CONTRAST

DIST Standard Operation Procedures

Information provision and deferred informed consent in the subacute phase

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1. PURPOSE

This standard operating procedure (SOP) describes the entire deferred *informed consent* (IC) process, also known as *deferred consent* (DC) or deferred consent procedure. This procedure consists of providing research-specific information to subjects and/or legal representatives by means of an information interview, handing over and discussing the subject information form (PIF) and finally signing the *informed consent* form (ICF) together according to the applicable laws and regulations.

2. SCOPE

This SOP applies to the local principal investigator (PI) and his/her delegates of investigator-initiated research subject to WMO who are involved in the deferred consent procedure in the Dutch ICH Surgery Trial (DIST), conducted as part of the *Collaboration for New Treatments of Acute Stroke* (CONTRAST).

3. DEFINITIONS AND ABBREVIATIONS

CCMO	Central Committee on Research Involving Human Subjects
Co-I	Co-Investigator
CONTRAST	Collaboration for New Treatments of Acute Stroke
CT	Computed Tomography
CTA	Computed Tomography Angiography
DC	Deferred Consent
DIST	Dutch ICH Surgery Trial
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form
ICH	Intracerebral hemorrhage
ISF	Investigator Site File; at participating center multicenter research
ISSF	Investigator Subject Site File; at Sponsor
REC	Medical Ethics Review Committee
PI	Principal Investigator
PIF	Subject Information Form
RN	Research Nurse
SC	Study coordinator
SOP	Standard Operating Procedure
Sub-I	Sub-Investigator
TMF	Trial Master File
VWS	Ministry of Health, Welfare and Sport
WMO	Medical Research Involving Human Subjects Act (Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen)

4. RESPONSIBILITIES

It is the responsibility of the local PI that the consent procedure (i.e. the information interviews, handing over and explaining the PIF and signing the ICF), is carried out carefully, proceeds as described in the study protocol (and any amendments) and complies with the applicable laws and regulations.

In practice, the study staff (e.g. the Co-I/Sub-I or RN/SC involved) will usually perform this task. In this SOP, these employees are referred to as the delegates. It is recommended that a physician be involved in all parts of the consent process or at least be available to answer any medical-substantive questions.

It is also the responsibility of the local PI to ensure that all study staff involved in the consent procedure are trained in this SOP. It is the responsibility of the central PIs to make this SOP available to all researchers and staff of the aforementioned trials.

Delegates must be listed on the Site *Signature and Delegation Log*. It is expected that all those involved in the consent procedure are demonstrably aware of the relevant parts of the legislation and regulations (WMO/GCP), *Declaration of Helsinki* and study protocol that are relevant to their research activities.

5. PROCEDURES

5.1 General

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

Many CONTRAST trials are investigating treatment in patients with an acute cerebral infarction or acute intracerebral hemorrhage (ICH). Because of this serious brain disorder, most patients in the acute stage will be incapacitated. According to the WMO (art 6, paragraph 4), it is permitted to allow actions to take place in the context of scientific research if the required permission cannot be given in the emergency situation and the study act can benefit the person who is in the emergency situation. This means that even after randomization and/or starting an intervention, permission can be requested from the subject or his/her legal representative. The MREC has allowed this under special conditions.

5.2 Postponed *informed consent* procedure

The consent procedure within DIST is substantially different from the usual consent procedure.

- The subject has already been enrolled in the study and may have undergone study actions (depending on the randomization result).

- Permission is requested for further participation in the trial and the use of the data collected up to that point in the context of the study.

- The investigator should explain the reasons why a deferred consent procedure is used for these studies.
    - The patient was in an acute emergency situation.
    - In this emergency situation, there was no time to ask for permission.
    - In this emergency situation, a patient or legal representative is insufficiently able to oversee the situation and to take in the information relevant to the investigation and to make an informed decision about it.
    - In addition, in most cases, due to the brain disorder, the patient is unable to absorb the information sufficiently to make an informed decision about it.

- The researcher must state that the deferred consent procedure has been approved by the MREC.

- At the end of this document you can find some suggestions for the postponed informed consent conversation

5.3 Preparation

1. Please state in the participant's source document (medical record) immediately after randomization that a deferred consent procedure will be used for this study and that consent will be requested as soon as possible.

   Text for medical record: "In view of the urgent nature of the situation and the condition of the patient, the requested consent prior to study participation has been waived and the *deferred consent procedure* (in accordance with the legislation) will be used. As soon as possible after randomization, as soon as the situation allows, permission will be requested from the subject or their legal representative for (the continuation of) study participation."

2. Make sure you are familiar with the background of the study and the relevance of study activities. Read the MREC-approved PIF and ICF carefully.

3. If the conversation cannot be conducted with the patient, the conversation should be conducted with the legal representative. Have the conversation with a maximum of 2 people.

4. If applicable, find someone who can act as an impartial witness if the person being asked for permission cannot write and/or read.

5. Use an interpreter if the person being asked for permission does not speak your language, unless the person conducting the authorisation procedure speaks the language of that person.

5.4 Deferred consent procedure for incapacitated and incapacitated patients

Required documents:

- In the case of a mentally competent subject: Use the form "Information letter and consent form patient"

- In the case of an incapacitated subject: Use the form "Information letter and consent form legal representative"

If the subject does not have a formal legal representative (curator or mentor), then approach for consent in this hierarchical order:

- the person authorized to do so in writing by the subject. If missing, then:
- the spouse, registered partner or other life companion. If missing, then:
- a parent, an adult child, or an adult sibling of the subject.

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

- In the event of restoration of the patient's mental capacity, after a legal representative has given permission in the previous instance: Use the form "Information letter and consent form patient in the second instance".

- In case of no consent from patient or legal representative: Use the additional form "Use clinical data in case of no consent" behind the relevant information letters. The patient or legal representative can object to the use of data that has already been collected, in encrypted (not directly traceable to the person) form. See also **chapter 5.6.**

- In the event of the death of the patient before consent could be obtained from the patient or legal representative: use the form "Information letter for representative after death". See **chapter 5.7**.

Procedures:

1. Inform the subject (or legal representative) verbally, in writing, and in understandable language about the study and the consent procedure. Hand the PIF/ICF.

2. Give the subject (or legal representative) ample time* and opportunity to read the PIF 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**. The researcher should assess whether the patient or his legal representative is ready to process the information and provide adequate consent. If this is not possible, describe the reasons for the lack of permission and what actions have been taken to speak to a legal representative in the source document (medical record) and try to get permission as soon as possible after this*.

3. Go through all sections describing what the subject (or legal representative) is consenting to.

4. Inquire whether the subject (or legal representative) has understood all aspects of the study and/or if there are any questions and, if so, answer all questions.

5. Have the patient (or legal representative) write down their name, date and sign the ICF in duplicate. If the subject (or legal representative) cannot write and/or read, verbal permission from the subject (or legal representative) together with independent witness signing is sufficient.

6. The principal investigator or delegate who conducted the explanation about the study procedures with the subject (or legal representative) should sign the ICF last.

7. Give the subject (or legal representative) a copy of the PIF and the signed ICF or have two ICF forms signed. The original signed PIF/ICF must be kept in the ISF.

8. Mention in the subject's source documents (medical record) that any questions have been answered and that he/she (or legal representative) has given written permission to participate in the study, and that a copy of the signed PIF/ICF (or 2nd signed original) has been provided with the date. Also think of informing the general practitioner and the treating physician of the test subject.

   If no permission is obtained, note this in the source documents and follow the procedure under **chapter 5.6** Procedure in case of no permission.

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

5.5 Procedure for regaining legal capacity

1. When the temporarily incapacitated subject has regained mental capacity, he/she must be informed about his/her participation in the study as soon as possible, i.e. at the next contact.

2. The subject should be given the opportunity to decide on further participation if any research activities (such as the 90-day assessment) are going to take place. Use 'Information letter and consent form patient in second instance' for this.

3. The same rules regarding the signing and storage of the PIF and ICF apply as described above. Please mention the above in the medical status.

5.6 Procedure in case of no consent

1. As part of the ICF, an extra appendix 'Use clinical data if consent is not given' is provided.

2. If the subject (or legal representative) does not consent to further participation in the trial, he/she must indicate separately in this appendix whether he/she objects to the use of the data collected up to that point, in encrypted (not directly identifiable to the person) form.

3. The same rules regarding the signing and storage of the PIF and ICF apply as described above. Please mention the above in the medical status.

5.7 Procedure in case of death of the subject before obtaining consent

1. In the event that the patient has died before permission could be requested, the legal representative must be **informed** of the fact that the patient has been included into a trial.

If this conversation allows, the legal representative should also be informed about the possible study treatment, 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 patient's death.

3. All data will be used as if full permission has been obtained.

6. SUGGESTIONS FOR OBTAINING DEFERRED CONSENT

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

- Permission is requested for:
  - further participation in the trial and;
  - the use of the data collected up to that point in the context of the study.

- Explain why a deferred consent process is used.
  - The patient was in an acute emergency situation.
  - In this emergency situation, there was no time to ask for permission.
  - In this emergency situation, the patient or legal representative is insufficiently able to oversee the situation and to take in the information relevant to the investigation and to make an informed decision about it.
  - Because of the brain disorder, the patient cannot absorb the information sufficiently to make an informed decision about it.
  - Now we can take our time and answer all your questions.

- Tell them that the deferred consent procedure is described in the law and has been **MREC** approved.

Explain what the study entails:

- Aim of the study / hypothesis
- Randomization and randomization result
- Study actions (which ones have had, which ones will follow, follow-up)
- Pros and Cons
- Further participation is voluntary
- All information is also in the information letter
- Permission requested as soon as the situation allows

Situation in case of no consent or death of patient

- See chapters 5.6 and 5.7

7. SPECIFIC INFORMATION PER STUDY

7.1. DIST

An additional document is available for the DIST in which tools are given for the conversation to be held with the patient and/or his legal representative in the acute phase:

1. by the healthcare provider in a general hospital for referral to a neurosurgical center;
2. by the healthcare provider in the neurosurgical center who includes the patient.

The document **DIST tools conversation in the acute phase** can be found on the DIST website: trial protocol and documents.

An overview of all study activities in the context of the DIST is included in Annex 1.

8. RELATED DOCUMENTS

- Information letter and patient consent form
- Information letter and consent form legal representative
- Information letter and consent form patient in second instance
- Information letter for representative after death

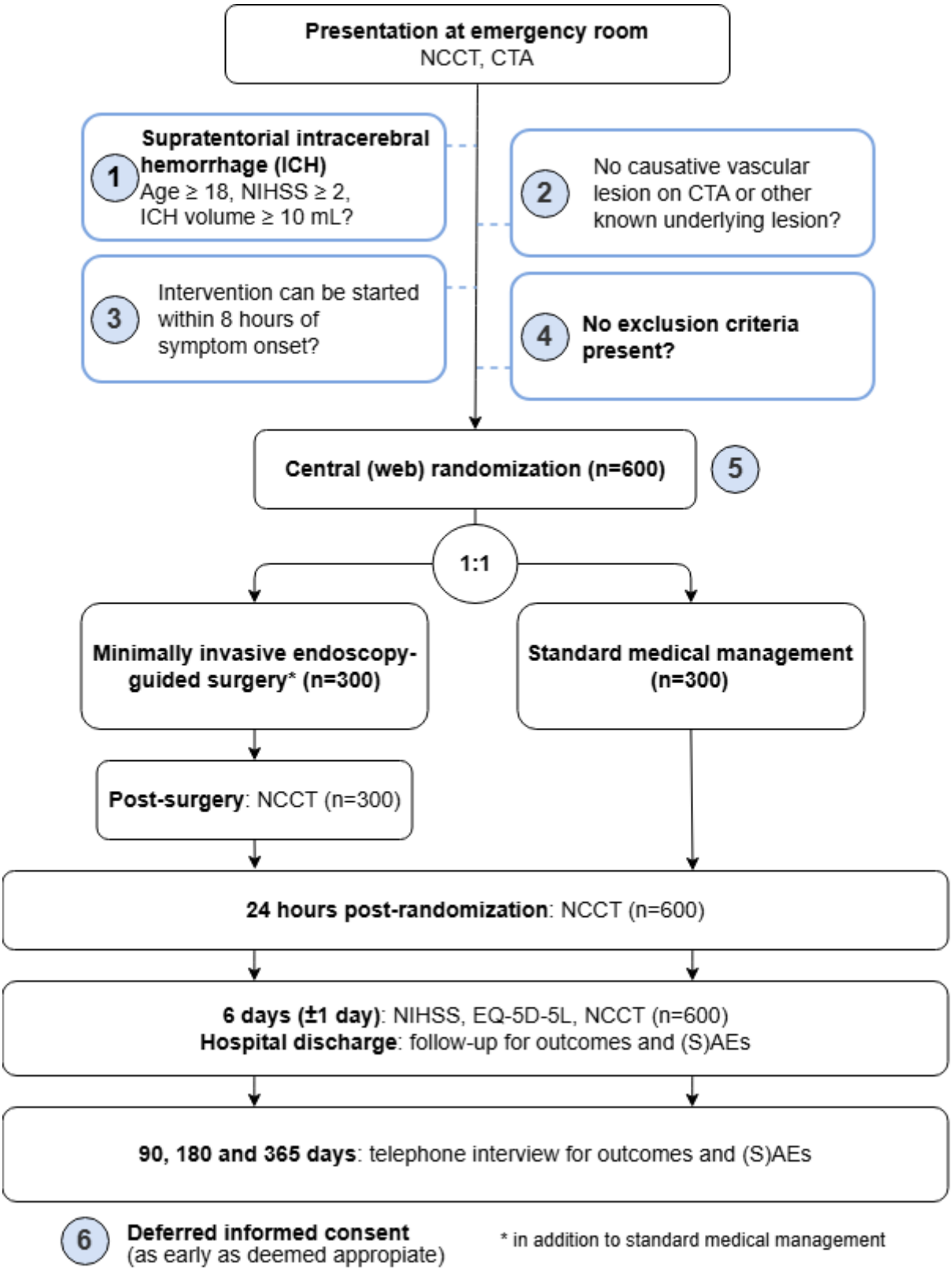
9. CREDENTIALS

- ICH E6 (R2) Guideline for good clinical practice
- Clinical Trials - Directive 2001/20/EC
- Clinical Trials - Regulation EU No 536/2014
- CCMO website: www.ccmo.nl
- Medical Research Involving Human Subjects Act (including Article 6 paragraph 4)

10. DOCUMENT HISTORY

Version	Description of change	Date of implementation
1.0	First version of SOP. Author: S.A. van den Berg. Authoriser: H.B. van der Worp	16-02-2018
1.1	Adjustment of period in which deferred consent must be obtained	29-03-2018
2.0	Adjustments of SOP for the new CONTRAST studies using a deferred consent procedure	28-02-2023

11. ANNEX 1: FLOW CHART STUDY ACTS DIST



CTA: Computed tomography angiogram; EQ-5D-5L: EuroQol 5-dimensions 5-level; ICH: intracerebral hemorrhage; NCCT: Non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; (S)AEs: (Serious) Adverse Events.