Notes Investigator Site File COLOR III

**Purpose Investigator Site File: one file for all essential documents as listed in the ICH-GCP directive.**

**Introduction**

For each study a Trial File is to be laid out at the beginning of the research, both at the location of the researcher/institution (Investigator Site File) as at the offices of the sponsor/initiator (Trial Master File). The final investigation can only take place if the monitor both the files of the investigator/institution and the sponsor has checked and confirmed that all the necessary documents in the correct files are present. All documents in the ICH-GCP guideline that are discussed, may be eligible for an audit or inspection by the competent authorities, and must be available.

In the offered Investigator Site File essential documents for clinical study are included. Keeping a complete investigator file contributes to quality management, is a check on completeness of the pieces and serves as a reference guide for interim reports to the METC, Visitations of official bodies or the simple delivery of production figures for internal use.

The local principal investigator is responsible for the Administration in order and track the trial through this Investigator Site File.

**Source**

WMO = Law medical-scientific research in humans. Anchored in it is the "guideline for Good Clinical Practice CPMP/ICH/135/95".

Link: http://www.ccmo.nl/attachments/files/ich-gcp-richtsnoer-gcp-vertaald-mrt-2003.pdf.

**Notes to the table of contents:**

(the paragraph numbering refers to the paragraphs from the ICH-GCP directive)

**1. Study personnel contact details**

List of names and contact details of the study team. This concerns both the study team in the Executive institution such as the contact details of the sponsor/provider.

**2. Subjects**

         **Subject screening log**: list of persons who are screened in the phase prior to the research (ICH-GCP § 8.3.20). This list also serves as a tool to document possible causes of a reactionary accrual.

         **Subject enrollment & identification log:** chronological list of included subjects to capture through a clinical research number(§ 8.3.22). On this list, the encryption of the research number to the individual patient is to be logged. This list may not leave the hospital due to privacy reasons.

This confidential list of names of all test subjects to whom a clinical research number is assigned upon admission to the research sets the researcher/institution able to identify each subject (§ 8.3.21).

**3. Protocol & amendments**

         **Signed protocol**: Signed protocol. To capture that the investigator and the sponsor have reached agreement on the protocol (section 8.2.2). This can take place by means of **protocol signature pages** (of all protocol/amendment versions) are logged.

         **Amendment (s):** signed amendments, if any. To capture that the investigator and the sponsor have reached agreement on the amendment (s) (section 8.2.2).

         **Checklist/flowchart**: specifically for this study made checklist, flowchart and/or information sheet for (research) nurses for information and improvement of logistics.

**4. Patient information**

         **Sample or patient information and Informed Consent form (PIF + IC):**

Add a hospital specific version of the ethical approved subjects information. To capture that the subjects will receive relevant written information (content and wording) in order to to enable them to give fully informed consent and to capture this permission in writing (§ 8.2.3). This patient information and the associated consent form 1 document the Ethics Committee approved.

Think of the version control:store the current version on top of it. Use outdated versions and keep that bottom up so they no longer will be used.

         **Original signed ICF's attached to Patient information.** These are the signed informed consent forms to record that each subject's consent is obtained in accordance with GCP and protocol and called on a date that precedes the participation in the research. Also to the permission for direct access. (section 8.3.12) This concerns access by persons who are described in the PIF/IC document. Save the entire document, so both patients information as-with-IC form.

Advice **:** make 2 copies of each signed Informed Consent form or leave the IC form 2 x signs. One copy for the patient and one for in the ISF. Additional one form can be filed in the medical record or 1 copy scanned. The original should be kept in the ISF. Due to advance in digitization of the medical record: Only a scanned copy of the IC in the electronic patient file is not (yet) legally valid. This is confirmed by the IGZ on 4-4-13.

         **Other written information**: for example, information leaflets, advertising texts.

**5. Safety information**

         **Sample SAE form:** SAE = Serious Adverse Event**.** Keep at the front of an original empty SAE form with accompanying instructions, if necessary. Add a method to a digital reporting procedure.

         **SAE/SUSAR reports:** Save here the notifications by the researcher to the sponsor of serious adverse events and related reports/correspondence in accordance with article 4.11 of the GCP directive (§ 8.3.16).

**Susars:** SUSAR = Suspected Unexpected Serious Adverse Reaction. These are reported by the sponsor reported to all local researchers. Save here this message and the associated correspondence.

         **Line Listings (Saes and Susars):** are periodic reviews of safety data provided by the sponsor are provided to the local researcher.

         **Safety reports:** eg. the annual report of the sponsor/provider about the safety data.

**6. Clinical trial site personnel**

         **Site signature and delegation log**: signature list to capture the involved staff and acts performed for the research. (§ 8.3.24). The local physician-investigator shall delegated tasks on this Log.

Delegation is allowed under 3 conditions:

·         That the person to whom the task transferred, is skilled and competent

·         Those competent to carry out the task itself

·         The physician is and remains responsible and serves to monitor and capture this.

         **Curriculum vitae (CV)**

Signed and dated recently Curriculum Vitae and/or other relevant documents to the qualifications of the investigator, sub-researchers, data manager and other staff involved in the study. To document the abilities of investigators to show the suitability to study and/or medical supervision and to exercise control over subjects (section 8.2.10).

         **Local principle investigator**: principal investigator of the local participating Center

         **Co-investigator (s)** : sub-researchers, fellow doctors.

         **Independent physician**: independent arts of the participating Center (or where applicable, for the entire study. See patient information: here is the doctor named.

         **Other trialpersonnel** : research nurses, data manager etc.

**7. Regulatory affairs**

         **Central METC** (medical ethical review Committee)**:**

**Central ETHICS BOARD approval letters** (initial review and amendments if applicable): dated, written approval of the Central ETHICS BOARD to capture that clinical research (and any amendments) is/are positively assessed and to the version number, and date of these documents. (section 8.2.7).

In the Central approval letter is specified on which participating centers the approval applies.

When a participating Center from multiple locations and the relevant clinical trial in multiple locations is running then the Board to specify these locations in the permission letter.

**METC composition:** composition of the METC to capture that the composition is in accordance with GCP (section 8.2.8): usually part of the written approval of the Central ETHICS BOARD.

         **Local approval:**

**Approval of the Executive Board:** written consent of the Board of Directors for the implementation of the research in the home institution. When a hospital from multiple locations and the clinical study also in multiple locations is running then the Board to specify these locations in the permission letter.

**Examination certificate:** here also the**"** archiving **"**examination certificate**.** Core of the CCMO directive External Review 2012 is the examination certificate of the participating Centre, which in the new procedure shall be issued by the head of the Department, division manager or by a person in an equivalent position.

         **Other correspondence:** other relevant information.

**8. Agreements**

         **Clinical Trial Agreements:** signed agreement between involved parties, e.g. researcher and sponsor, researcher and CRO (contract research organization), sponsor and CRO, researcher and authority. (section 8.2.6)

The CTA form needs to be kept here, this is the agreement between the research group (e.g. HOVON) and the lead investigator.

The EORTC study commitment statement/acknowledgement form can also be stored here.

         **Financial agreement:** to the financial agreement between the investigator and the sponsor of the research to capture (§ 8.2.4)

         **Other agreements:** here, for example, research agreements between researcher and support departments (lab, radiotherapy, pathology, etc.) are archived in which (financial) commitments are recorded specifically for the trial run.

Can also be stored here agreements with grant providers

(KWF, ZonMW, etc.).

         **Financial disclosure forms:** this specifies that there is no financial arrangements entered into with a researcher that affect the outcome of the investigation, that the researcher has no property right in respect of the product tested, that the researcher has no significant interest in the sponsor of the study and that the researcher has received no substantial payments of other species.
Disclosure of certain financial arrangements and any steps taken to minimize the risk of distortion.

**9. Insurance**

        **WMO insurance for research subjects:** WMO subjects insurance statement to capture that compensation is available for the test subject in case of injury resulting from participation in the research (§ 8.2.5) In practice a copy of a recent insurance certificate.

      **Liability insurance:** certificate of the liability insurance of the Center to cover the researcher/the study team capture where there is professional liability.

**10. Case Report Form (CRF):**

         **Sample CRF:** an example of the paper case report form or a print of the eCRF. Also a reference to CRF documents. Think of versioning, indicate what the old and current versions.

         **CRF completion guidelines**: instructions for a CRF and a schedule indicating at what point in the study, which specific CRF pages must be filled in.

**11. Quality of Life/Diaries**

         **Sample questionaires/diary:** an example of the questionnaire or daily diary etc.

         **QoL instruction**: fill in the instructions, when, how, where to send to etc.

         **QoL informed consent/addressform**: documented patient consent for the use of address/privacy data.

         **Completed QoL:** quality of life questionnaires completed by the patient that should be archived on the site.

         **Return address Stickers QoL:** address labels, self-addressed envelopes.

**12. Trial supplies**

         **Drug supplies**: the relevant information about the used medication such as instructions for the handling of the search product and research materials as far as not described in the protocol or IB (§ 8.2.14 t/m 17). Example is an information booklet for the patient of the study medication or surgery. Also known as: drug delivery/shipping records, drug dispensing records, instruction for investigational products and trial-related materials, drug storage and temperature guidance, temperature log.

         **Non-drug supplies**: relevant information about other study materials here archive. ' Laboratory supplies ' fall under 13 Laboratory.

**13. Laboratory**

         **Lab normal reference ranges:** to the normal values and reference intervals of the test provisions (section 8.2.11). This can be determined in the database which are abnormal lab results. Think of changes.

         **Lab certificate:** Certification or accreditation or established internal quality control, to the quality of the facilities for the implementation of the provisions and to support the reliability of the results (section 8.2.12).

         **Laboratory supplies:** other lab documents, manuals, sample labels, measuring lists etc.

**14. Side studies**

         **Instructions:** save here study specific practices, protocols etc. about side studies and translational research. These studies are usually extra quantities of body materials with which additional provisions are carried out.

         **Records, or retained body fluids and tissue samples:** documents on which all relevant details (date/time/quantity etc.) of the drop offs are documented.

**15. Product information**

         **Investigators Brochure (IB):** To capture that relevant and updated scientific information regarding the search product has been provided to the researcher (section 8.2.1).

         **Investigator Medicinal Product Dossier (IMPD):** For each Investigational Medicinal Product (IMP) that is used in pharmaceutical research must be an IMPD. An IMP is an active substance or placebo being examined or used as a reference to drug trials. Here are also registered drugs under that otherwise are used, be adjusted (e.g. composition and packaging) or used to get further information on the efficacy and or safety. That means also for placebos or reference drugs that are used within a pharmaceutical research, an IMPD has to be present.

         **Summary of Product Characteristics (SPC):** This summary of the product characteristics is a specific document that is necessary within the European Commission before a medicinal product is registered for marketing. It is a summary of the description of the product in terms of both properties as the clinical use.

         **Other pharmaceutical documents:** sample labels, pharmacy information, etc.

**16. Progress reports and research results**

         **Progress reports:** summary of the progress of the clinical research, is provided by sponsor/provider. Also newsletters that at certain intervals are sent by the Central PI fall below.

         **Summary of research results/scientific publications:** summary of the research results/scientific publications.

         **Clinical study reports:** report that the method, results and interpretation of the research.

**17. Monitoring**

         **Monitor plan:** Approved by the Central principal investigator plan in which is recorded what agreements there are to check whether and how:

         the rights and welfare of the subjects are protected.

         the data from the research that are reported correctly and fully verifiable in source documents.

         the implementation of the research is consistent with the at that time

approved protocol/amendment (s), GCP and relevant legal requirements. (§ 5.18).

         **Initiation visit log:** written record the date on which the initiation meeting for the study took place and who being present.

         **Monitoring visit log**: written record on what data the monitor visited the research location.

         **Monitoring reports:** A written report by the monitor after each visit to the research location, and/or some other form of communication in connection with the investigation in accordance with the sponsor's Sops.

**18. Decoding procedures for blinded trials**

         **Deblinderingsprocedure:** to record how, in emergency cases, the identity of a blinded product in research can be revealed without the facing Panel of the search for the remaining subjects to disconnect (section 8.2.17).

The researcher must adhere to the randomization procedures for research, if there are any, and should ensure that the code is broken only in accordance with the protocol. If it's a tainted research, then the researcher any premature breaking the code of the investigational product (s) direct recording and explain to the sponsor (for example, accidental breaking of the code, breaking the code associated with a serious adverse event).

**19. Relevant correspondence**

         **Trial initiation report**: report of the initiation meeting when you start the trial.

         **Investigator meeting minutes**: report of meetings of the researchers of the study during the term.

         **Source data location list**: overview of which source documents there are and where they are archived. For digital data should be indicated how the access is regulated.

         **Letter, emails, faxes and notes or telephone calls** : all relevant letters, mails etc.

         **Newsletters**: newsletters about the progress of the study.

         **Other relevant documents:** Notes to file, FAQs (frequently asked questions) etc.

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