Centrale
Commissie
Mensgebonden
Onderzoek

Memorandum

Flowcharts deferred consent for medical research in emergency situations

Introduction

The Medical Research Involving Human Subjects Act (WMO, article 6, paragraph 4), the Clinical Trial Regulation(CTR, article 35), the Medical Device Regulation (MDR, article 68) and the In-Vitro Diagnostics Regulation (IVDR, article 64) contain a provision allowing subjects, under strict conditions, to participate in medical research without having obtained informed consent from the study participant or legal representative in the usual manner. This possibility only applies to studies in an emergency situation. One of the conditions in this context is that informed consent shall be sought by the investigator without undue delay from the subject or his or her legal representative(s) for (continued) participation in the study as soon as the circumstances allow it. This is called 'deferred consent'.

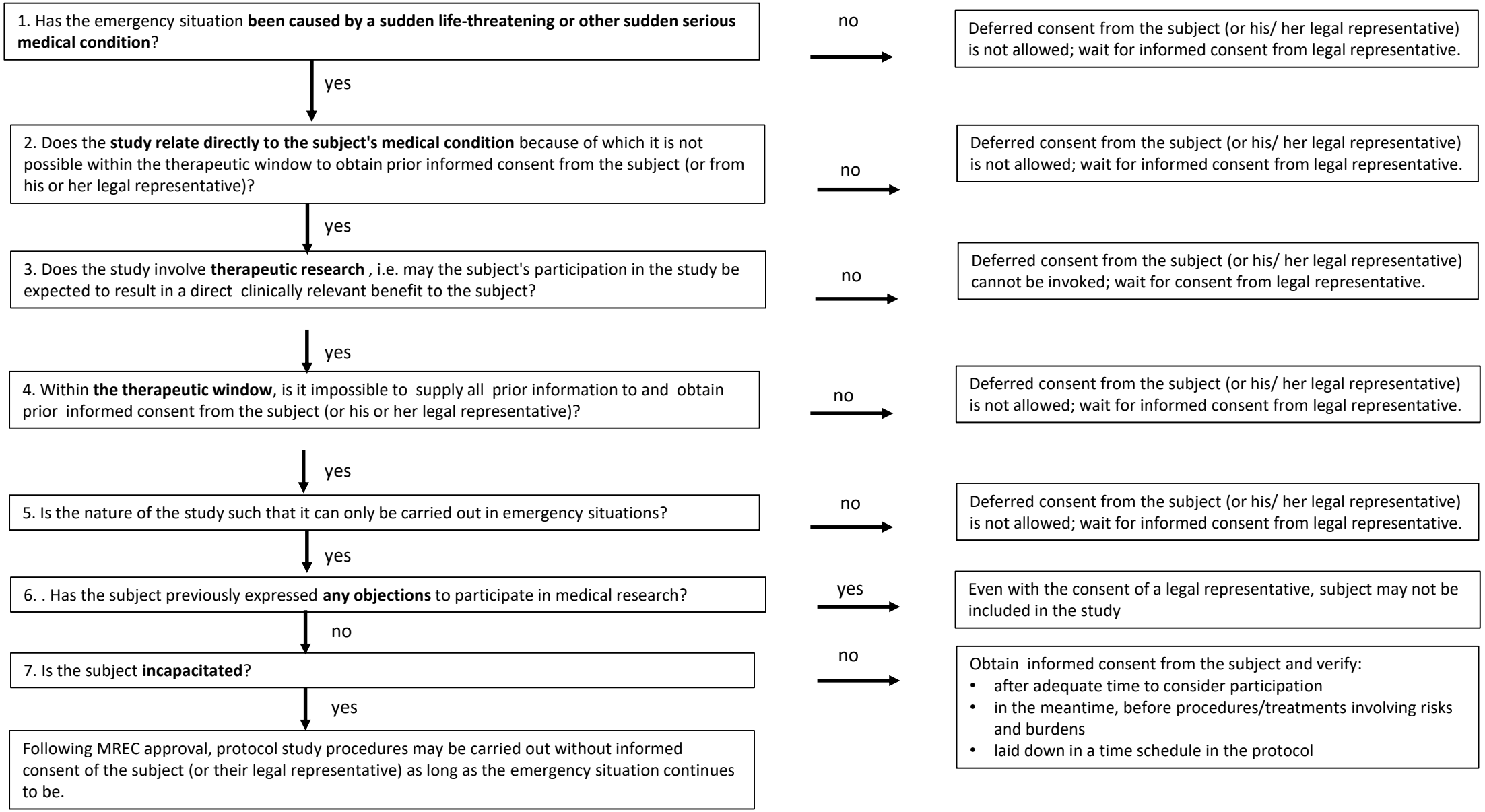
It was not always clear to investigators how to apply article 6, paragraph 4 of the WMO in clinical practice.[1] When exactly can deferred consent be applied or how should the conditions laid down in this provision be interpreted? How should the collected data and body material from subjects dying before informed consent could be obtained, be handled? The same applies to the articles of the aforementioned Regulations: many questions from Member States have arisen in this regard for which Q&A's are currently being drawn up by the European Commission/DG Sante. Against this background, the CCMO considers a guide clarifying the further interpretation and application of Article 6, paragraph 4 of the WMO and the relevant articles from the aforementioned Regulations of vital importance. This guidance also addresses the situation in which a subject died before deferred consent could be obtained. In this context, the question arises which conditions apply for the use of the collected data and body material of the deceased subject.

The legal provisions on deferred consent in medical research in emergency situations concern a legal exception to a basic requirement within the ethical standards of medical research, namely that subjects may participate in medical research only after they (or their representative(s)) have given their written informed consent. Therefore, it is reasonable to apply this exception as restrictively as possible, and in any case it must be applied very carefully. At the same time, medical research in emergency situations is essential. In interpreting the legal terms, account must (and can) be taken of what can be considered feasible and reasonable in clinical practice.

Additionally, the provisions on deferred consent in the aforementioned Regulations are more extensive and detailed than the analogous provision in the WMO. This also means that the requirement in the Regulations concerning minimal risk and burden for the subject, compared to the standard treatment of the subject's condition, has to be fulfilled. The CCMO has chosen to consider the more extensive conditions in these Regulations as leading and therefore these conditions are valid for all medical research covered by the WMO.

[1] In view of the corresponding text of Articles 35, 68 and 64 of the CTR, MDR and IVDR respectively, this guidance simply refers to Article 35 of the CTR.

Flowchart 1: deferred consent for medical research in emergency situations



Explanatory note to flowchart 1: justified call upon deferred consent?

Flowchart 1 is intended to establish whether the study concerns medical research in an emergency situation and if conducting medical research on the subject is allowed without prior informed consent from the subject or the legal representative. Below an explanatory note to each step is given.

1. Has the emergency situation been caused by a sudden life-threatening or other sudden serious medical condition?

Explanatory note
Deferred consent can only be applied in the case of a study in an emergency situation, meaning a situation of 'urgency caused by a sudden life-threatening or other sudden serious medical condition' (see Article 35(1)(a) CTR[2]).
Due to the urgency of the situation, the subject or his legal representative is unable to receive prior information on the study and unable to provide prior informed consent on participation in the study (Article 35(1)(a) and (c) CTR).

2. Does the study relate directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject (or from his or her legal representative)?

Explanatory note
The medical condition of the subject must be directly related to the medical emergency (Article 35(1)(e)), e.g. septic shock, life-threatening dysrhythmia, serious brain damage, et cetera.

3. Does the study involve therapeutic research, i.e. may the subject's participation in the study be expected to result in a direct clinically relevant benefit to the subject?

Explanatory note:
Deferred consent can only be applied if participation in the study will have the potential to produce a direct clinically relevant benefit to the subject. This benefit may be the result of a new investigational product or a an improved diagnostic or monitoring procedure (see Article 35(1)(b) CTR).

4. Within the therapeutic window, is it impossible to supply all prior information to and obtain prior informed consent from the subject (or his or her legally designated representative)?

Explanatory note
The time-frame between the patient's condition and the time at which treatment should be started is so short that the first investigational procedures, such as administration of an investigational medicinal product or performing a diagnostic test, have to take place within this short period of time. As a result, it is not possible to obtain prior informed consent (see Article 35, paragraph 1 under c, CTR). There must be a medical reason to perform the first study-specific action within this short period of time.

[2] Reference only to articles of law in CTR. However, MDR and IVDR contain identical articles on these points.

5. Is the nature of the study such that it can only be carried out in emergency situations?

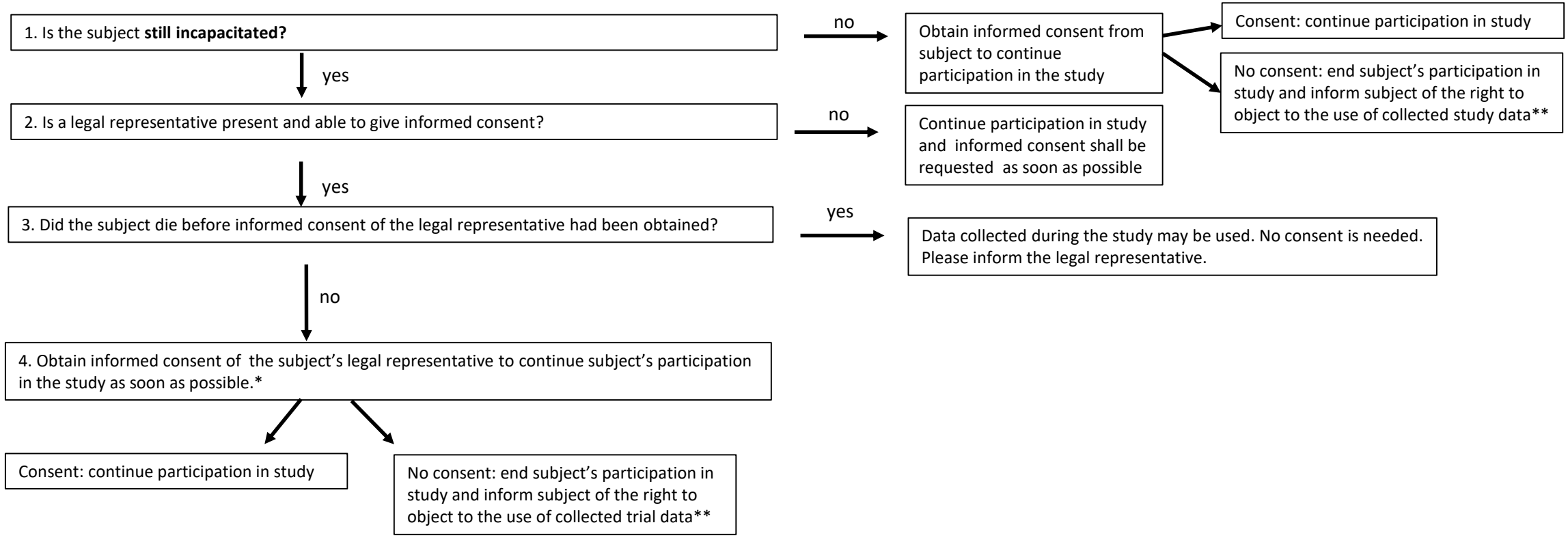
Explanatory note
Deferred consent can only be applied if - due to the medical condition and consequent necessary treatment of the study population concerned - it is not possible to obtain prior informed consent from any subject or legal representative (see Article 35(1)(e) CTR). Basically, this provision precludes research with so-called 'mixed populations'; the latter is the case if prior informed consent CAN be obtained from a number of subjects (or their legal representatives) and CANNOT be obtained from a number of others.[3] The CCMO considers such research to be permissible only in exceptional cases, i.e. if compelling reasons can be put forward, which are accurately described in the research protocol and accepted by the MREC.
If the research question can also be addressed in a 'non-emergency trial', deferred consent is not permitted (Article 35(1)(e) CTR).

6. Has the subject previously expressed any objections to participate in medical research?

Explanatory note
With regard to a specific subject, deferred consent can only be applied if the subject has not previously expressed any objections (in writing) to participation in medical research (see Article 35(1)(d) CTR). In practice, this will rarely occur. More often, a situation will arise in which a patient has stated in a declaration of will that he no longer wishes life-extending treatment, or that a policy has been agreed during admission not to resuscitate and/or give artificial respiration. If this is known, it will not be possible either to include the patient in a study leading to an undesired prolongation of life. This does not entirely rule out participation in medical research in emergency situations, e.g. if this is aimed at acute palliation or diagnostics. The protocol should provide clarity about the procedure regarding possible restrictive statements of intent for inclusion, and about the explanation given (afterwards) to the patient and the legal representative.

[3] Article 6(4) of the WMO seems to lead to a similar conclusion

Flowchart 2: Obtaining informed consent in medical research in emergency situations after inclusion incapacitated subject*



* This concerns obtaining informed consent to continue participation in the study. If the study has already been completed before it was possible to obtain written informed consent, there is no longer any need for informed consent. However, the subject (and/or his legal representative) must be informed about the study.
** See text in note on whether the objections should be honoured.

Explanatory note to flowchart 2: Conditions after the subject's inclusion on basis of deferred consent

The most important condition after the start of a study in an emergency situation (and inclusion of subjects on the basis of deferred consent) is that the investigator:

- provides information to the subject and his legal representative(s) *as soon as* possible;
- obtains informed consent from the subject or, if the subject is still incapacitated, from the subject's legal representative(s) to continue the subject's participation in the study *without undue delay***.**

Flowchart 2 shows the various options for obtaining informed consent following the inclusion of the incapacitated subject and the use of data already collected if the subject has died before informed consent could be obtained.

1. Is the subject still incapacitated?

Explanatory note
If affirmative, go to step 2. If the subject is no longer incapacitated and able to receive information, the informed consent of the subject to continue participation in the study must be obtained without undue delay. If the subject does ***not*** *consent, he or she shall be informed that he or she may object[4] to the use of data previously collected as part of the study.*

2. Is a legal representative present and able to give informed consent?

Explanatory note
If, as a result of the emergency situation, the patient is unable to give informed consent for participation in the study, this should be sought by the investigator from a legal representative as soon as possible. However, it may be difficult to inform relatives of very seriously ill patients with a high risk of rapid death, in a very uncertain clinical situation, in detail about participation in a study as soon as they arrive at the hospital.[i] In daily practice, the moment of obtaining informed consent is therefore often postponed until the clinical condition of the seriously ill patient has somewhat stabilised and the relatives have calmed down. Some investigators mention in their protocol a time-limit of 72 hours within which informed consent (from the subject or his/her legal representative) must be obtained for participation in the study.[ii]

The CCMO considers it acceptable, in cases where the legal representatives are not immediately approachable due to the acute situation, to give them some time to get used to the situation of their relative (comparable to asking permission from next of kin for organ donation), before informing them and obtaining informed consent. However, the latter does not mean that the CCMO is in favour of a systematic application of the postponement option (e.g. of 72 hours,). It would be reasonable to determine for each

[4] The aforementioned Regulations explicitly state that even after withdrawal of consent to participate in the investigation, personal data collected up to that point have been lawfully processed. However, specifically for the situation of deferred consent, the same Regulations include the possibility for the participant or his/her legal representative - if deferred consent is not given for the (continued) participation - to object to the use of data already collected. However, the aforementioned Regulations do not make it clear whether such objections should always be honoured. The MREC has no role in this particular issue. Where appropriate, the (former) study participant may lodge a complaint with the institution and/or the Dutch Data Protection Authority (Dutch DPA: Autoriteit Persoongegevens) on the grounds of failure to comply with the objection to the processing of personal data.

study to what extent a deferral period is necessary (depending on specific circumstances and factors).
The procedure (including fixed timeslots) for investigating (repeatedly if need be) the possibilities for informing and obtaining informed consent from legal representatives should be laid down in the protocol. It is up to the MREC to assess whether the procedure is appropriate in the light of the study in question.

It may also be taken into account that there is room in the aforementioned Regulations to differentiate between situations in which the investigational procedures (including data collection) have already been completed before the possibility of obtaining informed consent arises and situations in which the investigational procedures are (or must be) continued after deferred consent has been obtained. If the investigational procedures have already been completed, the legal representative's consent only relates to the processing and analysis of data (and body materials) in the context of the medical research. More time and space can be taken to inform the legal representative and to obtain informed consent. In cases where there is a continuation of the investigational procedures, this time limit should be as narrow as possible. The latter applies in particular if a new investigational procedure is carried out as part of the study and/or certain investigational procedures involving a burden or risk are repeated (such as an invasive test or administration of an investigational medicinal product).

3. Did the subject die before the consent of the legal representative had been obtained?

Explanatory note
Should the subject die before consent has been obtained, the question arises whether data and body materials collected during the study may be kept to be used for study purposes and, if so, under what conditions. In an article in the Tijdschrift voor Gezondheidsrecht [iv] as well as in the 3rd WMO evaluation report [i], Ploem et al. noted several legal interpretations of this issue. Jansen, Bakker and Kompanje argue - in a publication on the impact of not using data of deceased participants from whom no deferred consent had been obtained [v] - that disregarding those data can lead to unreliable conclusions on the investigated intervention. Other publications on medical research in emergency situations drawing of incorrect conclusions when the data of deceased participants (from whom no deferred consent was obtained) are disregarded. In the opinion of the CCMO, these arguments place too much emphasis on the importance of reliable results and in particular on the question of what the subject himself or herself would have wanted. As the study participant has died, this can no longer be formally established, partly because the next of kin of the subject, after death, no longer fulfil the role of legal representative. A study carried out under deferred consent was approved by an MREC, which gave greater weight to the possible benefits for the patient than to the chance of adverse effects. As long as consent cannot be obtained, the study may be continued. This situation actually continues after the death of the study participant. Therefore CCMO argues that basically, the data of deceased subjects may be used for the study in question (provided that those subjects have not objected to this in a general sense while alive). It should be noted that, even though after the death of the subject, the next of kin no longer have a formal legal role to play in the further conduct of the study, it is reasonable from the point of view of transparency and ethical awareness to inform them and to underline the importance of this issue for the proper completion of the study. Should a relative/ next of kin nevertheless object to this, one may - depending on the circumstances - consider honouring this objection. The CCMO considers this to be an appropriate working method, which - as expected - will not affect public support for the use of collected personal data and body material.

4. Obtain informed consent of the subject's legal representative to continue subject's participation in the study as soon as possible.

Explanatory note
If informed consent has been given by the representative(s), the subject's informed consent to continue participation in the study must be obtained as soon as the subject is able to do so (see step 1);
If the legal representative does not give his or her consent, he or she must be informed that he or she may object[4] to the use of data previously obtained from the study.

References

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ii. Kompanje EJO, Jansen TC, Le Noble JLML, et al. Uitgestelde toestemming voor inclusie van beslissingsonbekwame patiënten in studies van spoedeisende geneeskunde. Ned Tijdschrift Geneeskd 2008; 152: 2060.
iii. Timmers M., van Duijn D., Kompanje E.J.O., Medisch-wetenschappelijk onderzoek in spoedeisende situaties. Ned Tijdschr Geneeskd 2019;163: D3857.
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v. Jansen T.C., Bakker J., Kompanje E.J.O. Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trials. Intensive Care Med 2010; 36: 1962-1965.