Standard Operating Procedure for patient information and deferred informed consent in the CASES trial

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"SOP: Voorlichtingsgesprek en uitgesteld informed consent CONTRAST trials"

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Contents

1. Aim

This standard operating procedure (SOP) details the complete informed consent (IC) process, also known as "*deferred informed consent*", of the CASES trial. This procedure consists of providing the possible study participants and/or legal representatives with information about the trial through an informative conversation, handing over and discussing the Participant Information Sheet (PIS) and the final joint signing of the informed consent form (ICF) according to the local applicable laws and regulations.

2. Range

This SOP applies to the local Principal Investigators (PIs) and for all qualified research assistants (including research nurses) involved in the deferred consent procedure of participating centers within the CASES trial.

3. Definitions and abbreviations

CASES	Carotid Artery Stenting during Endovascular treatment for acute ischemic Stroke
CONTRAST	the Collaboration for New Treatments of Acute Stroke
CT	Computer Tomography
CTA	Computer Tomography Angiography
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form
ISF	Investigator Site File; participating center in multicenter research
ISSF	Investigator Subject Site File;
METC	Medical Research Ethics Comittees
NIHSS	National Institutes of Health Stroke Scale
PI	Principal Investigator
PIS	Participant Information Sheet
SOP	Standard Operating Procedure
Sub-I	Sub-Investigator
TMF	Trial Master File
VWS	Dutch Ministry of Health, Wellbeing and Sports
WMO	Dutch law pertaining to medical scientific research with human participants

4. Responsibilities

It is the responsibility of the local PI to ensure that the consent procedure (i.e., the informative conversation, the handing over and explanation of the PIS and the signing of the ICF) is carried out carefully and performed as described in the study protocol (and any amendments) in compliance with the applicable laws and regulations.

In practice, the research staff (e.g., involved co-/sub-investigators, research assistants or study coordinators) will usually perform this task. In this SOP, these employees are referred to as the delegates. It is recommended that a physician is involved in all parts of the consent procedure or at least is available to answer any medical questions.

It is the responsibility of the local PI to ensure that all delegates involved in the consent procedure are trained accordingly. It is the responsibility of the PI's of the National Coordinating centers (UMC

Groningen for the Netherlands and UZ Leuven for Belgium) to make this SOP available to all local PI's of participating centers within the CASES trial.

Delegates must be listed on the "Site Signature and Delegation Log". It is expected that all parties involved in the consent procedure are aware of the sub-objectives of the national applicable legislation and regulations, ICH-GCP guidance, Declaration of Helsinki and the CASES study protocol.

5. Procedures

5.1 General information

Each subject who is asked to participate in a medical-scientific research study (or his/her legal representative) must be fully informed about all aspects of participation in medical-scientific research. This means that, in addition to providing oral information, written information must also be provided in an understandable form and language. Also, if important new information becomes available during or possibly even after the end of the trial thought to be relevant to the subject, he/she or the legal representative should be informed about it.

Many CONTRAST trials investigate treatment in patients with acute cerebral infarction or acute cerebral hemorrhage. Due to this severe brain disorder, most patients will be unable to express their will in the acute setting. According to national laws (more specifically the "WMO art. 6, para. 4" in the Netherlands and the "Wet van 7 mei 2004 inzake experimenten op de menselijke persoon" in Belgium), it is permitted to have actions performed in the context of scientific research if in an emergency setting the required consent cannot be given and if the study action can benefit the person in this setting. This means that consent may also be obtained from the subject or his/her legal representative after randomization and/or the start of an intervention. The research ethics committees (METC's in the Netherlands and the Research Ethics Committee UZ/KU Leuven [Central Committee] together with the local Ethics Committees in Belgium) have allowed this procedure within the CASES trial.

5.2 Deferred informed consent procedure

The consent procedure of this trial (and other CONTRAST trials) is substantially different from the usual consent procedure.

- The subject has already been included and randomized in the study and (depending on the randomization result) may have undergone study actions.
- Consent is requested for further participation in the trial and for the use of the data already available in the trial so far.
- The delegate should explain why a deferred consent procedure is used for these studies.
    - The patient was in an acute emergency setting.
    - There was no time to ask for consent in this emergency setting.
    - In this emergency setting, a patient or legal representative is insufficiently able to oversee the situation, take in the information relevant to the investigation and make a well-considered decision.
    - In addition, in most cases, because of the brain disorder, the patient is unable to absorb the information sufficiently to make a well-considered decision.
- The delegate must state that the deferred consent procedure has been approved by the applicable research ethics committees.
- At the end of this document, you can find some suggestions for the deferred informed consent conversation.

5.3 Preparation

1. Immediately after randomization, specify in the subject's source document that a deferred consent procedure is being used for this study and that consent will be requested as soon as possible.

   Example text for in the source document: "Given the urgent nature of the situation and the patient's condition, the process of obtaining informed consent prior to study participation has been waived and the procedure of deferred consent will be used (in accordance with the national applicable legislations). As soon as possible after randomization, as soon as the situation allows for it, the subject or his legal representative will be asked for consent for (the continuation of) study participation."

2. Make sure you are familiar with the background of the study and the relevant study activities. Carefully read the PIS and ICF.
3. If the conversation cannot be held with the patient, the conversation will be held with the legal representative. Conduct the conversation with a maximum of 2 people.
4. If applicable, find someone to serve as an impartial witness if the person being asked for consent cannot read and/or write.
5. Organize an interpreter if the person being asked for consent does not speak the same language as the person performing the procedure.

5.4 Deferred informed consent in mentally competent and mentally incompetent patients

Necessary documents:

- In the Netherlands:
  - For mentally competent subjects: "Informatiebrief en toestemmingsformulier patient"
  - For mentally incompetent subjects: "Informatiebrief en toestemmingsformulier wettelijk vertegenwoordiger"
    - When the participant's mental competence is restored, see *section 5.5* (only applicable in the Netherlands).
- In Belgium:
  - For mentally competent subjects: "Information and consent form participant/legal representative" (available in Dutch, French and English)
  - For mentally incompetent subjects: "Information and consent form participant/legal representative" (available in Dutch, French and English)

If the subject does not have a formal legal representative (guardian or mentor) then the following person can sign the consent form (in this hierarchical order):

- The person authorized in writing to do so by the participant. If this person is missing, then:
- The spouse, registered partner of other life companion. If this person is missing, then:
- A parent, adult child, or an adult brother or sister of the subject.

Indicate in the source documents if certain representatives are missing so that it is clear why, for example, a brother has given consent instead of an adult child.

In case of no consent from patient of legal representative, see *section 5.6.*

In the event of the patient's death before consent was obtained from the patient of legal representative, see *section 5.7*.

Activities:

1. Inform the subject (or legal representative) orally, in writing and in understandable language about the research and the consent procedure. Include the PIS/ICF.
2. Give the subject (or legal representative) sufficient time* and the opportunity to read the PIS and ICF, to inquire about the details of the study, to ask questions and to decide whether to participate in the study.

   * Note: Consent should be obtained as soon as possible after randomization. It is up to the delegate to assess whether the patient or his/her legal representative is already able and at peace to process the information. If this is not possible, describe the reasons for the lack of consent and what actions were taken to speak to a legal representative in the source documents and still try to obtain consent as soon as possible afterwards.

3. Review all sections describing what the subject (or legal representative) consents to.
4. Inquire whether the subject (or legal representative) has understood all aspects of the study and/or whether there are any questions, and if so, answer all questions.
5. Sign the ICF together with the subject (or legal representative) and, if the subject (or legal representative) cannot write and/or read, have the independent witness sign it after spoken consent from the subject (or legal representative).
6. The PI or delegate who has discussed the trial with the subject (or legal representative) should be the last to sign the ICF.
7. Provide the subject (or legal representative) with a copy of the PIS and the signed ICF or have 2 copies signed. The original signed PIF/ICF must be kept in the ISSF (at the provider) or in the ISF (at the participating center in multicenter research).
8. Indicate in the source documents of the study participant that any questions have been answered and that he/she (or legal representative) has given written consent to participate in the study, and that a copy of the signed PIF/ICF (or 2nd signed original) has been provided, stating the date. Also consider informing the participant's general practitioner and treating physician.
   If consent is not obtained, indicate this in the source documents and follow the procedure under *section 5.6 "Procedure in case of no consent".*

   Example text: "PIS and ICF handed over and explained on DD-MM-YYYY. ICF signed on DD-MM-YYYY and one copy of PIS and ICF given to participant/patient (or legal representative). The participant/patient (or legal representative) has been fully informed and all questions about the study have been answered satisfactorily."

5.5 Procedure when mental competence is restored (only applicable in the Netherlands)

1. When the temporarily mentally incompetent patient has regained his/her mental competence, he/she must be informed as soon as possible, i.e., at the next contact, about his/her participation in the study.
2. The subject should be given the opportunity to decide on further participation if research activities (such as 90 days follow-up) are going to take place. Use form "Informatiebrief en toestemmingsformulier tweede instantie" for this purpose

3. The same rules regarding signing and storage of the PIS and ICF apply as described above. Include the above example text for acquired informed consent in the participant's source documents.

5.6 Procedure in case of no consent

1. There is an additional appendix "Use of clinical data in the absence of consent " (in Dutch: "Gebruik klinische gegevens bij geen toestemming").
2. If the subject or legal representative does not consent to further participation in the trial, he/she must indicate separately in this additional appendix whether he/she objects to the use of data already collected, in coded (not directly traceable) form.
3. In Belgium, the subject must also separately indicate whether he/she objects to the use of research data already collected for the purpose of possible future scientific research carried out in accordance with recognized ethical standards.
4. The same rules regarding signing and storage of the PIS and ICF apply as described above. Include this in the source documents of the subject.

5.7 Procedure in case of death

In the Netherlands:

1. In the event that the patient has died before consent could be obtained, the legal representative must be informed that the patient has participated in the study. If possible, the legal representative should also be informed about the study treatment that may have been received, the procedures of the trial and the use of the collected data.
2. A separate information letter will be sent to the legal representative by or on behalf of the local principal investigator 2-3 weeks after the death of the patient.
3. All data will be used as if full consent had been obtained.

In Belgium:

1. In the event that the patient has died before consent could be obtained, the legal representative must be informed that the patient has participated in the study. If possible, the legal representative should also be informed about the study treatment that may have been received, the procedures of the trial and the use of the collected data.
2. A separate information letter for the legal representative is available and will be handed over or sent by post.
3. All data will be used as if full consent had been obtained.

6. Suggestions for obtaining deferred consent

Discuss diagnosis, treatment, and any study treatment the patient has received.

- Consent is requested for:
  - further participation in the trial and;
  - The use of the data already collected in the trial's context.
- Explain why a deferred consent procedure is used.
  - The patient was in an acute emergency setting.
  - There was no time to ask for consent in this emergency situation.
  - In this emergency setting, the patient or legal representative is insufficiently able to oversee the situation, to take in the information relevant to the research and to make a well-considered decision.

    - Because of the brain disorder, the patient is unable to absorb the information sufficiently to make a well-considered decision
    - Now we can take our time and answer all your questions.
- Explain that the deferred consent procedure is described in the national legislation and has been approved by the responsible ethical committees.

Explain what the trial involves:

- Purpose of the research/hypothesis
- Randomization and randomization result
- Study actions (which ones had, which ones will follow, follow-up)
- Pros and cons
- Voluntary participation
- All information is also included in an information letter
- Permission requested as soon as the situation allows

Situation in case of no consent or in case of deceased patient

- See *sections 5.6 and 5.7*

7. Related documents

In the Netherlands (available in Dutch):

- Informatiebrief en toestemmingsformulier patiënt
- Informatiebrief en toestemmingsformulier wettelijke vertegenwoordiger
- Informatiebrief en toestemmingsformulier patiënt in tweede instantie
- Informatiebrief na overlijden

In Belgium (all available in Dutch, French and English):

- Information and consent form – participant/legal representative
- Information letter for legal representative in case of decease

8. References

- ICH GCP E6 (R2); Guideline for Good Clinical Practice
- Clinical Trials – Directive 2001/20/EC
- Clinical Trials – Regulations EU No 536/2014
- CCMO website: www.ccmo.nl
- Wet Medisch-wetenschappelijk Onderzoek met mensen (artikel 6 lid 4) – the Netherlands
- Wet van 7 mei 2004 inzake experimenten op de menselijke person – Belgium

9. Annex: study actions CASES