Centralised monitoring, including remote monitoring and statistical monitoring, can be a sound choice. In the study-specific *Monitoring Plan*, a form of monitoring is chosen and justified on the basis of risk classification, risk management plan, study design, experience of the research team, logistics and research resources.

5.2.1 ON-SITE MONITORING

With 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.



onitoring

There are different types of on-site visits:

- **Initiation visit:** Before a research site may start including subjects, an initiation visit explaining the protocol and research procedures must take place. It is checked that all essential documentation required before a study may be initiated is available. In addition, the logistics of the study are checked, tasks and authorisations discussed and associated qualifications verified. This is documented in a monitoring initiation report. The visit can be replaced by a (central) kick-off meeting before the start of the study. This must also be documented in minutes or a report.
- **Monitoring visit:** The monitoring visits are regularly scheduled on-site monitoring visits, during which procedures and activities are carried out to check quality and safety. See Appendix 3 for frequency and content of the 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 on-site monitoring visit. During the close out visit, it is checked whether data collection is complete, all applicable essential documents are present and/or all action points/findings have been resolved. In addition, the research site is informed about long-term archiving, possible inspections and other expectations. It is also possible to carry out a remote close out visit. This can involve a checklist that is sent to the research site, which refers to the matters listed above and must be signed by the investigator of the research site for confirmation.

5.2.2 CENTRALISED MONITORING

Centralised monitoring cannot entirely replace the on-site monitoring due to verification that informed consent forms are signed, verification of existing research subjects, verification of source documentation, etc.

There are different types of centralised monitoring:

- **Remote monitoring:** the monitor approaches the research team of a study site by telephone or email to check remotely/from their own workplace how the study is progressing. This could involve, for example, asking questions about the inclusion, about SAEs that have occurred, protocol deviations, changes in the personnel involved, etc. Documentation can also be requested to check certain processes, but in no case documents containing personal details.
- **Statistical monitoring:** collected data from all participating research sites as specified in advance in the study-specific Monitoring Plan are examined by the monitor in collaboration with the statistician/methodologist involved. The analysis can focus on trends, missing data, outliers and/or inliers. Based on this analysis, the monitoring can be targeted better, for example, when choosing the research site to be monitored and/or which source documentation requires verification. For statistical monitoring, promptly entering data in an eCRF is a precondition.

5.3 FOLLOW-UP OF MONITORING FINDINGS

For all of the forms of monitoring described above, it is necessary to document in a report which matters have been checked. Findings including points for improvement and action points are also summarised in it. This report is sent to the sponsor. The principal investigator of the centre where the monitoring was carried out also receives a summary of the findings, including points for improvement and action points. In the findings a distinction can be made between mild/moderate/critical findings. Depending on the nature and severity of the findings, corrective actions or improvement measures may be required. If the reported action points/findings are not or not completely dealt with by the set deadlines, the monitor contacts the principal investigator involved. If this does not lead to the desired result, then an escalation procedure is followed according to a set plan, which forms part of the study-specific *Monitoring Plan* and/or the UMC-wide policy.

6. Auditing

To safeguard the quality of research that is subject to WMO, every UMC should have an internal audit programme. The sponsor is responsible for setting up an adequate audit programme, in which all research groups in the UMC are randomly audited.

6.1 PROCESS

Auditing involves checking the quality assurance process and assessing whether the different parties have properly fulfilled their tasks and responsibilities. An audit is a systematic and independent verification of activities and documents concerning a study subject to WMO and is independent and distinct from routine monitoring. Auditing covers verifying whether activities are conducted and data recorded, analysed, reported and archived in agreement with the protocol, SOPs and relevant legal requirements.

An audit should be conducted by a trained, independent auditor (see Ch.2 Training). Independent means that the auditor is not involved in the study in any way. Audits should be conducted frequently to adequately reflect compliance with research policy. Each UMC will determine the manner in which audits and the audit programme are organized.

6.2 TYPES OF AUDIT

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

6.3 FOLLOW-UP OF AUDIT FINDINGS

The outcomes of an audit are communicated to those involved and the sponsor. This can take the form of an audit report or a checklist with findings. The sponsor is responsible for an adequate and prompt follow-up of the findings. If applicable, a Root Cause Analysis should be conducted and an improvement plan, such as a *Corrective and Preventive Action* (CAPA) plan be drawn up⁷ (see Abbreviations and Terms). If this does not lead to the desired result, escalation will take place according to an UMC-specific escalation plan that is part of the UMC-wide policy.

The RvB is informed annually about the audit programme's progress. If necessary, the RvB can be informed promptly. It is determined whether there are audit findings that could lead to UMC-wide improvements or revision of the current policy.

⁷ See ICH-GCP 5.20.1: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf



7. Contracts, agreements and liability

When conducting research subject to WMO, contracts and agreements must be drawn up to cover any possible financial and legal risks and to record agreements with third parties. The researcher can contact the relevant (legal) department of the UMC for assistance.

7.1 CONTRACTS AND AGREEMENTS

When the sponsor needs to engage external parties to conduct the research, contracts and/or agreements must be drawn up. A contract is defined as a written agreement. An agreement is an arrangement in which parties bind themselves to something.

External parties, also referred to as ‘third parties’, are parties that do not form part of the sponsor’s legal entity. For example, external companies or organisations that are hired to perform research activities or otherwise do work for the study, such as a participating hospital/UMC (in the case of a multicentre study), central laboratory, MRI centre, data management service, DSMB members. These third parties must receive a clear commission-agreement.

When a third party has access to study data, whether to analyse or store them or combine them with their own data, this often requires separate agreements, e.g. in connection with protecting the privacy of the research subject. This can take the form of a separate agreement, such as a *Data Processing Agreement*, *Data Transfer Agreement* or *Data Sharing Agreement*, but can also be incorporated in a *Clinical Trial Agreement*, consortium agreement or blanket agreement arranged as a standard appendix.

It is extremely important to make sound, written agreements with supporting departments/divisions in the UMC about the work and/or services to be provided and the conditions under which they are to be provided. Both the supporting department and the applicant/investigator must agree with these conditions. These written agreements are informal contracts; in legal terms even an email specifying agreements which the recipient agrees to in writing is sufficient.

Contracts must at least cover the tasks, any financial compensation, contract duration, liability, ownership of any results and risks. The contract is not concluded by an individual employee for/on behalf of the UMC, but by the UMC as an organisation. Contracts can have different formats, depending on the work that the contractual parties agree upon. Sometimes a *Clinical Trial Agreement*, inter-UMC contract, consortium agreement or umbrella contract (*Master Service Agreements* with work orders) is a suitable solution, for example in a collaboration with hospitals/UMCs/industry partners. Other forms of contracts include consultancy contracts, DSMB contracts, vendor contracts. The contractual parties discuss what type of contract to use. Often there are national templates available, for example for site contracts and vendor contracts⁸.

⁸ See <https://dcrfonline.nl/werkgroepen/clinical-trial-agreement/>



Specialised lawyers in the UMC are involved in preparing and reviewing contracts, partly because there are many pitfalls and risks in the field of privacy legislation and liability. Contracts must be signed by someone who is officially authorised to do so on behalf of the UMC. Be aware that verbal and/or written commitments are legally valid.

7.2 LIABILITY

As described above, liability must be contractually documented. In addition, each UMC has taken out a liability insurance policy for its employees. A claim can be made on this policy if the agreements were made in the name of the UMC.

8. Data and Safety Monitoring Board

For a clinical study, a *Data and Safety Monitoring Board* (DSMB; or independent *Data Monitoring Committee*) can be installed. 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 interest regarding the research.

Clinical research often takes years, during which a growing amount of study data becomes available. It can be very important to evaluate interim results with regard to safety and effectiveness. For example, safety problems could arise that render continuation of the trial unethical. In case of convincing evidence that the treatment is effective before the end of the study, it is justified to terminate the research and make the treatment available. It is important that such an interim analysis is performed independently under the supervision of a DSMB. This ensures that the course of the clinical study remains unaffected once it is recommended that the study should continue according to the protocol.

8.1 COMPOSITION

The 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. The DSMB is preferably supported by a second independent statistician. This enables for example those directly involved in the study to remain completely blinded regarding the interim analyses in a (double)blind study. This second statistician is neither a member of the DSMB nor a member of the research team, but performs the data analyses for the DSMB. The DSMB chooses a suitable chair from among its members or approaches a candidate chair who will recruit the remaining members of DSMB. The chair must have previous DSMB experience (preferably extensive) and proven capability to transform discussions impartially into a consensus.

8.2 CHARTER

Before the start of the study, the sponsor must describe in detail the composition, procedures and working method of the DSMB in a separate document, referred to as the charter. The charter must be submitted to the MREC for assessment as part of the research file. A DSMB charter should at a minimum contain the following: title and sponsor of the clinical study, including NL-number; risk estimation for the study; objectives of the study and the scope of the charter; DSMB composition (including names and signatures); role and responsibility of the DSMB; and the dates/frequency and organization of the DSMB meetings, including the method of preparation, progress, decision-making and reporting⁹. The principles on which the DSMB decision-making is based must also be documented, including any statistical termination rules.

⁹ See <https://www.ccmo.nl/onderzoekers/publicaties/formulieren/2005/01/01/standaardonderzoeksdoossier-k5-model-dsmb-charter>



8.3 RECOMMENDATION

The DSMB makes recommendations to the sponsor, without disclosing the interim results. This recommendation concerns the safety of the research subjects, of subjects yet to be recruited, and the scientific added value of continuing with the clinical study. In case of investigator-initiated research, the recommendation is often communicated to the principal investigator. However, if the recommendation has far-reaching consequences, it will also be communicated to the department head, and the responsible RvB. Examples of consequential recommendations are: terminating the study prematurely due to safety problems or for reasons relating to convincing effectiveness, or for safety reasons excluding a subgroup or terminating one arm of a multi-arm study. In such cases, the sponsor is responsible for notifying the evaluating MREC and the competent authority.

The DSMB issues a recommendation; it is up to the sponsor to decide whether or not to act on it. It should be clear that a decision to deviate (entirely or partly) 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. If the sponsor has delegated its duties, the RvB should weigh in on the decision or at least be informed. The decision must be communicated to the evaluating MREC and, depending on the type of research, to the competent authority, which can take a dissenting decision independently.

The DSMB also pays attention to the conduct of the clinical study, in particular those aspects that could have an impact on the quality and integrity of the collected data. Along with adequate recruitment (speed and nature), this generally involves: being up-to-date with data collection and data entry, ensuring that no (serious) 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 also expects to be kept informed by the research team of any relevant external developments (from another study or clinical practice).

A DSMB can make various recommendations during the conduct of a 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 of evident damage.
- Discontinue the study due to evident effectiveness.
- Discontinue the study due to prove futility.
- Discontinue the study due to impracticality issues.

8.4 REPORTING

It is the sponsor's responsibility to ensure that the DSMB receives an interim summary research report, containing an overview of recruitment and tables and analyses that (in case of randomised research) compare the subject 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. That is why it is preferable to have these interim reports prepared by a second statistician, who is not a member of the research team or the DSMB. The independence of this second statistician is especially important in (double)blind studies, as the blinding of all directly involved investigators must be maintained.

8.5 TYPES OF STUDY

For high-risk studies, a DSMB is almost always installed. If the additional risks are moderate, the decision whether to establish a DSMB will be made for each study individually. The MREC assesses the composition, setting up and procedures followed for a proposed DSMB. It can also determine that a DSMB must be installed. A DSMB is normally not required or sensible for phase I studies involving medicinal products (as a result of the presence of extra supervision or an internal safety committee) or for a study with negligible additional risks (or minimal exceedances of them). See Appendix 4 for an overview of the responsibilities concerning the DSMB in the case of investigator-initiated research.

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 manner. This applies to 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 it with other researchers. The NFU subscribes to the broadly applied principles of FAIR data management: the data must be *Findable, Accessible, Interoperable* and *Reusable*. These principles are elaborated in this chapter and are in line with the requirements from legislation, the ICH-GCP guideline, 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 *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. A DMP must describe which data are 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, a DMP must describe how the research subjects' privacy will be protected. Most UMCs have their own DMP template, but grant providers can also require the use of specific 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 describes the quality requirements the collection must meet. Most UMCs have drafted SOPs for this purpose. Good quality of data is also achieved by data validation, with which the data are checked 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.

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 (HANDS, Data reuse) or in patient records obtained in the context of healthcare. When reusing data, the purpose of the reuse must correspond to the purpose to which the research subject has consented. If the data are to be used for other purposes, then the research subject must consent to this separately, except in a few exceptional situations. Exceptions must be approved by the MREC. When the data is anonymised, permission is no

¹⁰ See <https://www.health-ri.nl/data-stewardship-handbook-hands>



longer required, but linking with other data sets at the individual level will not be possible.

9.2.2 COLLECTION OF NEW DATA

The data collection may only contain the research data specified in the study protocol (data minimisation). Traditionally, data was collected by the investigators in the paper CRF. Nowadays, it is more common to record data in an *Electronic Data Capture* (EDC) system, and this is recommended in this guideline. In an EDC system, data are entered by investigators via the eCRF or directly by research subjects via electronically sent questionnaires.

Research data that fall under the scope of the WMO should be recorded in an EDC system with:

- An audit trail that automatically records changes to the data (who, what, when), without deleting originally entered data.
- An audit trail that documents the reason for a change when data are revised (mandatory according to ICH-GCP guidelines).
- Possibilities to apply access minimisation: by means of secured access, preventing unauthorised access to the data, 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 along with instructions in its 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 are 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 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 that it is readily available for statistical analysis.

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

9.3 PRIVACY

Data from WMO research is almost never anonymous, it is rarely possible to say with certainty that no individual can be re-identified in a data set. To ensure the privacy of research subjects, each UMC has an information security policy that must be met with facilities to implement the policy. The UMC's Data Protection Officer can advise on this topic. In the context of accountability, all research subject to WMO must be registered in the processing register of the respective UMC. In addition, at an early stage of each project, the sponsor determines which technical and

organizational 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 surrounding the privacy of the research subjects are analysed and measures to reduce those risks are described. For example, by encrypting data on mobile devices or when exchanging with third parties (e.g. via *SURF filesender*). Pseudonymisation is another measure that can be taken to protect personal data. This involves the use of entering a code as an identifier, instead of entering directly identifiable data (name, address, patient number, date of birth) in the (e)CRF. The pseudonym and the identifiable data are recorded in the identification list (key file). Pseudonymisation 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 only, with the associated identification list being kept at the research site, and kept separate from the pseudonymised data. Pseudonymisation can also be done by an independent third party.

9.4 DOCUMENTATION CONCERNING DATA

All research steps and procedures used to arrive from the raw data to the analysis data and results must be documented. The procedures in the laboratory 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 the software used with version number. The data collection and the data set must be accompanied by metadata, for example, a good description of how the data collection was set up, a codebook for the data set (*data dictionary*) and contact details. More information about data documentation and standardisation can be found in [HANDS, Documentation and standardisation](#).

9.5 DATA STORAGE DURING THE STUDY

The data must be stored securely during all phases of the study. Each institute has its own procedures and facilities to realise this.

9.6 CLOSING DATA COLLECTION

After the collected eCRF data have been declared complete and clean, the data can be locked in the EDC system. Data outside the eCRF can be locked by revoking write permissions from anyone with 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 data in the eCRF.

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. The data must thus be deposited in a sustainable data archive or repository in which the data set can be cited and found. Data should preferably be made available before publication of the scientific article, so reference to the data set can be made in the article. For archiving of research data and research documents, see Ch.10 Management and archiving.

It is the sponsor's responsibility to document the procedures and agreements for making data accessible in the DMP at an early stage. These may include control of the data, choosing a licence, drafting terms of use, ensuring privacy, the role of any *Data Access Committee*, and ensuring that research subjects give informed consent for sharing the collected data. Long-term management of the data should be entrusted to a department head or data steward. More information about archiving and sharing data can be found in [HANDS, Archiving data](#) and [HANDS, Sharing data](#).

10. Management and archiving

This chapter describes the management and archiving of essential documents and data in the context of research subject to WMO, known as 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. SOPs for the proper and uniform implementation of management and archiving must be available at all UMCs.

10.1 TERMS

10.1.1 MANAGEMENT

During the preparation and conduct of research subject to WMO, the research file must be findable and accessible for 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. Directly traceable data (e.g. the identification list / key file and the informed consent forms signed by the research subjects) are stored separately from the pseudonymised data.

10.1.2 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 a predetermined storage period. Directly traceable data must be stored separately from the encrypted data.

10.2 RESEARCH FILE

ICH-GCP E6 R2 chapter 8 and ISO14155 annex E for research with 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)/ Sponsor File* 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 the participating centres. For other types of research subject to WMO, these overviews should be used as a guideline (ICH-GCP E6 R2 chapter 8 and ISO14155 annex E)⁷. 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 the 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. The file should comply with the following criteria (in conformance with the ALCOA principle for proof of data quality and integrity):

- **Accurate and complete:** The file presents the complete, observed reality, and the content is not manipulated. Changes in the file's content are traceable through e.g. 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 storage period.
- **Original:** The file contains original documents. According to ICH-GCP E6 R2, it is permitted to replace an original document with a copy if the requirements for certified copies are met (see also heading Digitalisation).
- **Available on demand:** The research file is accessible and readily available to authorised persons (e.g. auditors, inspectors) after their authorisation has been verified.

10.3 STORAGE PERIODS

The sponsor makes written agreements with the local investigator about the storage period of the research file. The legislation applicable to medical scientific research does not provide an unambiguous answer to the question of how long research data must be stored. The NFU recommends that UMCs adhere to the minimum storage periods recommended by the CCMO: 30 years for advanced therapeutic medicinal products (medicinal products used for gene therapy, cell therapy and tissue manipulation products), 25 years for research involving medicinal products and 15 years for other types of research subject to WMO¹¹. This storage period starts after the last visit of the last research subject.

The GDPR is taken into account when managing and archiving a research file. In the research information letter, participants are informed about the use of their data (including personal data), the storage period and which persons have access. They give written consent to this by signing the accompanying informed consent form.

When research data are stored for longer than the recommended storage period for that type of research, the sponsor must have linked to it in advance by means of a sufficiently specific purpose description. Unless the research data are stored in a fully anonymous format, the research subject is informed in advance and needs to give written consent.

A research subject can withdraw the consent given for the use of his/her personal data during the study. This applies to the study and/or to the storage and use of study data for future research. The study data collected up until the moment of withdrawal of consent remain part of the data set to be analysed to prevent methodological bias and are therefore also stored in the context of quality assurance of the study.

¹¹ See https://www.ema.europa.eu/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

Once the predetermined storage period has expired, the sponsor commissions destruction of the data. Documents and study data that can be traced back to the research subject are deleted irretrievably, so they can no longer be accessed. For the purpose of sharing data, the sponsor may store the anonymised frozen data set (including descriptive documentation), collected in the context of the study for a longer period (see Ch.9 Data management for more information about sharing data).

10.4 DIGITISATION

A research file can consist of paper (source) documents, digital (source) documents, or a combination thereof. A digital file must meet the same requirements as a paper file during the entire storage period. Changes to the research file can only be made by authorised persons and are recorded with an audit trail.

10.4.1 REPLACING PAPER DOCUMENTS

The sponsor is responsible for managing the essential paper documents and cannot destroy them unless (during or after the study) certified copies are placed in an electronic research file (see Abbreviations and Terms). This depends on the legal obligations and the requirements of supervisory authorities, regarding the sponsor's electronic research file, so that inspectors do not have to request original paper documents¹². The sponsor will monitor the appropriate internal processes and quality controls.

10.4.2 STORAGE LOCATION

Storage locations of both physical and digital documents and data are protected. This means that the sponsor and local principal investigators ensure that only authorised people have access and all changes are recorded. The UMC must ensure compliance with the archiving obligation and provide an adequate infrastructure for management and archiving. The sponsor and participating research institutions maintain a register of the location(s) where the research file is stored during and after the course of the study.

¹² See https://www.ema.europa.eu/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

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Appendices

APPENDIX 1

Minimum data sets

APPENDIX 2

Risk classification Checklist

APPENDIX 3

NFU Guideline for monitoring visits in relation to the estimated risk involved in research subject to WMO

APPENDIX 4

Responsibilities regarding the DSMB for investigator-initiated research

Appendix 1: Minimum data sets

These minimum data sets are a model for preparing the UMC-specific data set.

Category	Main information	Sub-information/details
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
		NL-number
		Principal investigator of UMC
		Email of principal investigator of UMC
	Status of research project	
Approvals	MREC number	
	Date of MREC approval	
Data management	eCRF/EDC system	
	Storage location of eCRF/EDC system	
Monitoring	Monitoring is/is not arranged	
		Who/which party is monitoring

Table 2: Required information in minimum data set

Category	Main information	Sub-information
General	Financing	
	Contract is/is not present	
	Type of research subjects	Patients
		Volunteers
		Minors/legally incompetent
GDPR	WMO research subject insurance	
	Processor of data	
	Project involves collection, processing or managing of data (files), medical information or bodily material	
	Anonymous or encrypted	
	Biobank is/is not involved	
	Informed consent is/is not present	If not, why not
Approvals	Date of approval competent authority	
	Date of approval RvB	
Data management	How are personal data and/or medical data (on paper) kept secure	Specify
	Validated eCRF/EDC system is/is not used	Specify
	Storage period of data	

Table 3: Additional optional information in minimum data set

Appendix 2: Risk classification Checklist

The extent to which a research subject is exposed to additional risks depends on the likelihood that damage will occur, on the severity of the damage occurring, on whether the damage is treatable and reversible, and on the uncertainty of these aspects. This is explicitly not limited to possible physical risks such as pain or discomfort. Research subjects can also be exposed to psychological risk (anxiety, stress) or social risk (privacy, stigmatisation, insurability). The likelihood of damage can be small, moderate or large. Occurring damage may turn out to be minor, moderate or severe. It is also possible that the risk of damage and its severity is different for research subjects and are higher for some groups (seriously ill, acutely ill, elderly, children, psychiatric patients, addicts) or in some situations (multicentre, multidisciplinary, polypharmacy, inexperienced research team) than others. Uncertainty is also a risk factor. If not much is known about a healthcare innovation and there may be unknown risks associated with it or the course of occurring damage cannot be accurately predicted, then the research subject's safety will decrease.

Inspect Table 1 for each identified **added risk** (compared to the standard treatment) regarding the safety of the research subject. The *Risk classification Checklist* is called a checklist as its aim is to help researchers substantiate the risk estimate. In some cases, certain aspects can be omitted or certain aspects can be weighed more heavily than others. One example is the vulnerability of the group of research subjects.

FREQUENCY AND DAMAGE

- What is the chance of damage?

RISK OF RESEARCH DESIGN AND IMPLEMENTATION

- How complex is the research protocol (feasibility of conducting the study, mono- or multicentre, number of research subjects to be included)?
- Was a methodologist/statistician involved in the development of the protocol (protocol design, endpoints properly defined, sample size calculation, etc.)?
- How complex is the therapeutic field?
- Chance of protocol deviations/violations occurring?
- How is the data collected and analysed ((e)CRF, design, privacy, validation, export, etc.)?
- How experienced and involved are the investigators, participating sites and other vendors?
- Facilities of the participating research sites, pharmacies and laboratories.
- The technical tools used in the research.

RISK OF INVESTIGATIONAL PRODUCT OR INTERVENTION / RESEARCH PROCEDURE

- Amount of knowledge and experience with the intervention, medicinal product, nutritional product or medical device in humans.
- Phase of clinical study involving medicinal product.
- Earlier application of the intervention (in humans).
- Class of the medical device.
- CE labelling and use, whether or not within intended use.
- Toxicity of intervention.
- Known risks.
- More or more serious side effects compared to standard care (or compared to no participation).
- Physical burden (pain, discomfort, adverse effects).
- Mental burden (anxiety, stress).

- Likelihood of unknown risks developing, e.g. in early phase of research involving medicinal products.
- Severity of potential adverse effects.
- Predictability of adverse effects.
- Possibilities to manage undesirable effects of the intervention.
- Reversibility of potential adverse effects.

RISKS FOR RESEARCH POPULATION

- Vulnerability (children, legally incompetent, acutely ill, addicts, comatose patients, etc.).
- Impact of the side effects and risks on the population to be investigated compared to healthy persons.

SOCIAL AND SOCIETAL RISKS

- For the research subject: privacy, stigmatisation, exclusion from insurance.
- For the study: public support, sensitivity of the research.

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 (see Ch.4 Risk and research)

Based on the above characteristics and aspects, the investigator must make a broad inventory of the added risks and ultimately arrive at an estimate in one overall risk classification in one of the following categories:

- Negligible risk
- Moderate risk
- High risk

Appendix 3: NFU Guideline for monitoring visits in relation to the estimated risk associated with research subject to WMO

Action	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 or nutritional products		
Monitoring frequency	<p>Monocentre study: Minimum of 1 on-site visit during the study¹³.</p> <p>Multicentre study: Minimum of 1 on-site visit in the coordinating centre during the study + 1 centralised¹⁴ monitoring per participating centre during the study¹³</p> <p>Depending on the findings, on-site visits can also be planned in the other centres.</p>	At least 1 on-site visit of each centre annually ¹³	At least 2 visits of each centre annually (with at least 1 on-site visit annually per centre) ¹³	At least 3 visits of each centre annually (with at least 2 on-site visits annually per centre) ¹³
Inclusion progress	Inclusion rate and percentage of withdrawal, regardless of the risk classification			
Trial Master File / Investigator Site File	Check the accuracy and completeness of essential documents (at centres monitored on-site)			
Informed consent form (ICF) present ¹⁵	Confirm presence of at least 10% of the total number of included* research subjects (per centre monitored on-site)	Confirm presence of at least 25% (preferably 100%) of the total number of included* research subjects per centre	Confirm presence of at least 50% (preferably 100%) of the total number of included* research subjects per centre	Confirm presence of at least 100% of the total number of included* research subjects per centre
Informed consent process and verification of implementation	<p>Enquire about informed consent process (can also be done via centralised¹⁴ monitoring)</p> <p>Verification of the entire IC process of at least 2 of the total number of included* research subjects (for each centre monitored on-site)</p>	<p>Enquire about informed consent process</p> <p>Verification of the entire IC process of at least 10% of the total number of included* research subjects per centre</p>	<p>Enquire about informed consent process</p> <p>Verification of the entire IC process of at least 25% of the total number of included* research subjects per centre</p>	<p>Enquire about informed consent process</p> <p>Verification of the entire IC process of at least 50% of the total number of included* research subjects per centre</p>
Inclusion/exclusion criteria ¹⁶	Verification of at least 2 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 centre	Verification of at least 25% of the total number of included* research subjects per centre	Verification of at least 50% of the total number of included* research subjects per centre

* included research subjects = Informed Consent signed.

¹³ Depending on the inclusion rate, duration of the study, number of research subjects and earlier observed deviations.

¹⁴ Monitoring of participating centres for other research subject to WMO with negligible risk can be done remotely or on-site. Choice for remote or on-site depends on several factors and may differ from one institute to another. The minimum criterion is that the coordinating centre is visited on-site at least once and participating centres remotely.

¹⁵ If informed consent forms are missing or if errors are identified in the IC process, the sampling is expanded as appropriate according to the intensity of monitoring. The monitor is expected to strive to achieve the described percentage, but it is possible that at the time of the visit, the percentage is not feasible because not enough subjects have been included yet. That is why the phrase “if possible” has been added to these percentages.

¹⁶ If incorrectly included research subjects are included in the study (violation of exclusion criteria regarding safety is especially important here) the sample is expanded as appropriate, regardless of the intensity of monitoring.

Action	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 or nutritional products		
Source Data Review and Source Data Verification ¹⁷	Verification of at least 2 included* research subjects (per centre monitored on-site). (Based on a defined list of variables, including the primary endpoint, which are clearly related to the safety and validity of the study).	Verification of at least 10% of the total number of included* research subjects per centre. (Based on a defined list of variables, including the primary endpoint, which are clearly related to the safety and validity of the study).	Verification of at least 25% of the total number of included* research subjects per centre. (Based on a defined list of variables, including the primary endpoint, which are clearly related to the safety and validity of the study).	Verification of at least 50% of the total number of included* research subjects per centre. (Based on a defined list of variables, including the primary endpoint, which are clearly related to the safety and validity of the study).
SAEs/SADEs/SUSARs/USADEs ¹⁸	The research subjects in the sample for the SDV/SDR are also checked for unreported SAEs (per centre monitored on-site). In addition, check of 5% of the reported SAEs (or request 5% of reported SAEs via centralised ¹⁴ monitoring).	The research subjects in the sample for the SDV/SDR are also checked for unreported SAEs. In addition, check of 10% of the reported SAEs/SADEs/SUSARs/USADEs.	The research subjects in the sample for the SDV/SDR are also checked for unreported SAEs. In addition, check of 25% of the reported SAEs/SADEs/SUSARs/USADEs.	The research subjects in the sample for the SDV/SDR are also checked for unreported SAEs. In addition, check of 50% of the reported SAEs/SADEs/SUSARs/USADEs.
Investigational product ¹⁹	Not applicable.	Check product accountability of research subjects selected for the SDV and which instructions research subjects receive.	Check product accountability of research subjects selected for the SDV and which instructions research subjects receive.	Check product accountability of research subjects selected for the SDV and which instructions research subjects receive.
Research procedures (e.g. randomisation, blinding, data management and privacy)	Check whether instructions for carrying out research procedures are present and whether the study personnel are trained in carrying out research procedures.			
Study data	Check whether study data are collected in a validated database.			
Equipment	Verify whether the equipment used (if involved in determining the primary endpoint) is included in the quality assurance system/programme.			
Laboratory & Pharmacy	Check whether the laboratory/pharmacy are certified for the tasks that they perform for the relevant study. For studies involving medicinal products, the pharmacy is visited one or more times during the study. If the laboratory is involved in measuring the primary endpoint, verification of the laboratory procedures is required (e.g. storage, temperature, etc.).			

* included research subjects = Informed Consent signed.

Table 4: Monitoring in relation to risk category

¹⁷ 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, confirm compliance with protocols and safeguard critical processes (source: TransCelerate) and whether there is a source present for collected data (medical status). The monitor is expected to strive to achieve the described percentage, but it is possible that at the time of the visit, the percentage is not feasible because not enough subjects have been included yet. That is why the phrase "if possible" has been added to these percentages.

¹⁸ If the reporting and/or appropriate notification of severe side effects or serious adverse events is incomplete or incorrect, the sample is expanded as appropriate, regardless of the intensity of monitoring. If these irregularities concern SUSARs or USADEs, the sample should be expanded to 100%.

¹⁹ Product accountability check at research subject, department, and/or pharmacy level (storage, expiry date, receipt, issuing to research subject, dosages, return and destruction).

Appendix 4: Responsibilities concerning the DSMB for investigator-initiated research

The table below presents the responsibilities of various parties if a DSMB is involved in investigator-initiated research (see Table 5).

Action	Medical Department head (delegated by RvB)*	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 sponsor via the principal investigator	I	I	A/R	I
Following up DSMB advice, or notification of not following up	A	R	I	I

Table 5: Responsibilities in case of investigator-initiated research

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

* Or another responsible supervisor, depending on the type of organization of an UMC.

Colophon

This guideline is issued by the Dutch Federation of Academic Medical Centres (NFU). For more information, please turn to the NFU at nfu@nfu.nl.

With contributions from:

NFU QUALITY ASSURANCE WORK GROUP:

- Denise Maily, MSc, Project Manager, Service Desk Clinical Research Office (UMCG)
- Dr. Jacqueline van Dalen, Sr. clinical research associate (clinical monitoring center, Amsterdam UMC, locatie AMC)
- Ir. Hanneke den Breeijen, Adviseur onderzoek (Erasmus MC)
- Marian Janson, Adviseur Good Research Practice (LUMC)
- Eugenie Ram, Kwaliteitsmanager onderzoek (UMC Utrecht)
- Dr. Dannie van den Brink, Sr. Consultant Research Policy, Quality & Support (Radboudumc)
- Drs. Marlie Leerssen-Nillesen, Manager Quality Control Unit (MUMC+/CTCM) /
- Engelen Septer-Bijleveld, BSc, Senior project manager (Julius Clinical)

(Co)AUTHORS (INCLUDING FORMER MEMBERS OF THE WORK GROUP):

- Valéry Hawinkels-Hellwig, MSc, Quality Assurance Manager (MUMC+/CTCM)
- Janine Stolwijk, MSc, Manager Clinical Research Bureau, locatie VUmc (Amsterdam UMC)
- Drs. Selma Camic, Manager Quality, Control & Support, Clinical Research Unit, locatie AMC (Amsterdam UMC)
- Drs. Fenna Mahler, Sr. Consultant Research Policy, Quality & Support (Radboudumc) /
- Dr. Liesbeth Knaepen, Chief Operational Officer (MUMC+/CTCM) /
- Ir. Olga Eriks, Consultant Data Management, Informatie Management Onderzoek (UMCG)
- Ir. Jan Lucas van der Ploeg, Consultant Data Management, Informatie Management Onderzoek (UMCG)
- Prof. dr. Rob de Haan, afdelingshoofd Clinical Research Unit, locatie AMC (Amsterdam UMC)
- Rudy Scholte, MSc, Hoofd Datamanagement Clinical Research Unit, locatie AMC (Amsterdam UMC)
- Dr. Ineke van der Veen, Coördinator researchdatamanagement, Sectie Advanced Data Management (LUMC)
- Prof. dr. Kit Roes, Hoogleraar Clinical Trial Methodologie (UMC Utrecht)
- Dr. Paula Jansen, Stafadviseur Onderzoek (UMC Utrecht)
- Irene Jonkers, MSc, Kwaliteitscoördinator onderzoek (UMC Utrecht)
- Drs. Marjan Draaijer, Kwaliteitscoördinator onderzoek (UMC Utrecht)
- Shanta Kalaykhan, Kwaliteitscoördinator onderzoek (UMC Utrecht)
- Dr. ir. Joanna in 't Hout, Universitair Docent Department for Health Evidence (Radboudumc)
- Dr. Marten Onnink, Sr. Consultant Research Policy, Quality & Support (Radboudumc)
- Dr. mr. Martijn Bakker, Teamleider juridische zaken (Radboudumc)
- Christel Jacquot, MSc, Risk Counselor / Clinical Research Monitor (MUMC+/CTCM)
- Dr. Arno Skrabanja, Quality Consultant (MUMC+/CTCM)
- Jeroen Sijstermans, BBA, Manager Contract and Budget Management Unit (MUMC+/CTCM)
- Dr. Martijn Bakker, LL.M., Team leader in legal matters (Radboudumc)
- Christel Jacquot, MSc, Risk Counselor / Clinical Research Monitor (MUMC+/CTCM)
- Dr. Arno Skrabanja, Quality Consultant (MUMC+/CTCM)
- Jeroen Sijstermans, BBA, Manager of Contract and Budget Management Unit (MUMC+/CTCM)

Editorial staff

Members of NFU Quality assurance work group

Images

CTCM B.V.
Erasmus MC
NFU

NFU Dutch Federation of Academic Medical Centres

Visitors' address

Oudlaan 4
NL-3515 GA Utrecht

Postadres

PO Box 9696
3506 GR Utrecht
The Netherlands

T +31 30 273 98 80

nfu@nfu.nl

www.nfu.nl

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