[The translation below is not certified and it has not been authorised by the CCMO; persons using this translation do so entirely at their own risk.]

Revised CCMO Directive on the Assessment of Clinical Trial Agreements

30 August 2011

Directive of the Central Committee on Medical Research Involving Human Subjects (CCMO), pursuant to Section 24 of the Medical Research Involving Human Subjects Act (WMO), concerning the assessment by medical research ethics committees of agreements relating to the funding or performance of research studies.

Article 1

1. The following definitions shall apply in the context of this directive:
    a. WMO: Medical Research Involving Human Subjects Act;
    b. research study: a study covered by the scope of section 1, letter b, of the WMO;
    c. sponsor: the party conducting the research study, as referred to in section 1, letter f, of the WMO;
    d. investigator: the party performing the research study, as referred to in section 1, letter g of the WMO;
    e. funder: the party providing the study's sponsor with the funding required to conduct the study;
    f. participating centre: participating centre as referred to in article 1.1 of the CCMO directive pursuant to section 24 of the WMO, concerning the review procedure for multicentre research and the external review of monocentre research (CCMO External Review Directive);
    g. a research study conducted at different locations by different researchers: research as referred to in section 1, letter m, of the WMO;
    h. agreement: the written undertakings entered into by the funder with the sponsor and by the sponsor with the investigator, participating centre or principal investigator, concerning the funding or performance of a research study, as well as written undertakings between investigators concerning that performance.
2. This Directive does not apply to a study in which the sponsor is also the sole investigator in the study.

Article 2

When assessing medical research in the light of the criteria laid down in, amongst others, Section 3 of the WMO, an accredited medical research ethics committee will take into consideration the agreement signed by the parties involved, where such an agreement exists and it contains provisions on the public disclosure of the results of the research study or contains criteria on the premature termination of the research study. In addition, the accredited medical research ethics committee will ensure that the terms and conditions of the agreement do not deviate from the protocol to the detriment of the research subject or contravene either the legislation and regulations governing the research or Articles 3 and 4 of this Directive.

Article 3

1. Provisions in the agreement on premature termination of the research study concerned in the agreement must circumscribe the conditions under which termination may occur, insofar as termination occurs after one or more research subjects have undergone treatments or have had conduct requirements imposed on them. Premature termination is only possible:
    a. if the judgement of the competent medical research ethics committee that has assessed the study is irrevocably revoked;
    b. if a reasonable case can be made for terminating the study in the interests of the health of the research subjects;
    c. if it transpires that continuation of the study cannot serve any scientific purpose, and this is confirmed by the medical research ethics committee that has issued a positive decision on the study;
    d. if one of the parties or the funder has been declared insolvent or a bankruptcy/winding-up petition has been filed in respect of one of the parties or the financier, or one of the parties or the financier is dissolved as a legal entity;
    e. if the principal investigator is no longer capable of performing the tasks of the principal investigator, and no replacement agreeable to both parties can be found;
    f. if one of the two parties fails to comply with the obligations arising from the agreement and, provided compliance is not permanently impossible, this compliance has not taken place within thirty days of the defaulting party receiving a written request to comply, unless failure to comply is not in reasonable proportion to the premature termination of the study;
    g. if circumstances beyond the control of the sponsor, investigator or funder make it unreasonable to require the study's continuation.
2. Provisions concerning the termination of the funding agreement or the agreement on the study's performance are equated with the provisions on premature termination of the research study, as referred to in subsection 1 of this article, except when the continuation of the entire study is assured despite the agreement's termination.

Article 4

The agreement must not include unreasonable restrictions with regard to the publication of the research results. The following restrictions, in particular, are deemed to be unreasonable:

a. the stipulation that public disclosure is only allowed after approval has been obtained from the party organising the study (i.e., the sponsor) or the party performing the study (i.e., the investigator);
b. entitlement of the sponsor or investigator to prohibit publication by the other party without giving reasons or by giving reasons that do not outweigh the importance of publishing the data;
c. a prohibition on public disclosure of the data, partially or in full, on condition that the proposed public disclosure has to be submitted to the other party, if the period of the prohibition exceeds ninety days, unless there are special circumstances which can justify a longer period;
d. a prohibition or restriction on public disclosure of the data, partially or in full, if it continues for more than 12 months after the study's termination and the research results have still not been published;

e. granting rights for public disclosure exclusively to the sponsor or investigator, unless there are particular circumstances in which this should not be deemed unreasonable.

Article 5
This Directive enters into force on 1 November 2011. This Directive replaces the previous *Directive of the Central Committee on Medical Research Involving Human Subjects (CCMO), pursuant to Section 24 of the Medical Research Involving Human Subjects Act (WMO), concerning the assessment of the agreement between the sponsor and the investigator by medical research ethics committees* of 1 January 2009, which is revoked by the entry into force of the present Directive.

Article 6
This Directive will be known as the Directive on the Assessment of Clinical Trial Agreements.

Article 7
This Directive will be posted in the Government Gazette, with explanatory notes in accordance with Section 24 of the WMO.

The Hague, 30 August 2011

On behalf of the Central Committee on Medical Research Involving Human Subjects,
Prof. G.H. Koëter, Chairman

Explanatory notes

This Directive is concerned with the conditions which a Clinical Trial Agreement must meet to obtain approval for the entire research file. The WMO includes standards for the assessment of the study prior to conducting it. Components of those standards are the likelihood that the study will provide knowledge in the field of medical science and that the knowledge will be made accessible. Any agreements made on the premature termination of the study or restrictions placed on the public disclosure of the results may be at odds with those standards. In practice, such arrangements turn out not only to be laid down in the research protocol but also generally in agreements which the party commissioning the study concluded with various parties involved in the study's performance. The inclusion in the agreements of extensive restrictions which would not be deemed reasonable in the assessment on the basis of the standards should be avoided.

The Directive, which was drafted by the CCMO and entered into force in 2009 in accordance with the wishes of the Lower House, was evaluated in 2010. It emerged from this that the Directive's impact on assessment had generally been positive and that it had provided clarity on the issue of what may be deemed to constitute acceptable restrictions. In this sense, harmonisation has also occurred, and following this the parties involved in conducting studies have moved closer towards each other and, by drafting a standard model agreement, are working on the comprehensive uniformisation of contractual obligations for commissioning/performing medical research.
It also emerged that the Directive was unclear on a few points. For example, the Directive made no distinction between termination of the agreement and termination of the study. The starting point for this is that the cessation of the agreement generally also results in the study's immediate discontinuation. Although this is still likely in the case of a study conducted in a single centre or participating centre, it need not jeopardise the entire study in the case of multicentre research. Moreover, precisely which agreement(s) the Directive referred to was not always completely clear. In addition, there was sometimes a lack of synchronisation between the Directive and the model Clinical Trial Agreement drafted by the CCMO, which resulted in both documents having to be amended.

<u>Main changes</u>
The overview provided here concerns the main substantive changes to the Directive, which are discussed in greater detail below in the notes on individual articles:

a. The agreements to which the Directive applies have been further specified in the preamble and notes, and by adding a definition.
b. Article 3, subsection 1, includes the provision that the restrictions on premature termination only apply if the research subjects have actually started to participate in the study.

c. Article 3, subsection 2, includes the provision that the restrictions do not apply to the agreement's termination, if such termination has no consequences for the performance of the entire study.
d. Article 3, subsection 1, letter d, supplements the criteria for premature termination with the provision that premature termination is permitted in the case of the dissolution of one of the parties to the agreement.
e. Article 3, subsection 1, letter e, supplements the criteria for premature termination by permitting premature termination if the principal investigator is no longer capable of acting as principal investigator and no replacement agreeable to both parties can be found.
f. Article 3, subsection 1, letter g, supplements the criteria for premature termination with the provision that a case of *force majeure* may lead to premature termination being permitted.
g. Article 1, subsection 2, excludes studies which are both commissioned and performed by the investigator.

The notes also discuss the central assessment of a standard agreement in the case of multicentre research, so that it is not necessary for the agreement to be assessed separately for each centre.

Relationship to the protocol

The legislation makes the assessment of the research protocol mandatory. This research protocol also includes documents on insurance policies, information provided to patients and the way in which consent is obtained. It is in fact a file which includes all the information and documents that are relevant for performing the study. The protocol, which forms the basis for the study's design and performance, may further stipulate the way in which study data are to be handled and may include rules on premature termination. This does not alter the fact that the study's funder or sponsor may also include similar rules in an agreement. It is even common for the agreement to include provisions on the agreement's premature termination which may have direct consequences for the study's performance.

Section 2 of the WMO stipulates that the study must be conducted in accordance with the research protocol written for that purpose. Section 33 of the WMO makes failure to comply with the obligation a punishable offence, which may lead to imprisonment. Therefore, from the statutory point of view it follows that the protocol takes precedence over other agreements concluded by the investigator, sponsor, funder (insofar as there is one) or facilitative institution. Nevertheless, one of these parties, especially the investigator, could enter into a conflict situation if the agreement includes provisions which must be deemed to be out of line with the obligations arising from the protocol. It is therefore important to ensure that the agreement contains no provisions which could give rise to such a conflict situation. For example, the protocol could refer in extremely limited terms to the termination of the study in the interest of the research subjects, whereas the agreement may include

extensive possibilities on financial grounds for terminating the agreement and thereby also the study.

The Directive applies to studies covered by the scope of the WMO but only insofar as a written agreement exists between the parties involved in the study's funding, design or performance, insofar as the agreement concerned includes restrictive conditions on the options for public disclosure of the research results, or includes criteria which form the basis for the study's premature termination, regardless of the way in which these restrictions are included in the agreement.

In some situations the sponsor and investigator are not separate, as is the case with an investigator-initiated study, for example. In such cases, when the investigator is also the study's sponsor, no letter of engagement for the study's performance will exist. Furthermore, there may be no need to lay down extensive agreements in a contract (for example if the study's funder is an institution or organisation which is closely affiliated with the investigator). Ethics committees can request the applicants to let them know in the submission letter if no Clinical Trial Agreement has been concluded. The ethics committee will then be able to accept the research file for review even without a signed research contract.

Notes on individual articles

Article 1

The new article 1 provides definitions to clarify the various terms. Most of the terms have been taken from the existing framework of legislation and regulations and therefore refer to the definitions included in that framework.

Besides fixed terms such as sponsor and investigator, the term funder is also defined in article 1, letter e, to make clear that the study's discontinuation may be unavoidable, if a financial backer becomes insolvent. This applies to situations in which the study's financial backer is not also the study's sponsor/conductor, as may be the case with organisations which grant subsidies, for example.

The scope of the Directive has been clarified with the definition of the term ‘agreement’: this refers to the assessment of agreements concerning the study's funding or performance, which are concluded by the investigator(s), sponsor or funder, when the aforementioned parties are not also the party that commissioned the study. The funder, often also referred to as the ‘Sponsor’, may have engaged an intermediary, such as a contract research organisation (CRO), to attend to the study's performance. It is therefore not always clear what the Sponsor's role is and what the CRO's role is, i.e., which party should be designated as the sponsor and which party should be designated as the investigator. This is not in itself important for the study's performance, provided there is clarity about which parties will perform the tasks arising from the various responsibilities of both the sponsor and the investigator. In the assessment of the clinical trial agreements it is a matter of including those components of the agreement which stipulate publication restrictions or regulate the premature termination of the study, or the agreement underlying the study. However the

starting point of the legislation is that the responsibilities are divided between predefined entities, such as the sponsor and investigator.
As a rule, a 'Sponsor' may also be considered to be the sponsor/conductor that offers the task of performing the study to the CRO, as the investigator. Therefore, when this investigator involves other parties in the study's performance, the agreement concluded to that end must also be involved in the assessment, provided the agreement includes provisions on publication freedom or premature termination as referred to in the second paragraph.
Moreover, the Sponsor may ask a CRO to arrange as an intermediary for the performance of the study to be offered to a third party, in which case the CRO would act as the sponsor's representative. The extent to which this representative also takes on the sponsor's responsibilities depends on what is agreed between the two parties to that end. The starting point will be that agreements on the study's performance which the representative concludes with third parties must be considered as agreements between the sponsor and investigator.
Insofar as a funder exists, as referred to in article 1, subsection 1, letter e, that party's limited role in respect of the sponsor will mean that no control of data publication or of the study's premature termination may exist. However, the agreement may include provisions for the premature termination of the funding. This could place the sponsor in a difficult position, as the sponsor would be obliged to ensure the study's performance, if it had already commenced.
When the sponsor and investigator are the same, as may be the case with an investigator-initiated study, there are no self-imposed contractual restrictions on publication freedom or conditions for the study's termination, so there is no reason for the agreement to be involved in the assessment. This situation is therefore excluded in the second paragraph.

Article 2

A further restriction of the scope is included in article 2. The aforementioned agreement only needs to be involved in the assessment to the extent that it includes restrictions on the public disclosure of the study results or criteria for the premature termination of the study or the agreement. More specifically, it states that the agreement must not deviate from what is stated in the protocol in a manner which is detrimental to the interests of the research subjects. It was a conscious decision not to stipulate that the agreement must not deviate from the protocol, as the two documents would then have to be drafted identically to avoid differences in interpretation. However, the possibility is not excluded of the protocol including more extensive restrictions or obligations than are contained in the agreement or vice versa. It is important that the provisions in the two documents remain within the limits of the research standards adopted in legislation. Moreover, in the case of multicentre research there is no need to prevent the sponsor from including a more extensive obligation in the agreement for a specific investigator than has been imposed in the protocol for the study as a whole. The important point is that any deviations must not have a detrimental impact on the research subjects and their participation. Needless to say, the contract must not, under any circumstances, contain any provisions that contravene the law. During the discussions on the WMO in the Lower House, explicit consideration was given to the two topics mentioned

earlier: criteria for premature termination and possible restrictions on the public disclosure of research results.[1]

The basic premise is that the ethics committee should base its assessment on a version of the research contract that has been signed by the parties involved. The committee is at liberty to determine the stage of the assessment at which it should be in possession of the signed version. Nevertheless, it should ensure at all events that a signed version of the research contract has been submitted before the research actually commences. Moreover, several comparable agreements may exist, such as when the sponsor contracts all the facilitative institutions separately but always uses the same agreement as the starting point. In that case it is sufficient to assess only one of the agreements, as long as the party that entered into the various agreements submits a statement confirming that the other agreements do not differ from the submitted document with regard to publication conditions or premature termination.

Article 3

A study that may be terminated prematurely by its funder, sponsor or even its investigator, automatically fails to provide sufficient certainty that it serves a scientific purpose. This negates the study's scientific value when considering whether it is reasonable to expose the research subjects to the risks and impact of the study, taking into account its value, so performing the study has to be deemed to be in breach of Section 3 (preamble and j) of the WMO.[2] This article has been included because the important point is termination after participation of one or more research subjects has taken place. After all, the assessment of the interests is of no concern if the study is terminated before participation has commenced.
If participation of the research subjects has started, the possibility exists of special circumstances arising which could justify the premature termination of the study. For example, premature termination of the research will clearly be considered if continuation has become scientifically meaningless or if termination is necessary in the interests of the research subjects. However, matters between the parties to the agreement can also justify termination, such as liquidation, insolvency or dissolution of one of the parties. In order to prevent one of the parties hereto from gaining excessive powers to rescind the agreement, these powers should be clearly and restrictively circumscribed in the research contract.
The agreement's termination may generally be equated with the termination of the on-site research study, unless provisions have been made to continue the study's performance after the cessation of the agreement in which the study's performance is regulated.
Moreover, in the case of a research study conducted at different locations the possibility exists of the agreement with a participating centre or investigator being terminated without affecting the scientific value of the study, as the study will be completed elsewhere. Examples of situations of this kind include the termination of cooperation with a participating centre or

[1] NV, Parliamentary Papers II 2002/03, 28 804, no. 5.

[2] NV, Parliamentary Papers II 2002/03, 28 804, no. 5, p. 13.

investigator in the case of a shortfall in inclusion, or because the intended inclusion for the study has already been achieved elsewhere. As this has no effect on the aim of protecting the scientific importance of the study and the research subjects involved, termination of this kind is beyond the scope of the Directive.

Article 4

In March 2002 the CCMO issued a statement setting out basic principles for the assessment of research protocols with particular regard to the publication of research results by the sponsor and the investigator. Following on from this statement, the Directive states that unreasonable restrictions on publication are not permitted and contravene Section 3 (preamble and j) of the WMO, as has also been noted by Parliament.[3] The parties to the contract are, of course, at liberty to agree among themselves the manner in which publication will occur, provided due emphasis is placed on the fact that the data will, indeed, be published and provided one of the parties is not unreasonably restricted from itself presenting the results to the public. In the case of multicentre research, the restriction that the public disclosure of their results by individual centres or investigators should wait until after all results have been centrally publicised will therefore be considered reasonable, provided central publication takes place within a reasonable period; a period exceeding 12 months would be deemed unreasonable. A sponsor may also stipulate that proposed publications by the investigators should first be submitted to him so that he can respond within a reasonable period or, for example, so that he has the opportunity to file patent applications. It is important that the parties should manage to resolve any differences of opinion through proper consultation, and that none of the parties should have a right of veto.

Article 5

This Directive, which replaces the previous Directive, enters into force on 1 November 2011 and applies thereafter to research protocols submitted for assessment to an accredited medical research ethics committee or the CCMO.

[3] NV, Parliamentary Papers II 2002/03, 28 804, no. 5, p. 15.