PRINCESS2

ULTRAFAST HYPOTHERMIA IN CARDIAC ARREST

PRINCESS2 TRIAL FOLLOW-UP MANUAL

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1. Introduction

The primary outcome of the PRINCESS2 trial is *survival with complete neurologic recovery at 90 days, defined as modified Rankin scale (mRs) of 0-1.* Several of the secondary endpoints also evaluates neurologic recovery at different time points. An adequate follow up by blinded assessor is therefore of great importance for the validity of the trial.

Outcome will be assessed at hospital discharge and at 90 days and 1 year from randomization. For further information on each assessment, see below.

Monitoring and data quality controls will be performed during the study.

2. The blinded outcome assessor

The outcome assessor performing the follow-up in the PRINCESS2 trial must be ***completely blinded*** for group allocation. The outcome assessor may be an occupational therapist, physician, research nurse, psychologist or similar. The number of outcome assessors at every site should be kept to a minimum, e.g. 1-2 per site. All outcome assessors should be aware of the importance of their role in collecting high quality unbiased data. All outcome assessors should also study this follow-up manual carefully.

3. Follow up at hospital discharge

At hospital discharge the patient should be assessed according to the mRs-scale. This is preferably done by a face-to-face visit with the patient but can also be done by collecting medical records from the last days at hospital.

4. Follow up at 90 days

Timing: The 90-day follow should take place at the earliest 90 days from randomization, and as close as possible to 90 days.

Setting: The 90-day follow-up will preferably take place face-to face. The patient will be invited to a clinic visit. For patients unable to attend the clinical visit, a telephone follow-up can be performed.

Patient invitation: An invitation should be sent 2-4 weeks ahead of the visit (by written letter or a telephone call). In this invitation, the following should be clearly stated:

- That the outcome assessor *has no knowledge of group allocation* (whether the patient belongs to the intervention group or control group) and that this should not be discussed at any time during the visit
- That the patient is strongly encouraged to bring a close relative or someone that knows them very well to the visit
- That the patient should bring hearing or vision aids if applicable

During the follow up meeting: The steps below should be followed:

1. Start by reminding the patient and their company that you are not allowed to have any information about the study intervention, and that they cannot reveal this to you during the follow-up visit.

2. Explain briefly the study and purpose of the follow-up and the tests. Explain that you will not be able to provide any information on results of the follow-up.
3. Perform the structured interview for the mRS scoring (see section 6.1)
4. If you do not have enough information to do a CPC-scoring, ask additional questions (see section 7).
5. Let the patient fill in the EQ-5D-5L questionnaire (see section 8)
6. You may now need to ask additional questions to complete the mRS and CPC scoring based on your general expression of the patient's outcome.
7. Inform the patient that they will be invited for a similar follow up at 12 months
8. Thank the patient and the person accompanying them for their participation and for their valuable contribution to the study.

After the follow-up meeting:

- Complete the mRS and CPC scoring
- Transfer the results to the eCRF as soon as possible
- Transfer the results from the EQ5D-5L to the CRF as soon as possible
- If data is missing despite several reminders/attempts to contact the patient, please note potential reasons in the eCRF comments field

5. Follow up at 1 year

At 1 year, the patients should be assessed according t the mRS-scale. This can be done at a clinic visit or during a telephone follow-up by a structured interview described in section 6.

6. Modified Rankin Scale (mRS)

The mRS measures overall functional outcome after a neurologic insult, including degree of disability and dependence in daily activities.

The final mRS score is represented by 7 categories:

0. No symptoms at all
1. No significant disability despite symptoms; able to carry out all usual duties and activities
2. Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3. Moderate disability; requiring some help but able to walk without assistance
4. Moderately severe disability, unable to walk without assistance and unable to attend to own bodily need without assistance
5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6. Dead

6.1 Structured interview and scoring

The mRS score is established by performing a brief structural interview with the patient and the person accompanying him/her. Start with question 1 *"Do you have any symptoms that bother you?"*. It is important to include a broad range of symptoms that are common after cardiac arrest such as; memory or attention issues, problems with executive functions (reduced planning or organization), fatigue, anxiety, depression or posttraumatic stress.

Use the mRS calculator available at www.modifiedrankin.com for scoring. If patients and the person accompanying him/her give conflicting answers about disabilities, generally use the worse outcome reported.

Question 1: Do you have any symptoms that are bothering you? (YES/NO)

Question 2: Are you able to do the same work as before? (YES/NO)

Question 3: Are you able to keep up with your hobbies? (YES/NO)

Question 4: Have you maintained your ties to friends and family? (YES/NO)

Question 5: Do you need help making a simple meal, doing household chores, or balancing a checkbook? (YES/NO)

Question 6: Do you need help with shopping or traveling close to home? (YES/NO)

Question 7: Do you need another person to help you walk? (YES/NO)

Question 8: Do you need help with eating, going to the toilet, or bathing? (YES/NO)

Question 9: Do you stay in bed most of the day and need constant nursing care? (YES/NO)

7. Cerebral Performance Category Scale (CPC scale)

The CPC scale ranges from CPC 1 to CPC 5 and measures functional outcome after cardiac arrest. Based on the information gathered during the follow up, especially while performing the structured interview for mRS scoring, the patient can be categorised according to the CPC-scale.

Worst level of performance for any single criterion is used for categorizing. Deficits are scored only if they result from a neurologic disorder.

CPC scale:

1. Good cerebral performance (conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (eg, mild dysphasia, non-incapacitating hemiparesis, minor cranial nerve abnormalities))
2. Moderate cerebral disability (conscious, with sufficient cerebral function for part-time work in sheltered environment or to do independent activities of daily life (eg, dress, travel by public transportation, prepare food), may have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes)
3. Severe cerebral disability (conscious, but dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. Includes a

wide range of neurologic dysfunction, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence to those who are paralyzed and can communicate only with their eyes (as in the locked-in syndrome).

4. Unconscious (coma or vegetative state, unaware of surroundings, no cognition. No verbal or psychologic interaction with environment).
5. Death (meeting criteria for brain death or dead by traditional criteria)

8. The EuroQol Health Survey 5 Dimensions, The 5 Levels Response Version (EQ-5D-5L)

The EQ-5D-5L is a standardized measure of health-related quality of life consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), and a VAS scale of overall self-reported health. The EQ-5D-5L could be interpreted descriptively as a health profile by the answers of each dimension that range from no problems to extreme problems. The EQ-5D-5L could also be converted into a single index value of health. The index value may be used to calculate Quality Adjusted life years (QALYs). The EQ VAS score is not included in the EQ-5D-5L scoring but is interpreted separately. In general, a score of >70 on the VAS scale is considered to indicate no health problems. For further information see https://euroqol.org/

8.1 Instructions for EQ-5D-5L questionnaire

1. Explain to the patient that you would like to know more about how they perceive their health.

2. Give the patient the paper version of the EQ-5D-5L.

3. Turn to the second page with the five dimensions and explain; *"Under each heading, please tick the ONE box that best describes your health TODAY"*. Explain that only one tick per heading (dimension) is allowed. You are allowed to read the items and the answers to the patient if needed, but neither you nor the person accompanying the patient are allowed to help or discuss their answer. You might need to clarify that they should answer each item based on what he/she think each items means, and that there are no right or wrong answers.

If the patient is not able to complete the EQ-5D-5L due to cognitive disability, the person accompanying the patient may assist, but this must be noted in the comments field in the eCRF. If there is an obvious reason for concern that the patient has provided a response that may not be accurate e.g. the patient actually lives in a nursing home but the patient states that they have no problems doing their usual activities, or when the person accompanying the patient does not agree with the patients answer, this person may also complete their own version of the EQ-5D-5L based on their perception of the patient's health, in addition to the version completed by the patient

4. When all 5 dimensions are completed, turn to the next page and present the EQ VAS scale for the patient. Tell the patient *"mark an X on the scale to indicate how your health is TODAY"* and then *"write the number you marked on the scale in the box below".*

If data on EQ-5D-5L is totally missing, describe in the comments field potential reasons why the patient was unable to answer, and if this was related or unrelated to their health.

Store the paperversion of the EQ-5D-5L together with other trial material at each site.