

Guidelines for researchers and sponsors with regard to the assessment by official bodies of clinical research involving gene therapeutics in the Netherlands

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Joint gene therapy office of the CCMO, VWS and IenM

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1 Foreword

An assessment of gene therapy research involving human subjects is an amalgamation of several different dimensions, such as genetic modification, environmental aspects and research involving human subjects. Different legal regimes apply to these different dimensions, which are often based on European legislation and regulations. In the case of gene therapy, in which these regimes therefore come together, there was only limited coordination of the implementation of the different laws. In addition, it was not clear to researchers and sponsors what the different bodies did, what they decided on, when and why. In short, the procedures were unclear to the researchers and sponsors and this caused unnecessary work and sometimes led to delays in decision-making.

Researchers and the bodies involved agreed that this was an undesirable situation and decided to set up a working group to bring about improvements. This working group consisted of the undersigned representatives of researchers (Dutch Society for Gene Therapy - *Nederlandse Vereniging voor Gentherapie*), the bodies involved and the ministries. The task put to the working group was to set up a joint procedure for implementation in those sub-areas in which there was common ground between the bodies involved. The preconditions were that the procedure (a) focuses primarily on solving existing bottlenecks, (b) stays within the boundaries of existing legislation and regulations, (c) is clear and unequivocal for both the bodies involved and researchers and (d) does not cause any delays in the procedures. You are currently reading the end result of the working group's work and we hope that, in this way, we have substantially improved the implementation of the assessment for the researchers and sponsors concerned. We would, of course, welcome any suggestions for further improvement. Moreover, a short evaluation form will be sent to researchers after each procedure.

This document is the second version of the guidelines, adapted to the situations that arose on 1 March 2006 and 1 March 2007. On 1 March 2006 the Medical Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen* – WMO) was adapted in order to implement the European Clinical Trials Directive 2001/20/EC. The Immunological Pharmaceutical Products Decree (*Besluit Immunologische Farmaceutische Producten* - BIF) concerning medical research involving human subjects will lapse when the new Medicines Act (*Geneesmiddelenwet*) comes into force. In anticipation of this development, the Dutch Health Care Inspectorate (IGZ) decided to terminate the batch release procedure for immunological medicines used in medical research as per 1 March 2007. This decision was taken in the knowledge that the detailed product information has been included in the evaluation of research dossiers since 1 March 2006 by the accredited Medical Ethics Review Committees and in some cases the Central Committee on Research involving Human Subjects (*Centrale Commissie Mensgebonden Onderzoek* - CCMO). This version of the guidelines also incorporates several changes on the basis of the initial experiences with the new method.

The working group consisted of:

- *Centrale Commissie Mensgebonden Onderzoek* [Central Committee on Research involving Human Subjects]
- *Commissie Genetische Modificatie* [Netherlands Commission on Genetic Modification]
- *Inspectie voor de Gezondheidszorg* [Dutch Health Care Inspectorate]
- *Ministerie van Volkshuisvesting, Ruimtelijke ordening en Milieu* [Ministry of Housing, Spatial Planning and the Environment]
- *Ministerie van Volksgezondheid, Welzijn and Sport* [Ministry of Health, Welfare and Sport]
- *Nederlandse Vereniging voor Gentherapie* [Dutch Society for Gene Therapy]
- *Rijksinstituut voor Volksgezondheid en Milieu* [National Institute for Public Health and the Environment]

2 Overview of assessment bodies

The following Dutch bodies can be involved in the assessment of clinical gene therapy research involving human subjects:

- The *Centrale Commissie Mensgebonden Onderzoek* (CCMO) [Central Committee on Research involving Human Subjects]
- The *Ministerie van Volksgezondheid, Welzijn en Sport* (VWS) [Ministry of Health, Welfare and Sport]
- The *Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieu* (IenM) [Ministry of Housing, Spatial Planning and the Environment] and the *Bureau Genetisch Gemodificeerde Organismen* (BGGO) [Bureau for Genetically Modified Organisms], which is responsible for processing permit requests, with additional advice in that processing being provided by the *Commissie Genetische Modificatie* (COGEM) [Netherlands Commission on Genetic Modification]

This chapter starts with a short, general assessment to determine which procedures apply to your research and which authorisations are therefore required. This is followed by a short description of the gene therapy office (*loket gentherapie*), the individual bodies involved, their statutory basis and the aspects of the research that they assess. Because the different regulations also contain differences in definitions of the parties involved in the research, more detailed information is also provided on these differences. If you require any additional information, contact addresses are included for each body together with references to their websites.

2.1. Decide which procedure is applicable

For gene therapy research, three authorisations may be required by three different bodies. A diagram has been included to provide an insight into which procedures have to be followed for which research (Figure 1). By answering two short questions, this diagram can be used to determine from which body/bodies permission has to be acquired. The diagram is intended to function as a guide. In the event of any doubt or lack of clarity as to whether your research has to be assessed, you are advised to contact the gene therapy office (see 2.2).

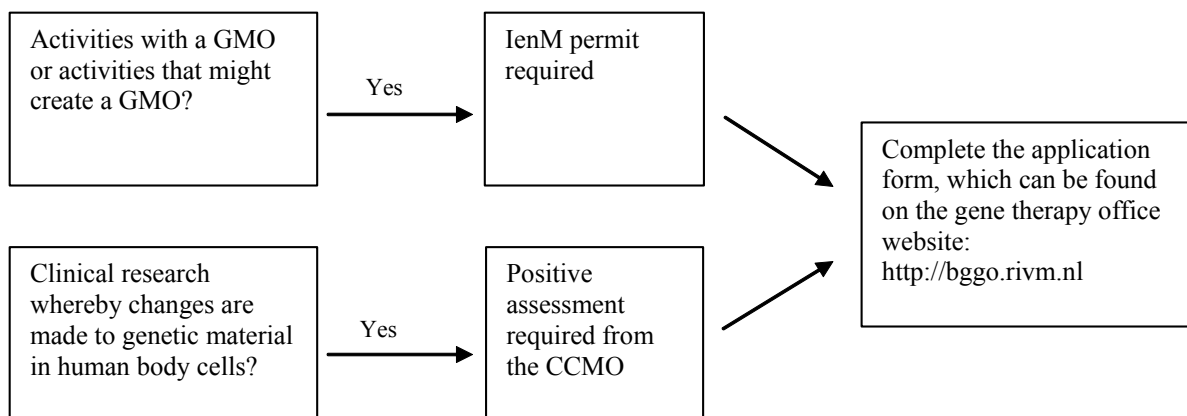


Figure 1: Diagram that can be used to ascertain which assessment bodies take a decision on your application

2.2. Gene therapy office

The gene therapy office was set up because multiple procedures may have to be completed before gene therapy research can start. This office receives the (combined) applications, changes, notifications and reports, streamlines the processing where possible, communicates the decisions to the applicant and serves as an information point. The aim of setting up the office was to streamline the different procedures, to provide more insight into the procedures for the researchers and to coordinate these procedures more effectively with the different assessment bodies.

Details and contact person

Name : RIVM/Bureau GGO (gene therapy office)
Postal address : PO Box 1
3720 BA Bilthoven
Netherlands
Visiting address : Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands
Telephone : +31 (0)30 274 4197
Fax : +31 (0)30 274 4401
Website : www.rijksoverheid.nl/ministeries/ienm
Contact person : Dr. D.A. Bleijs (bggo@rivm.nl)

Irrespective of the number of different procedures that have to be completed, an application can always be submitted to the gene therapy office. In the event of two or more procedures having to be completed, we strongly advise you to submit the application via the gene therapy office.

2.3 CCMO

Since the Medical Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen* - WMO) came into effect, all gene therapy research involving human subjects has to be assessed by the CCMO in accordance with the Central Assessment of Medical Research (Human Subjects) Decree (*Besluit Centrale Beoordeling Medisch Wetenschappelijk Onderzoek met Mensen* - BCB). The reason why gene therapy research is assessed by the CCMO – and not by (local) medical research ethics committees – is that the developments in the field of gene therapy are so new that there is little relevant expertise.

The committee will assess the research proposal according to the criteria of the WMO. For gene therapy research the assessment will focus particularly on the risks of the treatment for the human subject and for society. If the committee concludes that it does not have the necessary expertise to complete the assessment, it can seek advice from external experts on those aspects where it lacks the necessary expertise.

Definition of parties associated with the clinical research

- Performing party (i.e. sponsor): a person, company, institution or organisation that takes responsibility for starting, managing, or funding the scientific research.
- Executing party: the party that is responsible for implementing the scientific research at a particular location. In most cases this means the doctor / researcher.

Details and contact person

Name : Centrale Commissie Mensgebonden Onderzoek
Postal address : PO Box 16302
2500 BH The Hague
Netherlands
Visiting address : Parnassusplein 5, The Hague, Netherlands
Telephone : +31 (0)70 340 6700
Fax : +31 (0)70 340 6737
Website : www.ccmo.nl
Contact person : Dr. M.J.H. Kenter (ccmo@ccmo.nl)

2.4 VWS

The Minister of Health, Welfare and Sport (VWS) is responsible for issuing a statement of no objection regarding the proposed gene therapy research. The minister of Health, Welfare and Sport decides this on the basis of the Medical Research Involving Human Subjects Act (WMO). This statement is issued after the necessary information has been supplied (which is the same information that must be supplied to the CCMO) and if a check of the EMEA EudraVigilance Clinical Trial database has not found any side effects that would present unacceptable risks for the human subject.

Details and contact person

Name : Ministerie van Volksgezondheid, Welzijn en Sport
Directie Geneesmiddelen en Medische Technologie
Afdeling Toelating tot de markt en veilig gebruik
Postal address : PO Box 20350
2500 EJ The Hague
Netherlands
Visiting address : Parnassusplein 5, The Hague, Netherlands
Telephone : +31 (0)70 340 7911
Fax : +31 (0)70 3407187
Contact person : H.J.J. Seeverens, (hj.seeverens@minvws.nl)

2.5. IenM / Bureau GGO / COGEM

The Ministry of Housing, Spatial Planning and the Environment (IenM) is responsible for the regulations that protect people and the environment during activities involving genetically modified organisms (GMOs) and has the task of developing policy and regulations. The Minister of Housing, Spatial Planning and the Environment decides on permit applications on the basis of the Genetically Modified Organisms Decree (*Besluit Genetisch Gemodificeerde Organismen*).

Definition of parties associated with the clinical research

The applicant/permit holder is the legal entity that bears final responsibility for the work to be carried out. The applicant/permit holder is therefore usually the Executive Board (directors) of the hospital (the institution) where the treatment is to be carried out.

The permit holder must be able to enforce compliance with the licensing regulations when the work is carried out. It is therefore essential that the permit holder has authority over the employees involved in the clinical activities. The employees must therefore be employed directly by the permit holder. In cases in which the permit holder does not have authority over an employee, for example because a doctor providing treatment is a member of a partnership that is independent of the permit

holder, a work agreement must be arranged for the execution of the licensed work, for example by means of a contract with the applicant for zero hours. As regards the responsibility for any non-clinical activities that are not carried out in the institution in question, a contract must be entered into with the executing party (parties) of these activities, such that the final responsibility remains with the permit holder.

Details and contact person

Name : Ministerie van IenM
Portefeuille Milieu
Directie Risicobeleid
Postal address : Internal mail code 645
PO Box 30945
2500 GX The Hague
Netherlands
Visiting address : Rijnstraat 8, The Hague, Netherlands
Telephone : +31 (0)70 339 4893
Fax : +31 (0)70 339 1316
Website : www.rijksoverheid.nl/ministeries/ienm
Contact person : Dr. I. van der Leij (inge.vanderleij@minienm.nl)

The Bureau Genetisch Gemodificeerde Organismen (Bureau GGO) (Bureau for Genetically Modified Organisms) is responsible for the administrative and technical-scientific implementation of the granting of the permit on the grounds of the GMO Decree and for supporting the policy. In practice this means, among other things, the processing of permit applications for restricted use and introduction into the environment (this includes gene therapy research). The Ministry of Housing, Spatial Planning and the Environment is responsible for deciding on permit applications.

Details and contact person

Name : RIVM/Bureau GGO
Postal address : PO Box 1
3720 BA Bilthoven
Netherlands
Visiting address : Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands
Telephone : +31 (0)30 274 4197
Fax : +31 (0)30 274 4401
Website : bggo.rivm.nl
Contact person : Dr. D.A. Bleijs (bggo@rivm.nl)

The task of the Commissie Genetische Modificatie (COGEM) (Netherlands Commission on Genetic Modification) is to advise the Minister of Housing, Spatial Planning and the Environment, on request or on its own initiative, regarding the risks of genetically modified organisms (GMOs) for people and the environment. COGEM advises on the risks of applying and manufacturing GMOs, and on the safety measures that have to be taken to protect people and the environment. As regards gene therapy applications, COGEM does not advise on the possible risks for the patient. The commission advises on the risks of infection and spread of the GMO for staff involved in treatment, family members, the public, etc. Another of COGEM's tasks is to inform the ministers involved on ethical and social aspects of activities with GMOs. In the case of permit applications relating to the introduction of GMOs into the environment (including gene therapy), the Minister of Housing, Spatial Planning and the Environment requests advice from COGEM in the draft decision phase. The task of COGEM is laid down in the Environmental Management Act (*Wet*

milieubeheer) and is described in more detail in the Integral Policy Document on Biotechnology (*Integrale Nota Biotechnologie* - INB).

Details and contact person

Name : Commissie Genetische Modificatie
Postal address : PO Box 578
3720 AN Bilthoven
Netherlands
Visiting address : Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands
Telephone : +31 (0)30 274 2777
Fax : +31 (0)30 274 4476
Website : www.cogem.net
Contact person : Dr. F. van der Wilk (Frank.vanderWilk@cogem.net)

3 Informal preliminary consultation

The preliminary consultation is an informal consultation between the applicant and the bodies that decide or advise on the application. The preliminary consultation takes place before the application is officially submitted. The researcher/sponsor can use the option of a preliminary consultation attended by all bodies relevant to implementation and advice. The researcher/sponsor can also choose to conduct preliminary consultations with each body separately. In that case, the researcher/sponsor needs to contact each body individually (see Chapter 2). The rest of this chapter relates to a joint preliminary consultation.

3.1. Aim and status

The aim of the preliminary consultation is to exchange information so that, when submitting the application, the researcher/sponsor submits the right data, with the right degree of detail and has an insight into which aspects the different bodies focus during the assessment. This approach is intended to enable the official procedures to be completed as quickly as possible.

The preliminary consultation is an informal consultation that falls outside the statutory frameworks because it takes place before the application is officially submitted. The researcher/sponsor is not obliged to conduct a preliminary consultation. A report is drawn up on the preliminary consultation and this report can be useful to the researchers/sponsors when drawing up the documents required for the official submission. However, the researcher/sponsor cannot derive any rights from the preliminary consultation (or the report thereon).

3.2. Preparation by the researcher/sponsor

The researcher/sponsor is expected to submit as many documents as possible relating to the application (application form, research protocol, investigator's brochure, Investigational Medication Product Dossier, etc.) prior to the consultation so that these can be examined by the various bodies. If the researcher/sponsor has questions, these can be submitted in writing beforehand, possibly after prior consultation with the bodies involved (see Chapter 2). Thereby the preliminary consultation can be used for the more complex questions or for the uncertainties that still exist according to the various bodies. The draft application, the draft annexes to the application and any questions can be sent beforehand (electronically) to the gene therapy office (see paragraph 2.2).

3.3. Organisation

At the researcher's/sponsor's request, the gene therapy office will organise the joint preliminary consultation on behalf of the bodies involved.

As regards timing and location, the preliminary consultation will be linked as much as possible to the meetings of the CCMO (The Hague) and/or COGEM (Utrecht/Bilthoven). The preliminary consultation will in principle take place within one month of the researcher's request.

The researcher/sponsor will send all draft documents and any questions electronically to the gene therapy office, which will ensure that all bodies participating in the preliminary consultation receive the documents. The documents to be sent by the researcher/sponsor must have been submitted to the gene therapy office no later than 4 weeks before the date on which the preliminary

consultation is to take place. They can be submitted at the same time as the preliminary consultation request.

The gene therapy front office will act as the secretariat for the preliminary consultation and the preliminary consultation will always be chaired by a CCMO or COGEM member. The gene therapy office will also draw up the report on the preliminary consultation and send it to the researcher/sponsor no later than 2 weeks after the preliminary consultation has taken place.

4 The assessment procedures

As described in Chapter 2, a number of different bodies may have to give an opinion or reach a decision on gene therapy research involving people. Those bodies use different procedures, based on different legislation and regulations. In order to achieve a result as quickly as possible, one of the main preconditions in the establishment of the gene therapy office was to remain within existing legislation and regulations because that is based in almost all cases on European legislation and regulations. Changing it, if at all feasible, would take several years.

The guidelines are therefore based on the different existing procedures, although agreements have also been made between the bodies involved as to how more cooperation and coordination can be achieved. The intention is to make things simpler and clearer for the researcher.

This chapter first describes the form that the cooperation and coordination takes and then provides details on the individual procedures, using diagrams and short clarifications of the different steps.

4.1 Cooperation and coordination of procedures

The decisions of the CCMO, the minister of Health, Welfare and Sport, and the Ministry of Housing, Spatial Planning and the Environment are formally unrelated and the three bodies each retain their own responsibility. However, synchronising the procedures does enable the bodies to find out about each other's point of view and prevent contradictory decisions or statements to the applicant. For this reason, and with a view to making the whole process more transparent and simpler for the researcher, a number of improvements have been made:

- A single combined application form, which reduces the overlap in requested data (Annex 1).
- A single 'office' for the submission of the application, located at the GMO Bureau.
- Automatic distribution of the application form from the gene therapy office to all the bodies involved (see the gene therapy office website, section 2.2).
- All bodies appoint a permanent case manager per application. These case managers are jointly responsible for mutual coordination during the different procedures, including the possibility of attending commission meetings as members of the public.
- Feedback to the researcher/sponsor via the single office concerning the final assessments of the different bodies.

4.2 CCMO assessment procedure

The official assessment of the research protocol by the CCMO starts as soon as all documents have been received (see step 3 in the CCMO flowchart). A summary of the documents to be submitted is included in the gene therapy form (see chapter 6). Once the entire research dossier has been received, the submitting party will receive confirmation of receipt (see step 4 in the flowchart) which states the assessment deadline. If the research dossier is complete at least 2 weeks prior to the CCMO meeting, the research protocol will be discussed in that meeting. (The gene therapy office has no role to play in this phase because the CCMO will itself assess the completeness and can ask questions. After the discussion during the meeting (see step 5 in the flowchart), the submitting party will receive a letter that will include any questions from the committee (see step 6 in the flowchart). The letter will refer to a deadline by which a response from the submitting party is expected. After receiving the response, the CCMO will examine whether the questions have been answered satisfactorily. The research protocol may then be discussed again in a subsequent CCMO meeting. A statutory deadline of 90 days applies (see step 7 in the flowchart) for the assessment of

gene therapy research. In certain cases, this deadline can be extended by a second period of 90 days.

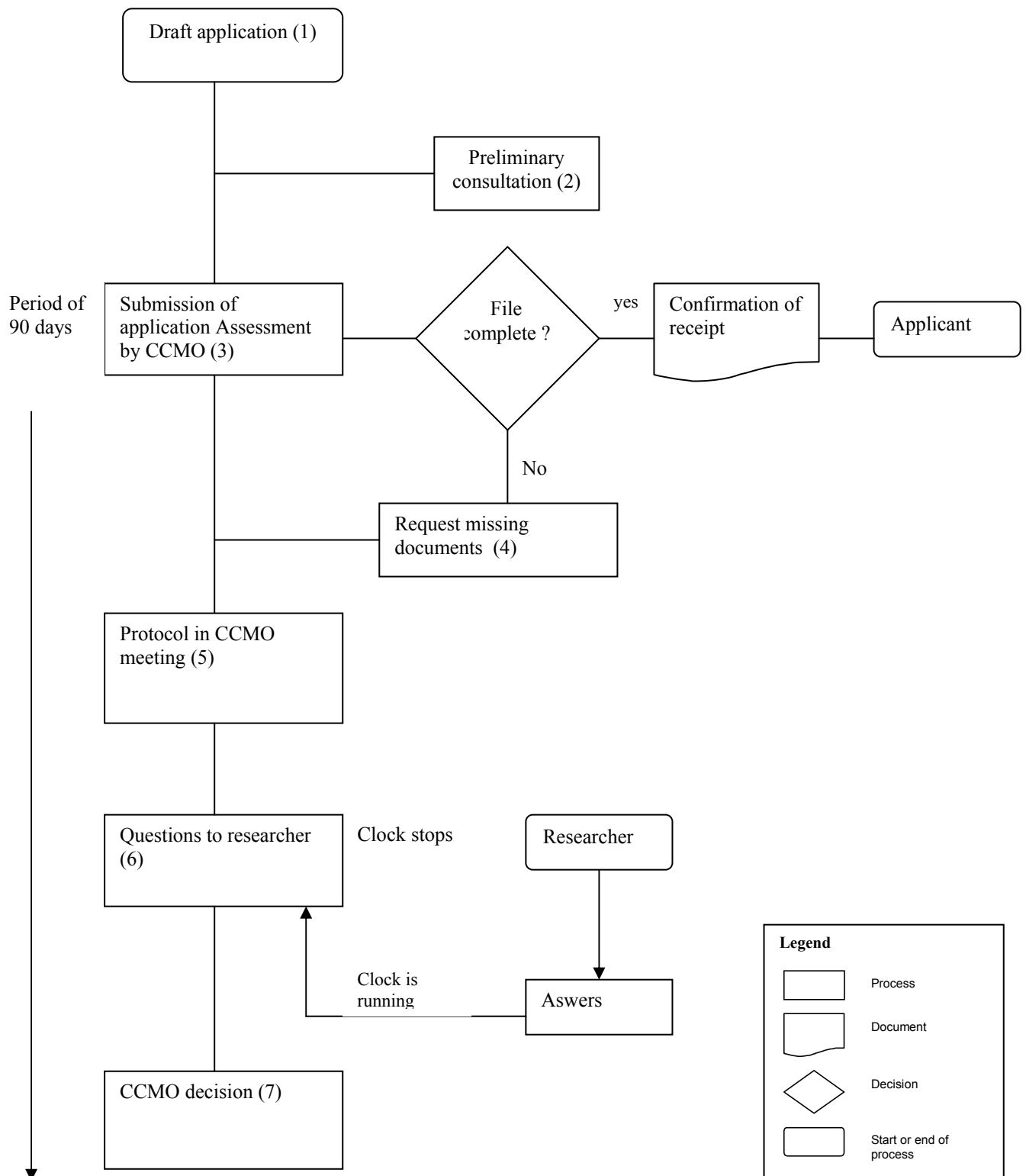


Figure 2: Diagram of the CCMO gene therapy assessment procedure

4.3 Minister of VWS declaration procedure

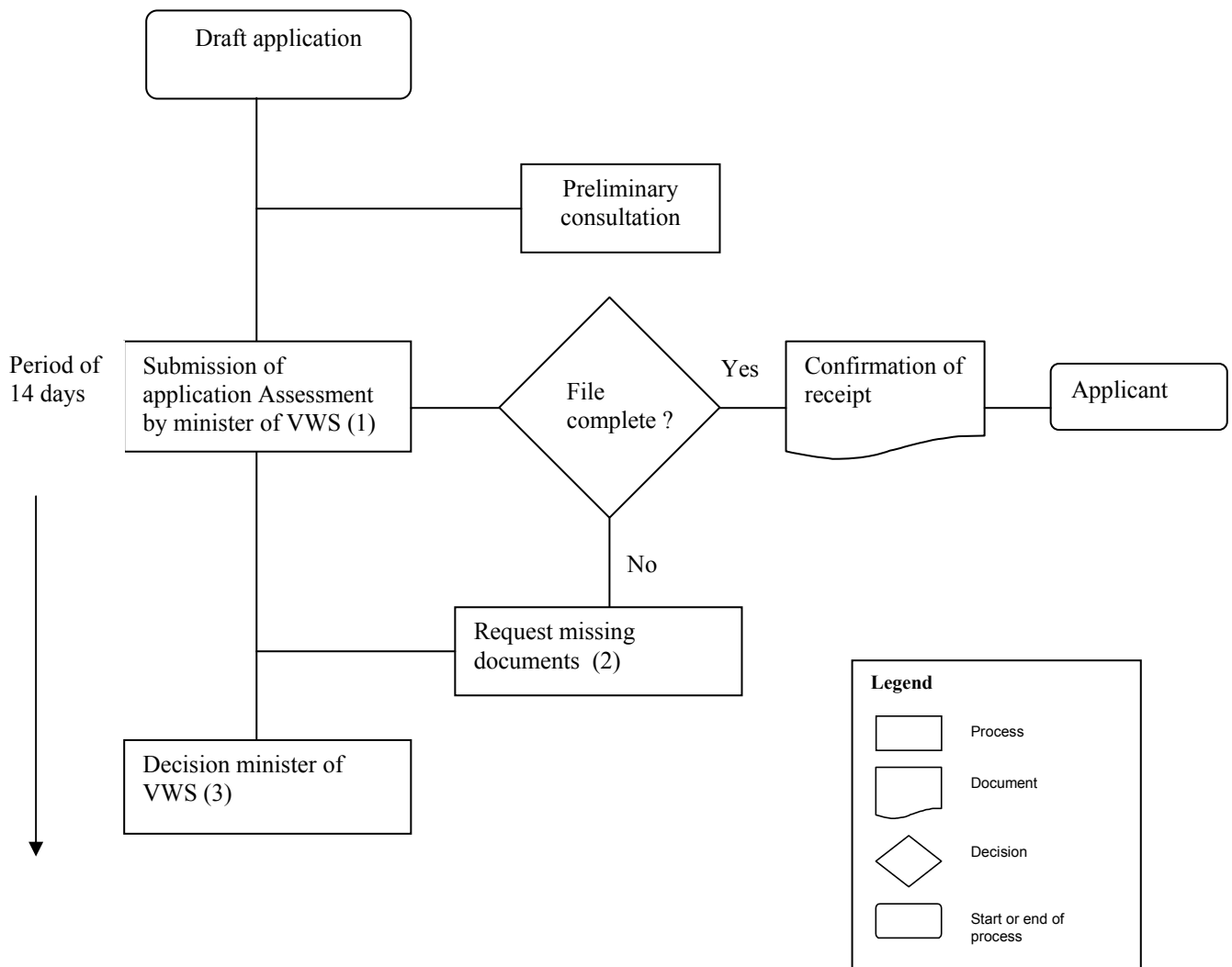


Figure 3: Diagram of the of the minister of Health, Welfare and Sport gene therapy assessment procedure.

The application for a statement of no objection to be issued arrives at the Ministry of Health, Welfare and Sport (VWS) via the central gene therapy office. The documents to be submitted with the application are the same as the documents that have to be submitted to the CCMO. After the file is received, the submitting party is sent confirmation of receipt, accompanied by a request for any missing data (see step 2 in the flowchart). The deadline for announcing the decision of the Minister of VWS to the applicant is 14 days after submitting the request for a statement of no objection. The 14-day assessment term starts as soon as all the necessary documentation has been received.

If, after receiving the necessary information, the Minister of VWS has not found any side effects in the EMEA EudraVigilance database that would present an unacceptable risk for the human subject, a written statement of no objection is issued. This is done by an announcement via e-mail to the gene therapy office, which will handle further communication with the submitting party.

4.4 IenM permit procedure

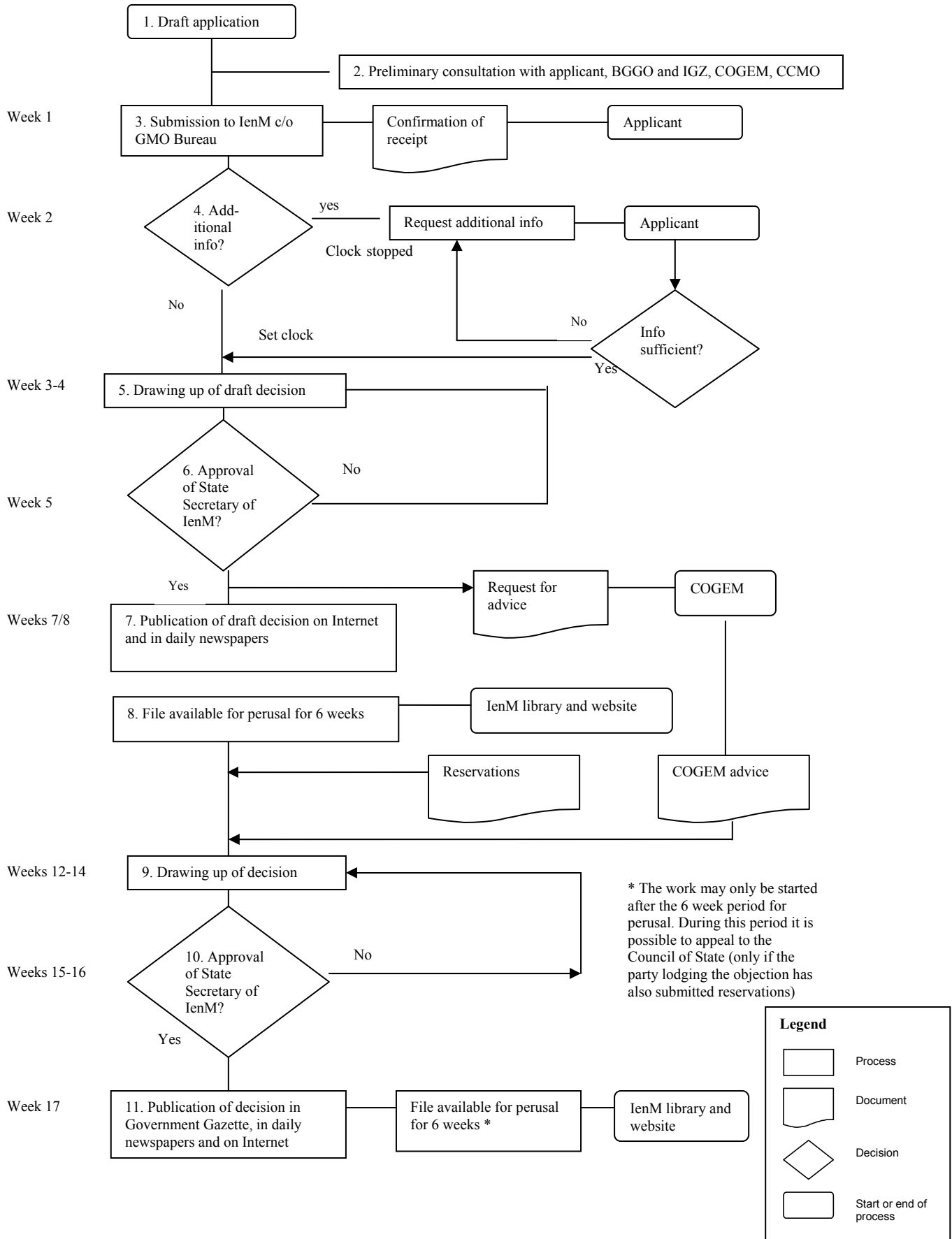


Figure 3: Diagram of the Ministry of Housing, Spatial Planning and the Environment gene therapy assessment procedure

In the case of gene therapy research, a permit application has to be submitted to the Ministry of Housing, Spatial Planning and the Environment (c/o GMO Bureau) (1). When submitting a permit application to the GMO Bureau, applicants need to realise that the scope of a permit is determined by the 'breadth' of the application. An attempt will be made to draw up the final decision in such a way that a number of clinical protocols can be executed under the permit. The information provided in the application will be used for this purpose. Before submitting such a broader permit application, it is advisable to contact the GMO Bureau for an informal consultation on the possibilities (2).

The procedure period starts as soon as it has been determined that the application is complete. A confirmation of receipt will also be sent (3). The procedure can be stopped as soon as a request is made for additional information. The procedure will then continue as soon as the requested additional information has been received (4).

A draft decision must have been drawn up within seven weeks (5), which, after it has been initialled by the Ministry of Housing, Spatial Planning and the Environment (6), will be made available for perusal together with the public part of the file (7). The applicants will be informed in writing of the publication of the notification relating to the making available for perusal of the draft decision and the file. The notification will be published in a number of relevant national and regional daily newspapers. Thereafter, third parties can, for a period of six weeks, submit objections relating to the proposed granting of the permit (8). During this period, COGEM will also advise on the application. After the deadline for perusal has expired, the objections and the COGEM advice received will be incorporated into the decision (9).

Apart from a permit application to the Ministry of Housing, Spatial Planning and the Environment, the intended work must also be reported to the other Member States of the European Union. The SNIF (Summary Notification Information Format) form to be used for this purpose will be sent to the applicant by the GMO Bureau. After the applicant has filled in the SNIF form and returned it to the GMO Bureau, the GMO Bureau will send it on to the European Commission after which it will be published on the Internet.

The decision must be signed by the Ministry of Housing, Spatial Planning and the Environment (10) no later than in week 17. Thereafter, the notification of the decision will be sent to the applicant before being published in national and regional daily newspapers (11). The decision will take effect as soon as the perusal deadline of six weeks has passed. If objections to the permit are submitted, the Council of State will inform the applicant and the Ministry of Housing, Spatial Planning and the Environment.

In the case of permits that were granted before 15 April 2004, the work may only start if, in addition to granting a permit, the Ministry of Housing, Spatial Planning and the Environment has also approved a clinical protocol. Each change to the clinical protocol (in the case of permits granted before 15 April 2004) means that a new protocol must be submitted to the Ministry of Housing, Spatial Planning and the Environment for approval.

In the case of permits granted after 15 April 2004, a description of the proposed work must be submitted before said work can be started. Approval is then not required for the individual clinical protocols.

5 Tips for the applicant

The assessment of gene therapy research involves a combination of different legislation and regulations and different bodies are involved. It may be the case that an applicant needs one or more of the following authorisations in order to start clinical gene therapy research:

- A positive assessment from the CCMO;
- A statement of no objection from the Minister of VWS;
- A permit from the Ministry of Housing, Spatial Planning and the Environment.

As described in Chapter 4, these are, in a formal sense, three separate procedures. However, the aim has been to keep things as easy as possible for the researcher/sponsor, as is shown by the organising of a joint preliminary consultation and the combining of the different application forms. Nevertheless, smooth procedures will, to a considerable extent, depend on the researcher himself or herself. This chapter contains a number of tips.

5.1 Engage in preliminary consultation

- Do not be hesitant to approach the gene therapy office or the bodies involved for information beforehand. Chapter 2 contains details of the contact people for the gene therapy office and each body plus their telephone numbers, e-mail addresses and website addresses. If the texts of the legislation and regulations in question are required, these can be found by entering the right search criteria at www.overheid.nl, option ‘Wet- en regelgeving’.
- You may also make use of the opportunity offered to engage in preliminary consultations with all the bodies involved. This can provide very useful information for the applicant before a definitive application is submitted. If the applicant submits written questions to the gene therapy office prior to the preliminary consultation, these can be dealt with during the preliminary consultation.

5.2 Submission of the official application

- Try to submit the application to all the bodies involved simultaneously because agreements have been made between the bodies involved to coordinate assessments where possible within the applicable deadlines. Those agreements are based on simultaneous submission.
- Section 4.1 describes the way in which the procedures have been coordinated and more details on the procedure per body are given (4.2 to 4.4). As regards the coordination between the different bodies, it is recommended that the applicant explicitly grants permission for consultation and the exchange of data between the bodies concerning his or her application. This permission is indicated on the application form (Annex 1).
- Do not wait until all applications can be submitted simultaneously if the application for the Ministry of Housing, Spatial Planning and the Environment is ready earlier. In such cases, you should apply for the permit from the Ministry of Housing, Spatial Planning and the Environment on the basis of the GMO Decree. This is because the procedure for the IenM permit is subject to statutory deadlines for public perusal and the applicable total deadline is the longest (120 days). This is followed, in decreasing order of length, by CCMO (90 days) and by VWS (14 days). In terms of substance, it is possible to apply for the IenM permit separately from the other authorisations because the research protocol is not part of the IenM application. In the past it was part of the IenM application and that resulted in problems

coordinating the different procedures. It is advisable to apply for as broad a IenM permit as possible because the possible increased scope of the permit may allow to a number of protocols to be covered by a single permit. The advantage is then that the procedure for the IenM permit will only have to be completed once for a number of protocols. It is advisable to contact the GMO Bureau to discuss this matter before a permit application is submitted.

6 Action in the event of changes to the research

This chapter describes what the researcher must do if an aspect of the research (or the organisation thereof) changes, either during the assessment procedures or during the implementation of the study. In order to ensure optimal coordination, changes must also be submitted to the gene therapy office. First of all, a list is provided of the changes that are relevant for one or more bodies. Then, an indication is given as to the action that needs to be taken per body. As indicated in Chapter 4, from a formal point of view, the different bodies carry out separate procedures once the application has been submitted to the gene therapy office. Nevertheless, there is coordination between the bodies, which therefore also applies to the passing on and processing of changes to the research.

6.1 Overview of the relevant changes

The following table shows which (type of) changes are important for which body. The table is intended as a guide. If you are in any doubt or if it is unclear whether your change needs to be reported, we recommend that you contact the gene therapy office (see 2.2).

Change	CCMO	VWS	IenM
Research protocol	X	X	(X)
Patient information	X	X	(X)
Management or organisation	X	X	(X)
Investigator's brochure	X	X	(X)
Investigational Medicinal Product Dossier (IMPD)	X	X	
Substantial amendments*	X		
Changes that are related directly to what is being granted**			X

* see also chapter 6.2

** N.B. all the above changes may be related to what is being granted (X). In the case of all IenM permits issued before 15 April 2004, the protocols are part of the decision. Any change to the protocol must always be submitted for approval in these cases.

6.2 CCMO changes

After initial approval by the CCMO, the following changes must be submitted to the committee for assessment: changes in the protocol or in the information for the test subject, which have consequences for 1. the safety or physical or mental integrity of the test subjects, 2. the scientific value of the study, 3. the management or organisation of the study, and 4. the quality or safety of the medicine to be researched (if applicable). Changes that meet one or more of these criteria are referred to as 'substantial amendments'. For an overview of what constitutes a substantial amendment, see also the handbook for 'Clinical Research with medicinal products in the Netherlands' on the CCMO website (www.ccmo.nl).

It is the investigator that determines whether or not an amendment is substantial in nature. If a substantial amendment is made, it must be submitted to the CCMO for assessment. The Minister of VWS must also be notified of the amendment using the 'Notification of Amendment' form (for a copy of the form, see the handbook on 'Clinical Research with medicinal products in the Netherlands' on the CCMO website). The amendment must not be implemented before the investigator has received a positive assessment from the CCMO and a statement of no objection from the Minister of VWS.

The request for assessment of an amendment must be accompanied by the following documentation:

1. Short description of the changes. The letter must also indicate the documents in which changes have been made and the reason why the changes are characterised as ‘substantial’;
2. The ‘Notification of Amendment’ form (see the handbook on ‘Clinical Research with medicinal products in the Netherlands’ on the CCMO website);
3. The changed documents (or parts of these), including both the old and new text;
4. The new versions of the changed documents, specifying version number and date.

If applicable, the following data in support of the application can be sent along:

- summary of results or data collected previously;
- a new risk / benefit analysis;
- possible consequences for subjects already included in the study;
- possible consequences for the results of the study.

The legal deadline for assessing amendments to gene therapy research is 35 days.

6.2 VWS changes

For the procedure to be followed regarding the changes that must be reported to the Minister of VWS, please refer to chapter 6.2, CCMO changes.

6.3 IenM changes

Type of changes

Any changes must be covered by the scope of the original permit and the application. The changes must be covered primarily within the scope of the risk analysis included in the permit and the regulations that have been drawn up in the permit on the basis of that risk analysis. When submitting an application it is a good idea to take account of the fact that all the data provided in the application is, in principle, part of the permit! For example, if the application refers to a number of patients to be treated, that number can not simply be adjusted by submitting a change. When a change is submitted, an indication must be given as to how this relates to the risk analysis (including the original application). If the change is not covered by the risk analysis of the existing permit, a new application has to be submitted.

Submission method

The change can, in principle, be submitted in the form of a letter, accompanied by all the information that is required for the assessment of the change.

Processing deadline

In the event that the change requires a new permit, the deadline and way in which a change is processed is the same as that for a new application (see section 4.4) on the understanding that the perusal deadline for the draft decision is six weeks. A change can be dealt with more quickly in those instances in which a change falls within the scope of the application and the permit granted.

7 Action in the case of undesirable events, side effects and unforeseen circumstances

This chapter describes how to act in the case of undesirable events, side effects and unforeseen circumstances.

7.1 Definitions

- **Undesirable event:** a damaging phenomenon affecting a patient or a test subject during clinical research that is not necessarily linked to this treatment.
- **Side effect:** a harmful and undesirable response to a research medicine, irrespective of the administered dosage.
- **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR):** an undesirable event or side effect that, irrespective of the dosage, is lethal, constitutes a danger to the life of the research subject, necessitates admission to a hospital or extension of the admission, causes lasting or significant invalidity or incapacity for work, or leads to congenital deficiencies or deformities.
- **Unexpected side effect:** a side effect whose nature and seriousness do not correspond to the information on the product as included in the research dossier for a research medicine for which no permit has been issued, or, in the case of a medicine for which a market permit has been issued, a side effect whose nature and seriousness do not correspond to the summary of the product's characteristics as included in the instructions for use.
- **Unexpected event with consequences for environmental safety:** an unexpected phenomenon during clinical research that is observed in a patient or in the patient's environment that may be connected to the genetically modified organism administered and that can have consequences for the safety of people and the environment.

7.2 In which situations should notification be given?

In the case of gene therapy research, a notification must be given if one or more of the following situations has arisen:

- All serious adverse events and all serious adverse drug reactions, both expected and unexpected;
- All serious unexpected and undesirable events that are not covered by the definition of an SAE/SADR, but that are still a risk for the test subject;
- Other events, as referred to in Article 10, paragraph 1 of the WMO: 'if the research progresses in a way that is substantially more unfavourable for the research subject than provided for in the research protocol'.
- Unexpected event with consequences for environmental safety. This means that all unexpected events that place the facts and considerations on which the risk assessment in the permit is based in a different light must be reported immediately. If an unexpected event can have an effect on elements in the application on which the conclusion of the risk analysis is based, this event must be reported.
- All unforeseen circumstances.

These five, not mutually exclusive, situations are jointly referred to in the rest of this chapter as 'undesirable situations'.

The rest of this chapter focuses on the procedure relating to individual notifications. The required periodical reports are discussed in chapter 8.

7.3 Who should be notified of undesirable situations?

Undesirable situations must be reported to the gene therapy office.

The researcher/sponsor himself/herself does not have to decide which bodies need to be informed. Such decisions are dealt with automatically by the gene therapy office (see 4.1). The researcher will receive feedback from the gene therapy office as to which bodies have been notified of the situation. Thereafter, the assessments of the undesirable situation by the various bodies are formally separated. The said bodies can decide, on the basis of their assessment, whether their previous permission still applies or must be changed or retracted.

7.4 By which deadline must notification be given?

Notification of all undesirable situations must be given 'immediately'.

7.5 How should notification of undesirable situations be given?

The gene therapy office must be notified of all undesirable situations in writing. It is preferable for the notification to be submitted beforehand by fax as well so that further distribution and assessment can take place as quickly as possible.

Each notification must be accompanied by the following:

- An accompanying letter.
- A completed CIOMS form, on which all relevant data can be reported. This form can be downloaded from the websites of all bodies involved.
- In addition, the permit holder must carry out a new risk analysis in which the event is incorporated into the existing risk analysis. The permit holder must substantiate whether and how the conclusions of the previous risk assessment must be amended. The new risk analysis must be sent to the gene therapy office by registered post as soon as possible after the initial notification.
- Diagram forms: one on behalf of the researcher/sponsor, one on behalf of the permit holder and, if applicable, one on behalf of the release applicant. The reason for this approach is that, from a legal point of view, the different bodies have to be informed by different parties. The simplest way of doing this is to authorise one and the same person to notify on behalf of all these parties.

7.6 What happens after notification?

The bodies involved have different procedures for the assessment and further processing of the notification, often based on different legislation and regulations. This procedure uses those different procedures as a point of departure, although agreements have also been made between the bodies involved as to how (more) cooperation and coordination can be achieved. The intention is to make things simpler and clearer for the researcher. The primary aspects are the following:

- In principle, the bodies involved maintain contact with the party that submitted the notification. This may involve a decision being made as to whether the research needs to be put 'on hold'.

- There is coordination between the bodies themselves to reduce the pressure on the notifying party as much as possible. Each of the bodies has a fixed contact person per research project in order to prevent unnecessary pressure being exerted on the notifying party. The final assessment of each of the bodies is sent via the gene therapy office to the notifying party. The idea is to do this as much as possible in one go so that it is immediately clear what the consequences are for the study.

8 Periodic reports

Both the CCMO and the Ministry of Housing, Spatial Planning and the Environment issue periodic reports on current gene therapy research. The CCMO uses a special form and the Ministry of Housing, Spatial Planning and the Environment includes the relevant requirements in the permit. If so desired, the two progress reports can be sent simultaneously to the gene therapy office.

8.1 CCMO progress report

The CCMO has to be sent annual progress reports on all the research that it has assessed. It has included a requirement to this effect in the text of its own assessments. In the case of gene therapy research, you are obliged to submit a progress report every year. For this purpose you have to fill in the progress report form (*formulier voortgangsrapportage*) (which can be downloaded from the website) and send it to the CCMO.

If necessary, the CCMO will request a more extensive report. This report will cover such matters as:

- The number of research subjects included in the study
- The number of research subjects who dropped out of the study
- All suspicions of serious side effects that there have been that year, plus a report on the safety of the research subjects.

8.2 IenM progress report

Every year, before the end of the calendar year, the permit holder is required to send a progress report on the work. In general terms, the report should cover:

- The number of patients included in the study
- The total number of patients included in the study
- The results of research that relate to the safety measures referred to in the permit
- Notifications of unforeseen circumstances. Reference must be made to any previous notification of these circumstances in a different context.