Standard research file for submission of a research proposal to a WMO review committee and/or the competent authority

A. Letters
- A1: Cover letter to review committee and the competent authority
- A2: Authorisation letter from the sponsor, if the submitting party is not the sponsor
- A3: Confirmation EudraCT number

B. Forms
- B1: ABR form including a summary: online at https://toetsingsonline.ccmo.nl and on paper (signed and dated)
- B2: Local addendum to ABR form (if applicable)
- B3: EudraCT Application Form: on paper (signed and dated) and in XML format via https://toetsingsonline.ccmo.nl
- B4: Gene therapy/GGO form (if applicable)
- B5: EudraCT Notification of Amendment Form
- B6: CCMO-form end of trial
- B7: Eudra CT end of study form

C. Protocol and amendments
- C1: Research protocol
- C2: Protocol amendments in chronological order

D. Product information
- D1: Investigator's Brochure (publication date: < 1 year old) and overview of SUSARs not yet mentioned in IB (including summary and assessment)
- D2: IMPD (or SPC, if applicable), incl. list of relevant research with the medicinal product being researched
- D3: Examples of labels in Dutch
- D4: Applicable statements/licences
- D5: Hospital pharmacist product details (if applicable)
- D6: Additional product details, e.g. for gene therapy: nucleotide sequence of the vector, in ASCII format (if applicable)

E. Information for research subjects
- E1: Information letter(s) for research participants/representatives
- E2: Consent form(s)
- E3: Any advertising texts or other enrolment materials
- E4: Other informational materials

F. Questionnaires, patient diaries, patient cards, etc. (if applicable)
- F1: Questionnaires
- F2: Patient diary
- F3: Patient card
- F4: Other

G. Insurance information
- G1: Insurance certificate for WMO research with human subject insurance or written request for exemption from insurance obligation

G2: Proof of coverage of investigator or sponsor, for example liability insurance

H. Résumés

H1: Independent doctor(s) résumé(s)

H2: Coordinating investigator résumé for multicentre research (if applicable)

I. Information per participating centre in the Netherlands

I1: List of participating centres and principal investigators

I2: Local feasibility declaration from the Board of Directors/Management per centre (for external review/multicentre research)

I3: Résumé (including list of publications) for the principal investigator per centre

I4: Other information per participating centre

J. Additional information regarding financial compensation (if not mentioned on the general assessment and registration form (ABR form))

J1: For research subjects

J2: For investigators and centres

K: Other relevant documentation:

K1: Copy of reviews by other institutions, e.g. grant giving body or scientific committees or recommendations by regulatory authorities)

K2: Overview list of authorised foreign institutions that the protocol has been submitted to, along with a copy of reviews by foreign MRECs/ECs or competent authorities 

K3: Signed research contract between the party organising the research (sponsor) and the investigator and/or institution.

K4: Scientific publications (regarding previous/comparable research provided by the submitting party)

K5: Other documents (e.g. letters for general practitioners/treating medical consultants, recommendation of the radiation committee)

L: Safety information

L1: SUSARs 

L2: Periodic SUSAR line listings 

L3: Annual safety report 

L4: SAEs

L5: Other relevant safety information

M: Progress reports and research results

M1: Progress reports

M2: Summary of research results/scientific publications

M3: Clinical study reports 

Commentary on standard research file

Background

The standard research file provides an overview of all documents that must be submitted to a Medical Research Ethics Committee (MREC) or the Central Committee on Research Involving Human Subjects (CCMO) for review. If the research in question involves medicinal products, the research file must also be submitted to the competent authority (CCMO or Minister of Health, Welfare and Sport). This includes both those documents that must be submitted with a Clinical Trial Application as well as documents that must be submitted, following positive judgement and/or declaration of no objection, to the assessing committee and the competent authority (if applicable). From January 1 2008 onwards digital submission of the research file to the competent authority is compulsory. See the FAQ document '*Mandatory digital submissions of research files for clinical trials with medicinal products to the competent authority in the Netherlands form 1 January 2008 onwards*' for more information.
The principles of the standard research file are based on the *Medical Research Involving Human Subjects Act (WMO)* and the *Regulation on Scientific Research with Medicinal Products.*
Documents should be filed in the order listed above, so that the assessing committee can quickly and efficiently check whether the research file is complete. The review process begins once the submitted research file is complete. Documents that are frequently only required for research with medicinal products are marked with a  symbool.

The documents

A1: Offer letter to review committee and the competent authority

The cover letter must clearly state which MREC and/or competent authority the research file is being offered to and which documents, including version numbers and/or dates, are beingsubmitted. If the submitting party is not the project leader/head of department/coordinating investigator, it is recommended that the cover letter be co-signed by these persons.
A specimen copy of an cover letter to the review committee and/or the competent authority is available from the CCMO website (www.ccmo.nl).

A2: Authorisation from the sponsor, if the submitting party is not the sponsor

If the submitting party is not the sponsor, an authorisation letter stating that the submitting party is authorised to submit the research file on behalf of the sponsor must be submitted.
For research with medicinal products, Section 13d of the WMO also applies, which states that the party organising the research (the sponsor) or his legal representative must hold offices within the European Union. The tasks and responsibilities of the legal representative must be described in detail in a contract. More information on this subject may be found in chapter 1.10 of the Instruction Manual, which may be found on the CCMO website under Regulations and Legislation, EU Guideline Implementation.

A3: Confirmation EudraCT number

Only applicable to research with medicinal products. The EudraCT number is a unique number linked to a research file for registration in the European database for research with medicinal products (EudraCT database). A EudraCT number may be obtained from the EMEA http://eudract.emea.europa.eu portal and consists of two steps:

1. Requesting a security code
2. Applying for a EudraCT number

The security code is sent to the e-mail address entered during the application procedure and remains valid for 24 hours. The following information must be submitted to obtain a EudraCT number:

- Contact details for the submitting party and his organisation
- The research protocol number for the party organising the research/sponsor
- The security code
- The e-mail address the EudraCT number must be sent to
- The country the research is being performed in

The EudraCT number is sent to the e-mail address entered during the application procedure. The e-mail listing the assigned EudraCT number must be submitted to the assessing MREC and the competent authority.

B1: ABR form and summary: online at https://toetsingsonline.ccmo.nl and on paper (signed and dated)

The ABR form is the general assessment and registration form. The ABR form must be completed online at the following portal https://toetsingonline.ccmo.nl. Once the ABR form has been completed and finalised it must be printed. The signed hardcopy version must be filed with the assessing MREC. For the competent authority from 1 January 2008 the ABR form should be submitted digitally.

B2: Local addendum to ABR form (if applicable)

Some MRECs have an addendum to the ABR form in which additional questions are asked. Ask the MREC the research is being submitted to for review whether they require an addendum to be filled in.

B3: EudraCT Application Form: on paper (signed and dated) and in XML format via https://toetsingsonline.ccmo.nl

Only applicable to research with medicinal products. The EudraCT Application Form may be filled in via the portal http://eudract.emea.europa.eu . You will need the assigned EudraCT number for this. Once the EudraCT Application Form has been completed, the data must be saved as an xml file and as a PDF file to your own computer. A signed hardcopy version of the EudraCT Application Form must be filed with the assessing MREC form 1 January 2008 onwards the form should be submitted digitally to the competent authority. The xml file can automatically (question B1a of the ABR form) be forwarded to the Medicines Evaluation Board via the portal https://toetsingonline.ccmo.nl for registration in the EudraCT database and therefore does not need to be submitted with the research file.

B4: Gene therapy/GGO form (if applicable)

Only applicable for gene therapy/GGO research. The application form for review of clinical research with gene therapy is available from the gene therapy office and may be found on the following website: http://213.154.234.72/Paginas/loket.htm.

B5: EudraCT Notification of Amendment Form
Only applicable to research with medicinal products and for substantial amendments.
In the event of substantial amendments, a signed and dated EudraCT Notification of Amendment Form must be filed with the assessing review committee and from 1 January 2008 onwards digitally to the competent authority. The form is available for downloading from the EudraCT website (https://eudract.emea.europa.eu/eudract/index.do).
If the substantial amendment also involves a change to the EudraCT Application Form (B3) and the ABR form (B1), these must also be changed and submitted to the assessing review committee and the competent authority the same way as required for a the submission for the Clinical Trial Application.

B6: CCMO-form end of trial
All WMO research brings with it a number of obligations required by the positive judgement obtained. This includes reporting the end of the research to the assessing review committee. If the research is ended prematurely, a reason must be given. The CCMO-form end of trial may be used for this purpose and may be downloaded from the CCMO website under Forms (www.ccmo.nl).

B7: EudraCT End of trial form
Only applicable to research with medicinal products.
Following (premature) termination of a research trial, the EudraCT End of trial form must be completed and filed with the assessing review committee and from 1 January 2008 onwards digitally to the competent authority. The form is available for downloading from the Eudra CT website (https://eudract.emea.europa.eu/eudract/index.do).

C1: Research protocol
A research protocol template is available for downloading from the CCMO website, under Forms for investigators (www.ccmo.nl).

C2: Protocol amendments in chronological order
Protocol amendments must clearly outline the changes, the reasons for changes and which passages in the original research protocol have been changed.

D1 through D6 are generally only required for research with medicinal products. This does not rule out that product information will have to be submitted for medical aids or 'novel foods'.

D1: Investigator's Brochure

An Investigator's Brochure is a summary of clinical and preclinical data regarding a/the research product(s) relevant for the evaluation of the research product(s) in research subjects. Chapter 7 of the Good Clinical Practice guideline (CMPM/ICH135/95) describes the requirements an Investigator's Brochure must fulfil. See:
http://www.emea.eu.int/pdfs/human/ich/013595en.pdf
The IB must be evaluated at least annually and revised where needed. More frequent revision may be desirable depending on the developmental stage and availability of new information. Relevant new information may be of such importance, however, that it must be submitted to the assessing WMO review committee and the competent authority before it is integrated into a revised IB, as required by GCP rules. Therefore, the IB may not be older than 1 year, unless annual evaluation has shown revision was not required. It must also be clear that the IB was evaluated less than one year ago.
Additionally, all relevant information regarding the safety of the product that has not yet been included in the IB must be submitted. At this time, this information is limited to a line-listing of the SUSARs that have occurred. This line listing must be accompanied by an assessment by the sponsor which clearly indicates whether this information has any consequences for the safety of the research subjects. If each SUSAR has been evaluated individually by the sponsor, a declaration in the cover letter indicating whether these SUSARs have any consequences for the human subjects participating in the study in question will suffice in lieu of a summarising assessment.
An extensive Investigator's Brochure is not always required for licensed products for which the pharmacological aspects are known to the doctor/investigators. A product information brochure or package information leaflet text may suffice, as long as it contains all information relevant to the investigator. This exception does not apply to licensed products used in a research setting for uses other than the authorised use.
For more information, see chapter 2.2 of the Instruction Manual, which is available from the CCMO website under Legislation and Regulations, EU Guideline Implementation (www.ccmo.nl).

D2: IMPD (or SPC if applicable), incl. list of relevant research with the medicinal product being researched

An Investigational Medicinal Product Dossier (IMPD) contains data on the quality, production and control of the medicinal product being researched. This information concerns the active product, placebo and reference product (if applicable). It also contains a summary of data from all clinical and non-clinical research. The Investigator's Brochure may be referred to for the latter.
An example of an Investigational Medicinal Product Dossier is available on the CCMO website under Forms for Investigators (www.ccmo.nl)

If a product is licensed, an SPC (summary of product characteristics) will suffice, if it is available. SPC texts for many medicinal products may be found on the MEB website (http://www.cbg-meb.nl/nl/prodinfo/gibhumaan.htm). The website also has a link to a template for an SPC.

For more information, see chapter 2.2 of the Instruction Manual, which is available from the CCMO website under Legislation and Regulations, EU Guideline Implementation (www.ccmo.nl).

D3: Examples of labels in Dutch

An example of the label on the medicinal product being researched must be submitted for review. The label must meet the requirements set in annex 13 of the Good Manufacturing Practice Guideline (2003/94/EG), available for download from http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/an13final_24-02-05.pdf.

The following information (in Dutch) must be listed on the label, unless there are good reasons not to do so:

1. Name, address and telephone number of the sponsor, CRO or investigators (these are contact details which are important when information about the product, the research or deblinding is required in the event of an emergency)
2. Pharmaceutical formulation (tablets, capsules, etc.), the dosage form, the number of dosage units (in open label research: name and dosage of the product)
3. The batch and/or code number (for tracing contents and packaging activities)
4. A research reference code, allowing identification of research, centre, investigator and sponsor (unless listed elsewhere).
5. A research subject/treatment number and if required, a visit number
6. The investigator's name (if not listed under points 1 or 4)
7. Instructions regarding use (can be achieved via referral to included information or the instruction to use the research product as instructed by the doctor)
8. Solely destined for clinical research (or similar text)
9. Storing conditions
10. Storage life (use-by date, expiration date or re-test date); to be referred to as month/year with clear instructions
11. Keep out of reach of children (unless the research medication is not taken home)

Point 1: The address and telephone number may be omitted, if the research subject has been given a card or other document including this information and the research subject has been instructed to carry it with him/her at all times.

Exceptions:

a. Research medicinal products in an inner packaging together with an outer packaging, designed to stay together. The outer packaging then lists all the information (points 1-11), and the inner packaging only lists: 1 (only the name), 2, 3, 4, 5.
b. Research medicinal products in an inner packaging that is too small to list all information (e.g. vials). All information must then be listed on the outer packaging and the inner packaging must only list: 1 (only the name), 2 (only the dosage form

(exception.: oral fixed dosage forms), name and dosage of the product in open label research), 3, 4, 5

c. Research medicinal products not requiring any unique manufacturing methods or packaging, which is authorised and with participating patients who exhibit the same characteristics as the patients for which the medicinal product is authorised. In this case, the following must be added to the original label (the original text must, of course, still be legible): 1 (only the name), 4.

The use of symbols and pictograms is permitted.

In the event of re-labelling, because the use date has changed, an additional label must be affixed to the packaging listing the new expiration date and the batch number. The original information, particularly the batch number and/or the production code, must remain as visible as possible.

GENERAL EXAMPLE

Name of pharmaceutical company (Name of research product) 30 tablets, 500 mg each, oral Batch code XXX Protocol number Centre XXX Patient number XXX Use according to doctor's instructions Only for use in clinical research Store at room temperature (max 30° C) Do not use after mm/yyyy Keep out of reach of children

D4: Applicable statements/licenses

The Netherlands Healthcare Inspectorate website has an FAQ regarding licence applications for manufacturing or importing research medicinal products (www.igz.nl). For more information, see chapter 2.3 of the Instruction Manual, which is available from the CCMO website under Legislation and Regulations, EU Guideline Implementation (www.ccmo.nl).

A licence for the manufacture or import can be applied for with the Farmatec Unit of the Central Information Point for Professions in Healthcare (CIBG). The license application may be completed using a form available for downloading from Farmatec's website (www.farmatec.nl). This concerns manufacturing and/or import licences. A manufacturing licence is required for the preparation of medicinal products in the Netherlands. This applies to production, packaging and labelling of products. Hospital pharmacies may only prepare

research medicinal products based on a valid licence. Preparation does not cover preparing the product for administration.
Whether an import licence is required depends on whether the research medicinal product is being imported from a non-EU country or an EU country. No import licence is required in the latter case.

Information regarding licences for research involving genetically modified organisms is available from the Gene Therapy Office (http://213.154.234.72/Paginas/loket.htm). See also the Gene Therapy Manual, available from the same website.

D5: Hospital pharmacist product details (if applicable)
These are documents from the hospital pharmacist regarding execution of the medicinal product research, such as the prescription request forms, issuing of study medication, technical information required for preparation, if the pharmacist prepares the medication himself, etc.

D6: Additional product details (if applicable)
For gene therapy, the nucleotide sequence of the vector must be submitted for review on diskette in ASCII format. Other additional product details may include reports from preclinical/animal research, for example.

E1: Information letter(s) for study participants/representatives
E2: Consent form(s)
Annex IIIb3 of the review manual (http://www.ccmo-online.nl/hipe/uploads/downloads_catp/Toetsingshandleiding_2002.pdf) includes information regarding the requirements a Dutch information letter and informed consent form must meet. There may also be additional instructional documents. Ask the MREC the research is being submitted to for review for further information.

E3: Any advertising texts or other promotional materials
All written information presented to (potential) participants in the medical research must be submitted to the MREC for review.

E4: Other informational materials (if applicable)
For example: general brochures regarding participating in medical research, IVF treatment, etc.

F. Questionnaires, patient diary, patient card (if applicable)
F1. Questionnaires
All questionnaires that must be completed by research participants must be drafted in Dutch and submitted for review, unless they are commonly used validated questionnaires.

F2. Patient diary

Diaries that must be kept by research subjects must be drafted in Dutch and submitted for review.

F3. Patient card

A patient card is a card that research participants carry with them, listing the research they are participating in along with contact details for the sponsor and/or investigator in order to alert them in the event of an emergency. Such a card is commonly used in clinical medicinal product research.

F4. Other

G. Insurance information

G1: Insurance certificate for WMO research with human subject insurance or written request for exemption from insurance obligation

People participating in research covered by the Medical Research Involving Human Subjects Act (WMO) must be insured against any potential damages caused by the research. This is checked during the medical ethics review, usually based on the insurance certificate. Exemption from this insurance obligation is possible under certain conditions. See Section 4 of the insurance decree, available from the CCMO website under Legislation and Regulations (www.ccmo.nl). If an exemption is desired, a request must be included in the submitted application.

G2: Proof of coverage of investigator or sponsor

The new WMO, which came into force on 1 March 2006, outlines rules regarding the liability of the sponsor or the executing party in medical research in Section 7, Subsections 5 through 8. These rules apply to all the research projects covered by the WMO.
This means that, in addition to WMO research subject insurance (G1), there must be a guarantee that the sponsor or the executing party is capable of fulfilling the responsibilities stemming from liability. No specific requirements apply to the liability insurance. A general, professional or product liability insurance policy is sufficient by definition. There is a possibility for sponsor or executing party liability not to be covered by insurance, but instead guarantee the fulfilment of responsibilities in another manner. Bank guarantees, a blocked third-party account or another form of financial security may be used. This means that a sufficiently solvent sponsor or executing party, for whom sufficient guarantees that he can fulfil his obligations have been made, is not required to have insurance or other financial security. This also applies to a national government service, institution or company who, as long as they are appointed by the minister, also do not require insurance of this nature.

For multicentre research, liability coverage for the executing party is sufficient. If the insurance certificate/certificates belonging to one or more executing parties are submitted, this means that insurance documents belonging to all executing parties must be submitted. The insurance certificate for the hospital applies to persons employed by a hospital, a copy of

which will be required for each participating hospital. A copy of a professional liability insurance certificate will suffice for research with general practitioners.

H1: Independent doctor(s) résumé(s)
A recent résumé for each independent doctor must be submitted for review.

H2: Coordinating investigator résumé
A coordinating investigator is an investigator who bears the responsibility for the coordination of investigators operating in the various centres participating in multicentre research. Not all multicentre research will have a coordinating investigator. There is no requirement to appoint one.

I1: List of participating centres and chief investigators
An overview list of all potentially participating centres must be submitted. This list must include contact details and the name of the chief investigator per centre.

I2: Local feasibility declaration from the Board of Directors/Management per centre (for external review/multicentre research)
The CCMO External Review Directive is applied for the review of protocols for multicentre research and external review for monocentre research in the Netherlands. The directive is available from the CCMO website, under Legislation and Regulations. A template for a locale feasibility declaration is also available from the CCMO website. Please use the following link: (http://www.ccmo-online.nl/hipe/uploads/downloads/RET_modelverklaring.doc)

I3: Principle investigator résumé per centre
A recent résumé for the principle investigator per participating centre must be submitted for review. A list of publications is a required part of the résumé.

I4: Other information per participating centre
For example the recommendation of the local MREC.

J1:Additional information regarding financial compensation for research subjects
Only applicable, if the information in ABR form is not sufficient.

J2: Additional information financial compensation for investigators and participating centres
Only applicable if the information in ABR form is not sufficient. This could include contracts between sponsor, investigator and research institution, for example. These contracts are not requested as standard, but must be made available should the assessing MREC request them.

K1: Copy of review by other institutions
Examples include reviews by subsidy providers or the institution's scientific committee. Recommendations made by a regulatory authority such as the FDA, EMEA or MEB also fall under this category of document.

K2: Overview list of authorised international intuitions that the protocol has been submitted to, along with a copy of reviews by foreign MRECs/ECs or competent authorities
This only applies to research with medicinal products. If the research is also being carried out in other countries of the European Union, an overview of competent authorities the protocol has been submitted to must be included. Additionally, a copy of the decision made by foreign MRECs and/or competent authorities must be included, if available.

K3: Signed research contract between the party organising the research (sponsor) and the investigator and/or institution.
From 1 January 2007, based on a commitment to the Second Chamber of Parliament by the Minister of Health, Welfare and Sport at the time, Minister Hoogervorst, a copy of the signed research contract between the party organising the research (sponsor) and the investigator and/or institution must be submitted to the CCMO in its function as review committee. If no research contract is signed, this must be mentioned in the cover letter. Without such a mention, the research file will be considered incomplete as long as the research contract is missing. Review will not commence. The submitting party will be asked to provide a copy of the research contract. Submission of the research contract is limited to the CCMO at this time. After about one year, the CCMO will draw up a balance sheet. It will then decide whether the evaluation of the research contract will become a permanent part of the review process for the CCMO as well as the accredited MRECs, as desired by the minister.
It may be that some accredited MRECs will already require that a copy of the research contract be submitted along with the research protocol. If this is the case, you are requested to fulfil this demand.

K4: Scientific publications
Scientific publications about previous and/or comparable research associated with the research being submitted. These publications have been provided by the party submitting the research file for review.

K5: Other relevant documentation
Examples of other relevant documents include the letter to general practitioners/treating medical consultants or recommendations by a radiation committee.

L1 through L3 are generally only required for research with medicinal products.

L1: SUSARs

SUSAR is the abbreviation of Suspected Unexpected Serious Adverse Reaction.
If an adverse event arises during a study in the patient/subject, then this concerns a SUSAR, if the following three conditions are met:

1. the event must be serious, that is to say, the event (regardless of the dose):
    - is lethal, and/or
    - threatens the life of the subject, and/or
    - makes hospital admission or an extension of the admission necessary, and/or
    - causes persistent or significant invalidity or work disability, and/or
    - manifests itself in a congenital abnormality or malformation.
2. there must be a certain degree of probability that the event is a harmful and undesirable reaction to the medicinal product under investigation, regardless of the administered dose (in other words, there is an adverse reaction).
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    - for an authorised medicine: the SPC text (Summary of Product Characteristics: in the Netherlands this is the IB1 text). In the case of an international multicentre research with an authorised product, the sponsor may choose an SPC. If there is, in comparison to the authorisation, a different dosage form, indication, patient group or dose, then the summary of the product information is supplemented with the relevant supplemental information for the concerned study.
    - for an unauthorised medicine: the Investigator's Brochure.

SUSARs must be reported to the assessing review committee (accredited MREC or CCMO), from 1 January 2008 onwards digitally to the competent authority (CCMO or Minister of Health, Welfare and Sport), the Medicines Evaluation Board (MEB) and the accredited institutions in other involved member states.
The assessing review committee only receives accelerated reports, i.e.
within the legally defined term of 7 or 15 days, for the following SUSARs:

- SUSARs that have arisen in the study that was assessed by the review committee
- SUSARs that have arisen in other studies of the same sponsor and with the same medicinal product and that could have consequences for the safety of the subjects involved in the study assessed by the review committee.

None of the remaining SUSARs need to undergo accelerated reporting to the assessing review committee. These are included in an overview line-listing that must be filed with the assessing review committee once every six months. This line-listing provides an overview of all SUSARs of the research medicinal product.
The competent authority and the MEB must receive accelerated reports of all SUSARs.
SUSARs that have already been reported to the EMEA Eudravigilance database do not need to be reported again to the competent authority and the MEB, as both have direct access to the Eudravigilance database.

For more information, read the FAQ "Reporting incidents/adverse effects in medicinal product research" on the CCMO website (www.ccmo.nl).

L2: Periodic SUSAR line-listings

Once every six months, a line-listing of SUSARs must be filed with the assessing review committee (accredited MREC or CCMO). This line-listing provides an overview of all SUSARs for the study medicinal product that have occurred since that last update of the Investigator's Brochure or the SPC text.

L3: Annual safety report

The sponsor must provide an annual safety report about the medicinal product being researched to the assessing review committee, from 1 January 2008 onwards digitally to the competent authority and the Medicines Evaluation Board. This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregate summary table of all reported serious adverse reactions, arranged by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

L4: SAEs

SAE is short for Serious Adverse Event. An SAE is an undesired medical incident involving a patient or test subject, which is not necessarily associated with the treatment, that:

- is lethal, and/or
- threatens the life of the subject, and/or
- makes hospital admission or an extension of the admission necessary, and/or
- causes persistent or significant invalidity or work disability, and/or
- manifests itself in a congenital abnormality or malformation.

L5: Other relevant safety information

Examples of other relevant safety information are results of toxicity studies in animals, results of temporary safety analyses by a safety committee, scientific publications revealing new safety information, etc.

M1: Progress reports

The assessing review committee must be updated on research progress by the sponsor or the executing party once a year. A progress report contains, at the very least, an estimate of the degree to which research goals are being met, reporting of undesired events and other reports that may affect the research progress review. If the research involves medicinal products, progress reporting may be combined with the annual safety report.
Please visit the following link for a sample progress report: http://www.ccmo-online.nl/hipe/uploads/downloads_catp/CCMO-formulier%20Voortgangsrapportage.dot

M2: Summary of research results/scientific publications
Once the research is completed, a summary of the results and/or any scientific publications must be filed with the assessing review committee. For more information on this subject, please see: CCMO statement on publication policy (www.ccmo.nl)

M3: Clinical research report
Only applicable to research involving medicinal products.
A final report must be filed with the assessing review committee and from 1 January 2008 onwards digitally with the competent authority within one year of research termination. For a sample report, see Annex 1 of the ICH E3 Guideline on the Contents and Structure of Clinical Trial Reports (CPMP/137/95), at http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf or http://www.ich.org/LOB/media/MEDIA479.pdf .