EuroHYP-1: European multicentre, randomised, phase III clinical trial of therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke

Clinical trial phase	Phase III
Clinical trial short title	EuroHYP-1
EudraCT number	2012-002944-25
Eudamed number	CIV-12-09-008821
Indication	Acute ischaemic stroke
Planned trial period	July 2013 – March 2017 (45 months)
Version number	5.0
Date	24 June 2016

Sponsor	University Hospital Erlangen represented by the Dean at Medical Faculty Friedrich-Alexander-Universität Erlangen-Nürnberg Maximiliansplatz 2 91054 Erlangen

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Sponsor

Date	Professor Dr. med. Dr. h.c. Jürgen Schüttler Dean, Medical Faculty Friedrich-Alexander-University Erlangen-Nürnberg

Coordinating Investigator

I have read this clinical trial protocol, approve of its content, and declare that the clinical trial will be conducted in accordance with the Declaration of Helsinki, the ICH-GCP principles and all applicable regulations.

Professor Dr. med. Dr. h.c. Stefan Schwab
International Coordinating Investigator
Department of Neurology
University Hospital Erlangen

Date _____

Signature _____

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-HT	5-hydroxytryptamine
5-HT_{1A}RA	5-HT_{1A} receptor agonist
5-HT_3RA	Selective 5-HT_3 receptor antagonist
A	Assessment
AE	Adverse event
AHA	American Heart Association
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
bpm	Beats per minute
BSAS	Bedside Shivering Assessment Scale
BT	British Telecommunications
C	Celsius
C5a	Complement Component 5a
CCS	Center for clinical studies
CD	Compact disc
CDC	Center for Disease Control
CE	Conformité Européene
CI	Confidence interval
cm	Centimetre
CPR	Cardiopulmonary resuscitation
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CT	Computed tomography
CYP	Cytochrome P450
d	Day
DAMOCLES	Data Monitoring Committees: Lessons, Ethics, Statistics
DSMC	Data and safety monitoring committee
DVD	Digital versatile disc
DVP	Data validation plan

DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylinidiaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQoL 5 dimensions 5 level questionnaire
ERC	European Resuscitation Council
ESO	European Stroke Organisation
EU	European Union
EudraCT	European clinical trial database
FLAIR	Fluid attenuated inversion recovery
FP7	Seventh Framework Programme
GCP	Good clinical practice
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acid protein
GSTP	Glutathione S-transferase P
h	Hour
H-FABP	Heart-type fatty acid binding protein
HIE	Hypoxic ischaemic encephalopathy
HT	Hypothermia
IB	Investigator’s brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IL	Interleukin
IMD	Investigational medical device
IMP	Investigational medicinal product
INN	International non-proprietary name
INR	International normalized ratio
IRB	Institutional review board
ISO	International Organization for Standardization
ITT	Intent to treat
IU	International unit
i.v.	Intravenous
IVC	Inferior Vena Cava

IVTM	Intravascular temperature management
kg	Kilogram
l	Litre
LBP	Lipopolysaccharide-binding protein
MBL	Mannose-binding lectin
mg	Milligram
mHLA	Monocytic human leukocyte antigen
ml	Millilitre
mm^3	Cubic millimetre
MCAR	Missingness completely at random
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
msec	Millisecond
N	Number of non-missing observations
NDKA	Nucleoside diphosphate kinase a
NGAL	Neutrophil gelatinase-associated lipocalin
NIHSS	National Institutes of Health Stroke Scale
NNT	Number needed to treat
NSE	Neuronspecific enolase
NYHA	New York Heart Association
PCT	Procalcitonin
Ph.Eur.	European Pharmacopoeia
PI	Principal investigator
p.o.	Per os
PPS	Per protocol set
ProANP	Pro atrial natriuretic peptide
ProBNP	Pro brain natriuretic peptide
RMP	Risk management plan
RNA	Ribonucleic acid
RNABP	RNA binding protein
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System software

SC	Standard of care
SE	Standard error
SMP	Safety management plan
SmPC	Summary of product characteristics
SMS	Short message service
SOP	Standard operating procedure
S_pO_2	Oxygen saturation in peripheral blood
SSL	Secure socket layer
sTNF RI	Soluble tumor necrosis factor receptor I
TIMP	Tissue inhibitor of metalloproteinases
TP	Treatment phase
UFD	Ubiquitin fusion degradation protein
ULN	Upper limit of normal
UK	United Kingdom
USA	United States of America
USB	Universal Serial Bus
WBC	White blood cells
WHODAS	World Health Organization Disability Assessment Schedule

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1 SYNOPSIS

Clinical trial title

EuroHYP-1: European multicentre, randomised, phase III clinical trial of therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke

Clinical trial phase

Phase III.

Clinical trial design

Multicentre, open-label, randomised, parallel-group, with blinded outcome assessment.

Indication

Acute ischaemic stroke.

Clinical trial objectives

Primary objective

To determine whether systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

Secondary objectives

- To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, in patients with acute ischaemic stroke on
  - mortality at 3 months.
  - neurological outcome at 3 months.
  - quality of life at 3 months.
  - cerebral infarct size at 48±24 hours.
- To determine the safety and tolerability of systemic cooling in patients with acute ischaemic stroke.

Other objectives

To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, in patients with acute ischaemic stroke on

- selected biomarkers.
- other imaging parameters.
- cost-effectiveness parameters.

Total number of patients and number of countries

800 patients in approximately 15 countries.

Number of clinical trial sites

Minimum 60.

Planned clinical trial period

July 2013 – March 2017 (45 months).

Clinical trial population, diagnosis and main criteria for inclusion

The trial population consists of patients of both sexes, aged ≥18 years, with acute ischaemic stroke and a score on the NIHSS of at least 6 at screening [Assessment 1, within 90 minutes before the start of the treatment phase TP].

- Written informed consent obtained from the patient or his/her legally acceptable representative or under such other arrangements as may be legally established in participating countries.
- Estimated body weight of 50kg up to and including 120kg.
- Possibility to start therapeutic hypothermia within 6 hours after onset of stroke.
- Possibility to start therapeutic hypothermia within 150 minutes after start of alteplase administration in patients receiving thrombolysis at the trial site or within 150 minutes after start of endovascular treatment, if this is later.
- Possibility to start therapeutic hypothermia within 150 minutes after admission to trial site in patients not receiving thrombolysis or in patients who have received thrombolysis at a different site.
- mRS score ≤2 prior to onset of stroke.
- GCS motor response subscale score ≥5.

Investigational medical devices (CE marked)

During the treatment phase [TP], cooling in patients randomised to therapeutic hypothermia will be performed using one of the following four cooling devices:

- Medivance/Bard Arctic Sun temperature management system with
  - Heat exchange control unit Arctic Sun 2000 or Arctic Sun 5000
  - ArcticGel Pads
- BrainCool BrainCool System and BrainCool cooling pads
- MTRE CritiCool temperature management system with
  - Heat exchange control unit CritiCool
  - Accessories
  - CureWrap 3500
- Zoll intravascular temperature management system with
  - Heat exchange control unit CoolGard 3000 or Thermogard XP
  - CoolGard Start-up Kit
  - Intravascular temperature management catheters ICY 3893 AE or ICY 3893 CO or Quattro 4593 AE or Quattro 4593 CO

The choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly and may not be switched during treatment. The use of any other cooling device or system is prohibited during the course of the clinical trial except for the EMCOOLS Brain.Pad (see below).

EMCOOLS Brain.Pad and EMCOOLS Flex.Pad

For the purpose of induction of cooling, the EMCOOLS Brain.Pad and EMCOOLS Flex.Pad may be used in patients randomised to therapeutic hypothermia during the first hour of the treatment phase [TP, Hour 1] for a maximum of 60 minutes in addition to the administration of 4°C isotone saline or Ringer's lactate and concomitantly to one of the cooling systems mentioned above. Its use is left at the discretion of the investigator.

Investigational medicinal products, dose and route of administration

For the purpose of prevention and treatment of shivering, patients randomised to therapeutic hypothermia will receive the following investigational medicinal products:

- Pethidine hydrochloride (INN) 50mg/ml solution for injection
- Buspirone hydrochloride (INN) 10mg tablets

Buspirone will be administered as tablets *via* the oral route to patients randomised to therapeutic hypothermia prior to induction of cooling and prior to administration of pethidine. Repeat doses of 10mg p.o. may be administered as long as a maximum

dose of 30mg/24h is observed. Patients who have difficulties swallowing will not receive buspirone unless they have a nasogastric tube.

For the prevention of opioid-induced nausea and vomiting, the administration of a 5-HT_3RA as support medication is recommended. An i.v. bolus, slowly administered over at least 30 seconds, or an infusion over 15 minutes of either ondansetron 8mg or granisetron 3mg will be administered to patients randomised to therapeutic hypothermia prior to the induction of cooling and prior to the administration of pethidine. In accordance with the recommendations of the respective SmPC, repeat doses of the selected 5-HT_3RA may be administered for the prevention and treatment of nausea and vomiting during the cooling and re-warming periods as long as the minimum interval between subsequent injections is respected and the maximum daily dose is not exceeded.

For patients randomised to therapeutic hypothermia, a bolus of pethidine 50mg, injected i.v. over a period of about 2 minutes, will be administered prior to the induction of cooling. Subsequently, if the patient experiences discomfort or shivering, or other signs of poor tolerance of cooling become apparent or are anticipated, a bolus of pethidine 25mg i.v. may be given as long as an interval between pethidine injections of at least 30 minutes is respected and a maximum dose of 500mg/24h is not exceeded.

All patients (i.e., in both treatment groups) will have their S_PO_2 levels continuously monitored through peripheral pulse oximetry for at least 24h. If in a patient receiving pethidine, S_PO_2 levels fall below 90% despite oxygen administration *via* a nasal cannula or if there is a decrease of ≥2 points on the GCS motor response subscale compared to the value at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], no further pethidine doses will be administered until the patient has recovered to a S_PO_2 level ≥90% and the motor response has returned to the value at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] minus 1 point.

Duration of study treatment per patient

Hypothermia and best medical treatment group

Maximum of 22 hours (cooling period 12 hours, re-warming period up to 10 hours).

Best medical treatment alone group

22 hours.

Follow-up

All patients will be followed up until outcome assessment [A7, Day 91±14 days].

Number of assessments

8 assessments.

Variables for analysis

The primary and secondary outcomes and the primary safety variable will be analysed using the ITT population.

Exploratory analyses which include additional variables as well as the above variables, but using the per protocol population, will be conducted and the results discussed and contrasted to the primary results.

Values to be used in the primary analyses

Efficacy variables

Primary outcome measure

Score on the mRS at outcome assessment [A7, Day 91±14 days], as analysed with ordinal logistic regression and expressed as a common odds ratio.

Secondary outcome measures

- Death or dependency, defined as a score on the mRS >2 at outcome assessment [A7, Day 91±14 days].
- Death at outcome assessment [A7, Day 91±14 days].
- Score on NIHSS at outcome assessment [A7, Day 91±14 days].
- Brain infarct size at imaging assessment [A4, Hour 48±24 hours].
- WHODAS 2.0 score at outcome assessment [A7, Day 91±14 days].
- EQ-5D-5L score at outcome assessment [A7, Day 91±14 days].

Primary safety variable

- Occurrence of SAEs until outcome assessment [A7, Day 91±14 days].

Variables for explorative analyses

The analyses of the primary and secondary outcomes will be repeated using the per protocol set (PPS). In addition, the variables defined below will be subjected to analyses using the ITT as well as the PPS.

Intervention variables

- Time until achievement of target temperature, duration of active cooling, duration of therapeutic hypothermia, total dose of anti-shivering and support medications, distribution of IMDs used for cooling purposes, and BSAS during the treatment phase [TP] (hypothermia group only).
- Patient experience at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

Economic variables

- Type and number of disposable IMD items used during the treatment period [TP] and the re-warming period.
- Distribution of patients' location in hospital at 12:00 hours from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Length of hospital stay after stroke onset, defined as interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Patients' destination at day of discharge from hospital.
- Number of visits to health care professionals and hospital, and home time at outcome assessment [A7, Day 91±14 days].
- Total length of stay and total healthcare resource use during interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to outcome assessment [A7, Day 91±14 days].
- Costs of primary hospital admission, defined as interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Total costs of stroke during interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to outcome assessment [A7, Day 91±14 days].

Safety variables

- Incidence of pneumonia from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first].
- Occurrence of AEs and SAEs related to the administration of IMPs or treatment with an IMD.

The following variables will be evaluated for supportive safety purposes:

- Values of blood pressure, heart rate and respiratory rate during the treatment phase [TP], at assessment 2 [A2, End of Hour 24±2], at assessment 3 [A3, Hour 48±4 hours], at assessment 5 [A5, Hour 72±4 hours], at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

Other variables

- Change in biomarker concentrations from baseline [sample collected between beginning of screening assessement A1, within 90 minutes before the start of the treatment phase TP, and 60 minutes after start of the treatment phase TP] to assessment 2 [A2, End of Hour 24±2] and to assessment 5 [A5, Hour 72±4 hours].

Further variables for analysis include patient disposition, frequencies of protocol deviations, concomitant therapies, and the results of the patient survey.

Statistical analysis methods

Final statistical analyses will be carried out by statisticians at The Copenhagen Trial Unit. The Copenhagen Trial Unit is independent of the DSMC and will perform the final statistical analysis once the sample size has been reached or when the EuroHYP-1 steering committee stops the trial.

Pseudonymised, cleaned and validated data, masked to intervention, will be delivered by the data management work package to The Copenhagen Trial Unit for analysis. The results reported to the EuroHYP-1 steering committee will be blind to the intervention. Unblinding will only happen after all analyses are finalised and two unbiased conclusions have been written, one assuming that one group is the hypothermia group and the other assuming that the same group is the normothermia group.

Efficacy, safety and economic variables

All analyses will be based primarily on the ITT population and additionally, for sensitivity purposes, on the PPS.

Primary outcome measure

The primary efficacy variable, the score on the mRS at the outcome assessment [A7, Day 91±14 days], will be determined with multi-level, ordinal logistic regression. If the assumption of the ordinal regression analysis model is not fulfilled, the groups will be compared using non-parametric method (Mann Whitney) and the result will be the primary result. If the assumption of the model is fulfilled, the result of an adjusted analysis will be the primary result. The adjusting variables will include the following minimisation factors:

- Intention to perform thrombolysis (yes *vs*. no).
- Method of cooling (surface *vs*. endovascular).
- Sex (male *vs*. female).
- Stroke severity (NIHSS 6-12 *vs*. 13 or higher).
- Age (≤65 years *vs*. >65 years).
- Visibility of a relevant ischaemic lesion on the first brain imaging (yes *vs*. no).
- Time since symptom onset (≤4 hours *vs*. 4–6 hours).

The primary efficacy variable is a candidate for an analysis using multiple imputations (see criterion defined above). If the variable is subjected to such an analysis the result will be the primary result.

Secondary outcome measures and safety variables

Logistic regression with and without adjustment (see above) and the general linear univariate model with or without adjustment will be used as appropriate. If the assumptions of the general linear univariate model cannot be fulfilled, a non-parametric test will be used (Mann Whitney).

Interim analyses

The DSMC will monitor the safety of the patients in the EuroHYP-1 trial by reviewing the available clinical data after 50, 100, 200, 400, and 600 patients have been recruited and followed up until outcome assessment [A7, Day 91±14 days] and *ad hoc* as needed. With respect to efficacy and hazard, the committee will conduct interim analyses on partially cleaned data after outcome assessment [A7, Day 91±14 days] of the first 400 patients. Details on procedures and threshold values are defined in the DSMC charter.

2 CLINICAL TRIAL ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	Function	Address
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2.2 External responsibilities

The sponsor will maintain a list of all principal investigators in a separate document.

The administrative structure for external responsibilities includes, but is not limited to, the following participants:

Name	Function	Address
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2.3 Committees

2.3.1 EuroHYP-1 executive committee

The EuroHYP-1 executive committee is responsible for the design of the trial, for maintaining the quality of the trial conduct and the safety of patients, and for drafting trial publications. The EuroHYP-1 executive committee has the right to stop the clinical trial if indicated. Protocol modifications can only be made if commissioned by the EuroHYP-1 executive committee. A list of its members is kept in a separate document.

2.3.2 EuroHYP-1 steering committee

The EuroHYP-1 steering committee approves the clinical trial protocol and its amendments prior to their submission and implementation. The steering committee has final responsibility for trial publications. The chairperson of the EuroHYP-1 steering committee is one of the addressees of the DSMC for recommendations regarding the trial conduct. A list of its members is kept in a separate document.

2.3.3 EuroHYP-1 data and safety monitoring committee

Efficacy and safety data from the clinical trial will be evaluated by a DSMC at predetermined points in time, to ensure that the continuation of the trial is appropriate and to make recommendations to the sponsor, the chairperson of the EuroHYP-1 executive committee and the chairperson of the EuroHYP-1 steering committee. The DSMC will consist of permanent members who are not associated with the sponsor or with the operative conduct of the trial. A description of the scope of work and operating procedures for the DSMC is provided in Section 11.5.2.2. A list of DSMC members and a copy of the DSMC charter will be kept in a separate document.

2.3.4 EuroHYP-1 ethics board

The EuroHYP-1 ethics board approves the design of the clinical trial and all aspects of protection of patients' rights in the clinical trial protocol and its amendments prior to submission to regulatory authorities and IECs/IRBs. The ethics board also approves the charter of the DSMC and the working instructions for reviewers of the outcome adjudication committee as well as the SMP from an ethical point of view. A list of its members and a copy of its charter are kept in a separate document.

2.3.5 EuroHYP-1 scientific advisory board

The EuroHYP-1 scientific advisory board will be consulted by the EuroHYP-1 executive committee and steering committee regarding the design and implementation of the clinical trial. The scientific advisory board will review the clinical trial protocol and its amendments prior to submission to regulatory

authorities and IECs/IRBs and implementation. It will also review the trial set-up plans prior to implementation and monitor the trial progress. Whenever required, the EuroHYP-1 scientific advisory board will advise the EuroHYP-1 executive committee and steering committee on improvements to trial performance. A list of its members is kept in a separate document.

2.3.6 EuroHYP-1 outcome adjudication committee

The EuroHYP-1 outcome adjudication committee is commissioned by the sponsor to assess the primary efficacy variable of the clinical trial. All members of the EuroHYP-1 outcome adjudication committee are specialists highly experienced in the field of stroke. Its members are blind to the patient's treatment assignment when performing their assessments. A list of members together with copies of the manual for investigators and the working instructions for reviewers are kept in a separate document.

2.3.7 EuroHYP-1 serious adverse event adjudication committee

The EuroHYP-1 SAE adjudication committee is commissioned by the sponsor to review and assess all SAE reports and to ensure expedited reporting of relevant reports to regulatory authorities and IECs/IRBs (if applicable). A list of its members and a copy of the SMP are kept in a separate document.

3 INTRODUCTION

3.1 Clinical trial background

3.1.1 Epidemiology and pathophysiology of ischaemic stroke

Acute ischaemic stroke is a condition caused by occlusion of one of the cerebral arteries or arterioles and is typically characterised by the sudden onset of a focal neurological deficit. Common deficits include dysphasia, dysarthria, hemianopia, unilateral weakness, ataxia and sensory loss. Thirteen to 23% of patients die within the first month and of those who survive, a third are left dependent on others in their activities of daily living [Feigin 2009, Heuschmann 2011].

The social and economic burden of stroke is enormous. Stroke is the second cause of lost disability-adjusted life years in high-income countries and the second cause of death worldwide [Lopez 2006]. In people aged 55 years or more, the incidence generally ranges from 4.2 to 6.5 per 1,000 person-years [Feigin 2003]. The direct lifetime costs per ischaemic stroke in Germany have recently been estimated at € 43,129. Rehabilitation and chronic nursing care account for the largest part of these costs [Kolominsky-Rabas 2006]. As stroke incidence rates rise exponentially with age, the social and economic burden of stroke will further increase with the ageing of the population [Lopez 2006].

Ischaemic brain injury results from a complex cascade of events running from energy depletion to necrosis or apoptosis [Dirnagl 1999]. Intermediate factors include excitotoxicity, free radical formation and inflammation. Initially after arterial occlusion, a central core of very low perfusion is surrounded by an area with dysfunction from metabolic and ionic disturbances, but in which structural integrity is still preserved, the so-called ischaemic penumbra. In the first minutes to hours, clinical deficits therefore do not necessarily reflect irreversible damage. For this reason, the penumbra is the target of treatment for acute ischaemic stroke. Depending on residual blood flow and duration of ischaemia, the penumbra may eventually be incorporated into the infarct if reperfusion is not achieved [Dirnagl 1999].

3.1.2 Current treatment options

About 500 treatment strategies have been shown to improve outcome in animal models of acute ischaemic stroke [O'Collins 2006]. By contrast, only early intravenous thrombolysis with alteplase, the administration of aspirin, and decompressive surgery have been proven efficacious in patients despite numerous clinical trials of other treatment strategies [Van der Worp 2007, Donnan 2008].

The use of intravenous thrombolysis is currently limited to the first 4.5 hours following the onset of symptoms [Hacke 2008, Lees 2010], and even in high-income countries, only a small minority of patients with acute stroke receives this therapy [Douglas 2005, van Wijngaarden 2009]. In addition, about half of the stroke patients

remain dependent or die despite thrombolysis [Wahlgren 2007, Wahlgren 2008, Wardlaw 2009, Lees 2010, Wardlaw 2012].

Aspirin can be given to a broad range of patients with acute ischaemic stroke, but the benefit is small, with a NNT of 79 to prevent poor outcome in a single patient [Sandercock 2008].

Decompressive surgery is highly effective, but it is indicated only for the very small minority of patients with space-occupying infarction [Vahedi 2007, Hofmeijer 2009].

Given the limitations of established treatment options on one side and the immense public health challenge and economic impact of stroke on the other side, there is an obvious unmet need for new, effective therapeutic strategies.

3.2 Clinical trial rationale

One of the reasons for the failure of allegedly neuroprotective strategies to improve functional outcome in patients may be that most inhibit only a single step in the chain of events leading to cell death [STAIR 1999, Gladstone 2002]. By contrast, hypothermia affects a wide range of cell death mechanisms, including energy depletion, disruption of the blood-brain barrier, free radical formation, excitotoxicity, and inflammation [Zhao 2007, Yenari 2008]. In a systematic review of animal studies of therapeutic hypothermia for acute ischaemic stroke, comprising 277 comparisons and involving over 3,000 animals, cooling reduced infarct size by 44% [95% CI 40 to 47%]. The effect of cooling on functional outcome was broadly similar [Van der Worp 2007].

Moreover, convincing clinical evidence of the neuroprotective properties of therapeutic hypothermia is available from randomised clinical trials and from meta-analyses by the Cochrane Collaboration in the fields of global cerebral ischaemia after cardiac arrest and resuscitation in adults and hypoxic-ischaemic brain injury in newborns (see Sections 3.2.1.1 and 3.2.1.2).

3.2.1 Evidence from other indications

3.2.1.1 Hypothermia in cardiopulmonary resuscitation

A Cochrane review [Arrich 2009] identified three randomised clinical trials that investigated the effects of therapeutic hypothermia on neurological outcome and survival in patients after CPR and that used comparable protocols and endpoints. The trials involved a total of 383 patients (195 in the cooling group, 188 receiving standard treatment). For all trials, the investigators provided individual patient data to the reviewers.

Patients in the hypothermia group were more likely to have a favourable neurological recovery during hospital stay [RR 1.55; 95% CI 1.22 to 1.96] with a NNT of 6 [Bernard 2002] and to survive to hospital discharge [RR 1.35; 95% CI 1.10 to 1.65] with a NNT of 7 [Zeiner 2000] compared to standard post-resuscitation care. The incidence of adverse events was comparable between both groups.

Therapeutic hypothermia as part of post-resuscitation care is now recommended in both the AHA and the ERC guidelines for CPR [Nolan 2010, Peberdy 2010].

In the recent international Target Temperature Management 33°C versus 36°C after Out-of-Hospital Cardiac Arrest (TTM) trial which was not included in the above-mentioned Cochrane review, 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause were randomised to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36°C group (225 of 466 patients) (hazard ratio with a temperature of 33°C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P = 0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P = 0.78). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (risk ratio, 1.01; 95% CI, 0.89 to 1.14; P = 0.87). Based on the results of this trial, it is concluded that in unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer any greater benefit compared with a targeted temperature of 36°C [Nielsen 2013]. The absence of a normothermic group means that this study cannot challenge the findings of the previous Cochrane review.

3.2.1.2 Hypothermia in hypoxic ischaemic encephalopathy in newborns

Another Cochrane review [Jacobs 2007] assessed the impact of therapeutic hypothermia on survival and neurodevelopmental outcome in newborns with HIE. Therapeutic hypothermia resulted in a clinically relevant reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [RR 0.76; 95% CI 0.65 to 0.89] with a NNT of 7 [95% CI 4 to 14]. Cooling also resulted in a reduction in mortality [RR 0.74; 95% CI 0.58 to 0.94] and of neurodevelopmental disability in survivors [RR 0.68, 95% CI 0.51 to 0.92]. Adverse effects of hypothermia included an increase in the need for inotropic support of borderline significance and an increase in thrombocytopenia.

The authors concluded that therapeutic cooling provides a statistically significant and clinically relevant favourable effect on long-term outcome in newborns with HIE.

3.2.2 Hypothermia in acute ischaemic stroke

3.2.2.1 Evidence from animal and clinical trials

In a systematic review of animal studies of therapeutic hypothermia for acute ischaemic stroke, including 277 experimental comparisons and involving 3,353 animals, cooling reduced infarct size by 44% [95% CI 40% to 47%] on average. The effect of hypothermia on functional outcome was broadly similar. The

benefit of hypothermia was inversely related to the temperature achieved [Van der Worp 2007].

In most clinical trials involving therapeutic hypothermia for other indications (see Sections 3.2.1.1 and 3.2.1.2), the target body temperature ranged from 32°C to 34°C [Den Hertog 2009]. Cooling to these levels generally requires deep sedation, tracheal intubation, mechanical ventilation, and admission to an intensive care unit. While this course of action is routinely followed for CPR and HIE patients, this is highly impractical for stroke patients, even in a clinical study setting, due to the limited availability of beds in such services in most countries. Moreover, deep sedation precludes a close assessment of the patient's neurological status after intravenous thrombolysis and would thereby exclude the majority of patients from hypothermia within the time window of 6 hours.

Fortunately, cooling to a lesser extent may still mediate substantial clinical benefit for patients with ischaemic stroke. In animal studies, cooling to 34°C or below resulted in a reduction of infarct size of 40% or more. Yet infarct size was still reduced by 30% [95% CI 21% to 39%] with cooling to 35°C, suggesting that even mild hypothermia has considerable potential as a neuroprotective strategy [Van der Worp 2007]. Moreover, there is evidence from three randomised, controlled clinical trials indicating that therapeutic hypothermia is feasible in awake patients with ischaemic stroke (Table 1).

Table 1 Summary of randomised, controlled clinical trials involving therapeutic hypothermia in awake patients with acute ischaemic stroke

Clinical trial acronym	COOL AID	NOCSS	ICTuS-L	Helsinki
Target body temperature	33°C	34.5-35.5°C	33°C	35ºC
Method of cooling	Endovascular (IVC)[1]	Surface	Endovascular (IVC)[1]	Surface
Duration of cooling	24 hours	9 hours	24 hours	12 hours
Time window for inclusion[2]	12 hours (presentation)	6 hours (cooling induced)	6 hours (presentation)	6 hours (cooling induced)
Number of patients enrolled (HT/SC)	40 (18/22)	44 (22/22)	58 (28/30)	36 (18/18)
Number (%) of patients treated with alteplase	28 (70.0)	2 (4.6)	26 (44.8)	36 (100)
Anti-shivering medication (mean dose[3])	Pethidine i.v. (12.5mg/kg = 1,000mg), buspirone p.o.	Pethidine i.v. (346mg = 5.8mg/kg)	Pethidine i.v. (14.5mg/kg = 1,160mg), buspirone p.o.	Pethidine i.v (total dose unknown), dexmedetomidine
Number (%) of patients reaching target temperature in HT	13 (72.2)	17 (77.3)	20 (71.4)	16 (89%) reached <35.5ºC
Death or dependency	No difference after 30 days	No difference after 90 days	No difference after 90 days	No difference after 90 days

Clinical trial acronym	COOL AID	NOCSS	ICTuS-L	Helsinki
Number of deaths till end of follow-up/group size	HT 5/18 SC 4/22	HT 7/22 SC 5/22	HT 6/28 SC 5/30	HT 0/18 SC 2/18
Number of complications or SAEs/group size	HT 16/18 SC 14/22	HT 4/22 SC 5/22	HT 40/28 SC 22/30	HT 19/18 SC 12/18
Number of pneumonia cases/group size	HT 2/18 SC 2/22	HT 1/22 SC 2/22	HT 7/28 SC 2/30	HT 7/18 SC 2/18

HT = hypothermia and best medical treatment group; SC = best medical treatment alone group
[1] Cooling catheter inserted into IVC
[2] Interval between onset of stroke and admission to hospital ("presentation") or induction of cooling ("cooling induced")
[3] Reported value (first value) converted into calculated value (second value) assuming a mean body weight of 80kg

None of the three clinical trials was powered to demonstrate superiority of one treatment over the other. While the COOL AID and ICTuS-L trials were designed as safety and/or feasibility trials from the beginning [De Georgia 2004, Hemmen 2010], the NOCSS trial was planned as a confirmatory trial, but for different reasons failed to recruit the necessary number of 1,000 patients [Weber 2008]. Nevertheless, valuable insights can be derived from these trials for the design of a confirmatory phase III trial.

- Time is the most critical factor in the treatment of cerebral ischaemia [Dirnagl 1999, Lees 2010]. In two of the three trials quoted above, COOL AID and ICTuS-L, the time window for inclusion into the trial was probably too long. Patients had to present themselves in hospital within 12 hours (COOL AID) and 6 hours (ICTuS-L) after onset of stroke to be eligible. Patients had then to undergo a CT or MRI, and most received alteplase. Cooling therefore started rather late.
- In all three trials, the majority of patients randomised to cooling reached the target temperature, irrespective of the cooling method and the target level of hypothermia.
- Cooling failures mainly fell into two categories:
  - Technical problems with the medical device used.
  - Strong thermoregulatory reactions which could not be overcome in some patients.
- None of the three trials used rapid infusion of cold saline or other isotonic solution for induction of hypothermia, although this principle is well established [Nolan 2010]. Such infusion might have led to faster achievement of target body temperature.
- Pethidine, an opioid approved in various countries for treatment of severe pain, was used in all three trials as anti-shivering medication, an off-label indication. In the trials targeting a body temperature of 33°C (COOL AID and ICTuS-L), the mean doses administered over 24 hours amounted to 1,000mg and 1,160mg, respectively, for a patient with a body weight of 80kg. These quantities are well above the recommended daily doses for pethidine (e.g., 500mg in Germany [Sanofi-Aventis Deutschland 2014]) and led to clinically relevant sedation of

patients in at least one trial (ICTuS-L). In the NOCSS trial, which targeted a body temperature of 34.5°C to 35.5°C for 9 hours, about 350mg of pethidine was administered.

- In the ICTuS-L trial, a substantially higher number of SAEs and pneumonias occurred in cooled patients compared to normothermic participants.

  Unfortunately, the authors provide neither an explanation how SAEs were defined, nor a list of the SAEs observed, nor statements on the relatedness of the SAEs to the cooling procedure *per se* or to pethidine administration. This precludes any firm statement on the relative risk of hypothermia over standard treatment.

  Likewise, the algorithm used for a diagnosis of pneumonia is not given, and it is unclear whether the diagnosis led to any therapeutic consequences such as treatment with antibiotics or discontinuation of hypothermia. In absolute figures, the difference is small with seven cases of pneumonia in cooled patients *vs*. two incidences in normothermic patients.

  The risk of other clinically relevant AEs such as death, deep vein thrombosis, urinary tract infection, pancreatitis, renal failure or cardiac arrhythmia was similar in both groups. The primary efficacy variable, death or dependency after 90 days, was not negatively influenced by these events.

  In the other two trials, no difference between groups regarding SAEs or pneumonia was observed.

3.2.2.2 Justification for a confirmatory phase III clinical trial

After many disappointments with potentially neuroprotective interventions, therapeutic hypothermia today represents the best chance for acute ischaemic stroke patients to gain major benefit in terms of neurological and functional outcome. The proof of principle for therapeutic hypothermia has been provided in patients after CPR and in newborns with HIE. Although these patient populations differ from patients with acute ischaemic stroke, the underlying pathophysiological mechanisms leading to neuronal cell death are broadly similar.

Important preliminary work on the effect of therapeutic hypothermia compared to normothermic treatment in awake patients with acute ischaemic stroke has been published in recent years [De Georgia 2004, Weber 2008, Hemmen 2010]. Although too small to demonstrate superiority of one treatment over the other, the three clinical trials provide clarifications on various parameters pivotal for the success of a confirmatory phase III clinical trial, e.g., on target body temperature, time to onset and duration of cooling and the use of anti-shivering medication (see Section 3.2.2.3), thus creating a rational basis for the determination of an acceptable balance between desired therapeutic effect and tolerability of cooling.

3.2.2.3 Considerations regarding major clinical trial design issues

3.2.2.3.1 Cooling methods

Two major approaches for inducing and maintaining therapeutic hypothermia in stroke patients are available: surface cooling and endovascular cooling [Van der Worp 2010].

Surface cooling is not invasive, widely available and can be combined with concurrent thrombolysis, but may elicit strong responses from thermoregulatory defence mechanisms.

Endovascular cooling via a cooling catheter inserted into the IVC should not be initiated during intravenous thrombolysis because it may result in groin hematomas and requires some expertise for the correct placement of the device. However, hypothermia can be quickly induced and well maintained, even in patients with an elevated BMI, and the method allows supplemental surface warming for patient comfort and shivering suppression.

Both approaches have been successfully applied and proven to be safe in other clinical scenarios and in the feasibility trials in patients with ischaemic stroke. Most centers familiar with therapeutic cooling have already chosen a preferred method. The choice of the cooling method will therefore be left to the discretion of the local investigators.

In order to accelerate the induction of hypothermia, all patients randomised to cooling will receive 20ml/kg estimated body weight of 4°C isotone saline or Ringer's lactate over a period of 30 to 60 minutes. The infusion of such volumes of fluids is generally safe and well tolerated in patients with cardiac arrest or ischaemic stroke [Kim 2005, Kim 2007, Kollmar 2009]. In addition to infusion of cold fluid, surface cooling to the neck and shoulders with the EMCOOLS Brain.Pad [Kallmünzer 2011] during the first hour of treatment may be performed.

3.2.2.3.2 Target body temperature

In a systematic review and meta-analysis of animal stroke studies, the benefit of hypothermia was inversely related to the temperature achieved [Van der Worp 2007]. Therefore, the target body temperature should be set as low as tolerated in the awake patient. In animals, cooling to 34.0°C and 35.0°C resulted in a reduction of infarct size of 30 to 45% [Van der Worp 2007].

Hypothermia leads to activation of the physiological thermoregulatory defence mechanisms [Sessler 2009] which have to be overcome to achieve therapeutic hypothermia. Generally, an anti-shivering regimen is administered to alleviate patient discomfort and suppress shivering.

To achieve a target body temperature of 33°C in awake stroke patients, high doses of pethidine, well above the maximum daily doses recommended for treatment of severe pain, had to be administered in the COOL AID and ICTuS-L trials. The ample doses of pethidine lead to sedation and sometimes impaired respiration in these

patients. It is therefore, that in this trial the target temperature is set between 34.0°C and 35.0°C requiring much lower doses of pethidine.

The range between 34.0°C and 35.0°C rather than a fixed target temperature will allow investigators some flexibility during cooling without violating the trial protocol.

3.2.2.3.3 Time of onset and duration of cooling

Based on results from preclinical studies, time is the most critical factor in the treatment of stroke [Dirnagl 1999]. This is supported by findings from a pooled analysis of randomised clinical trials of intravenous thrombolysis with alteplase, in which the benefit was greater the sooner treatment was started [Lees 2010]. Expediting the delivery of care is therefore considered a crucial factor in any acute ischaemic stroke trial.

In the above-mentioned meta-analysis of animal studies, the effect of hypothermia was most consistent when treatment was started before or at the onset of ischaemia, but the benefit remained substantial with treatment delays of up to 6 hours [Van der Worp 2007]. In the HACA trial, cooling improved functional outcome after cardiac arrest, despite a median interval of 8 hours between the restoration of spontaneous circulation and the attainment of the target temperature [Zeiner 2000]. There are no data on the latest time possible to start cooling in patients with acute ischaemic stroke. However, it is expected that the potential benefit will be greater the earlier cooling is started.

The time window for treatment with alteplase, if indicated, is limited from onset of stroke to 4.5 hours thereafter, in accordance with its SmPC currently approved in the EU. With a time window of 6 hours to start of therapeutic hypothermia, all patients who receive thrombolysis within the recommended 4.5 hours after symptom onset may be enrolled into this trial.

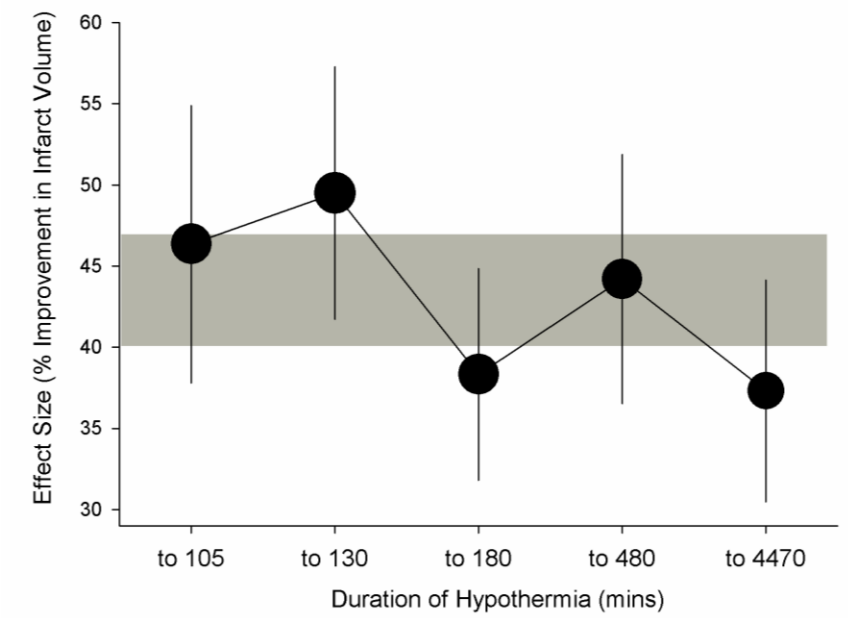
To promote the rapid induction of hypothermia in this trial, cooling will be started

- within 150 minutes after start of intravenous alteplase administration in patients receiving thrombolysis at the trial site or within 150 minutes after start of endovascular treatment, if this is later.
- within 150 minutes of admission to the trial site in patients not receiving intravenous alteplase or in patients who have received thrombolysis at a different site.

No adequate information is available with regard to the optimal duration of hypothermia in acute ischaemic stroke patients. On theoretical grounds, efficacy may increase with the duration of cooling. Animal studies that compared the effect of cooling for 12 hours or more with that of cooling for 3 hours or less found a considerably larger benefit with longer treatment durations. However, in meta-analysis of results from animal studies of hypothermia for acute ischaemic stroke, no relation was observed between the duration of cooling and the effect on infarct size or functional outcomes (Figure 1) [Van der Worp 2007]. Most information was available for cooling for a period of 2 to 6 hours. Periods of hypothermia beyond

24 hours may not be well tolerated by awake patients and may be associated with a higher risk of complications [Van der Worp 2010].

Figure 1 Relation between duration of hypothermia and effect size (reduction in infarct volume) in animal models of acute ischaemic stroke



A period of 24 hours of therapeutic hypothermia proved to be safe in patients with global cerebral ischaemia after cardiac arrest [Zeiner 2000]. Randomised phase II trials have demonstrated that in awake patients with acute stroke, endovascular cooling for 24 hours [Hemmen 2010, de Georgia 2004] and surface cooling for 12 hours [Piironen 2014] are feasible. There are no published randomised trials in patients with acute stroke that have tested surface cooling for longer durations, and its feasibility and safety are therefore uncertain. Shorter durations of cooling are likely to be better feasible and acceptable to patients and may be associated with a lower risk of pneumonia.

The aim of hypothermia is to prevent irreversible damage in ischaemic brain tissue. By far most of this irreversible damage and infarct expansion occur in the first 6 to 12 hours after symptom onset [Dirnagl 1999], and hypothermia should therefore be targeted to this time frame. Considering all available evidence summarised above, including the data from animal studies, a duration of 12 hours of therapeutic hypothermia has therefore been chosen for this trial.

3.2.2.3.4 Anti-shivering medication

Irrespective of the method used to lower core body temperature, cooling induces the activation of the thermoregulatory defence mechanism. Shivering is one of these physiological responses orchestrated within the central nervous system. In healthy volunteers, the core body temperature thresholds for shivering and vasoconstriction are 35.7±0.5°C and 36.8±0.3°C, respectively [Kurz 1997]. Shivering is associated

with several physiological responses, including a two- to five-fold increase in metabolic rate [Eyolfson 2001, Mahmood 2007] and increases in heart rate, blood pressure, and respiratory rate. In addition, shivering is distressing for the patient. For these reasons, shivering during therapeutic hypothermia must be avoided.

Pethidine, a piperidin derivative, is a synthetic opioid receptor agonist often used for the treatment of post-anaesthetic shivering [Wrench 1997]. In addition, it has been shown to be one of the most effective agents for the prevention and treatment of shivering when applying therapeutic hypothermia. Pethidine prevents and manages shivering far better than roughly equianalgesic doses of other opioids [Pauca 1984, Guffin 1987]. Specifically, due to unknown mechanisms the agent inhibits shivering twice as much as vasoconstriction. Pethidine can shift the shivering threshold to about 33.5°C, more than 2°C lower than normal [Kurz 1997]. Based on recent studies of pharmacological agents for the reduction of shivering during therapeutic hypothermia, pethidine is therefore considered the first-line therapy in the management of shivering [Logan 2011].

With pethidine monotherapy, relatively high doses are required to reduce the shivering threshold, potentially leading to substantial sedation and respiratory depression [Mokhtarani 2001].

Buspirone, a partial 5-HT_{1A}RA, is an anxiolytic agent with the potential of reducing the shivering threshold by almost 1°C in humans [Mokhtarani 2001].

It has been shown that the combination of low-dose pethidine in combination with low-dose buspirone reduces the shivering threshold to 33.4±0.7°C and therefore to the same extent as high-dose pethidine monotherapy, while eliciting only mild sedation or respiratory depression [Mokhtarani 2001]. Given the different modes of action and receptor affinities of the two compounds, the effect was assumed to be synergistic rather than additive.

Nausea and vomiting are typical side effects of strong opioids such as pethidine. Selective 5-HT_3RAs are highly effective anti-emetics that have widely been used in clinical routine for years. In order to prevent and treat these unpleasant but anticipated side effects of pethidine, patients may receive, as supportive therapy, a 5-HT_3RA prior to and during pethidine administration.

Therefore, in order to overcome the thermoregulatory defence mechanism of the body and to minimise patient discomfort during cooling, a combination of pethidine i.v. and buspirone p.o. will be used in patients randomised to therapeutic hypothermia. Patients will receive loading doses of the medication prior to induction of cooling, followed by further administrations on an as-needed basis up to the 24-hour maximum doses which are in line with current dosing recommendations in the EU for the two compounds. Patients who have difficulties swallowing will not receive buspirone, unless they have a nasogastric tube. For the prevention and treatment of opioid-induced nausea and vomiting, the administration of a 5-HT_3RA as support medication is recommended. For further details see Section 7.2.1.

3.3 Risk-benefit assessment

3.3.1 Risks to patients

Therapeutic hypothermia and best medical treatment group

About half of the patients with ischaemic stroke remain dependent or die during the first three months after onset of symptoms, even if treated with alteplase and subsequently with aspirin [Wahlgren 2007, Wahlgren 2008, Wardlaw 2009, Lees 2010, Wardlaw 2012]. Moreover, a quarter to half of the patients will develop complications during the first weeks after stroke [Kumar 2010]. Given the high risk of mortality and morbidity, it is essential that a DSMC closely assesses the efficacy and safety data during the course of the trial and helps the sponsor distinguish stroke-related from study-specific risks.

At their regular meetings, DSMC members will receive all reports on fatal SAEs as well as unblinded summaries of data aggregated by treatment groups for review in closed meetings in accordance to the DSMC charter (see Section 11.5.2.2). Feedback, blinded for treatment, will be provided to the sponsor, the chairperson of the EuroHYP-1 executive committee and the chairperson of the EuroHYP-1 steering committee in open meetings and in written conclusions. The feedback will contain comments on trial progress and conduct, and recommendations on whether the trial should continue, undergo a protocol amendment or be stopped altogether, depending on safety and efficacy findings. The DSMC will follow processes recommended by the DAMOCLES statement [DAMOCLES Study Group 2005].

In case the DSMC recommends stopping the trial, the sponsor will suspend patient enrolment with immediate effect and inform competent authorities and ethics commissions within the legal timeframes about this decision.

If the DMSC recommends stopping the trial for safety reasons, cooling must not start or must be stopped in patients randomised to therapeutic hypothermia group who at that moment are in screening [A1, within 90 minutes before the start of treatment phase TP] or in treatment phase [TP, beginning of Hour 1 to end of Rewarming], respectively. However, all patients enrolled in this trial at the moment of suspension will be followed up until outcome assessment [A7/8].

If indicated, enrolment into the study may resume only after

- an appropriate amendment has been made to the clinical trial protocol following consultations with the EuroHYP-1 DSMC, the EuroHYP-1 ethics board, the EuroHYP-1 scientific advisory board, the EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee, **and**
- having obtained approval by competent authorities and ethics commissions of such amendment to the clinical trial protocol.

For further details see Section 6.4.2.

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking and are used in strict adherence to their intended use. The use of any other cooling device or system is prohibited during the course of the clinical trial. The

choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly (except for the EMCOOLS Brain.Pad which may be used along with cold fluid infusion during induction of cooling) and may not be switched during an individual treatment.

For therapeutic hypothermia maintained by endovascular cooling, a catheter has to be inserted into the IVC *via* one of the femoral veins using the Seldinger technique. The technique has safely been used for decades and is well established. All trial sites performing or intending to perform endovascular cooling will receive video training of the proper procedure to follow.

The main risks associated with catheter placement are accidental arterial puncture, formation of local haematoma, DVT and lesion of the femoral nerve.

- The femoral artery adjacent to the femoral vein is easily identifiable by palpation, and accidental arterial puncture is reliably avoided when the primary puncture is performed about 1cm medially from the artery.
- Immediately after insertion of the cooling catheter, the insertion site will be inspected for signs of bleeding. If bleeding occurs, manual pressure will be applied to the site until bleeding stops. During and until 3 hours after removal of the cooling catheter, the catheter insertion site and the surrounding tissue will be visually inspected at regular intervals for detection of local haematoma. After removal of the catheter at the end of the cooling period, manual pressure will be applied for 5 minutes to the insertion site. Most bleedings at the insertion site are self-limiting and do not require any intervention. In case of a larger haematoma accompanied by a clinically relevant fall in blood haemoglobin levels, treatment will follow local standard procedures.
- Theoretically, the insertion and placement of the cooling catheter may induce the slowing of blood flow velocity in the IVC and cause DVT in pre-disposed patients. In the COOL AID trial, DVT was diagnosed by routine Doppler ultrasound in three patients at 2, 9 and 13 days after enrolment, respectively [De Georgia 2004]. Doppler ultrasound examinations were conducted in the hypothermia group only, and the only case of pulmonary embolism occurred in the normothermic group. In the ICTuS-L trial, DVT occurred in four patients in the hypothermia group and in one patient in the normothermic group [Hemmen 2010]. In two cases, the event was judged to be possibly related to the cooling catheter.

  Patients not treated with thrombolysis will receive anti-thrombotic prophylaxis according to local standards. In patients receiving thrombolysis with alteplase, the start of anti-thrombotic medication will be postponed until 24 hours after start of thrombolysis in accordance with international guidelines [Adams 2007; ESO Guidelines 2008]. Patients in whom hypothermia will be performed by endovascular cooling will have the cooling catheter removed right after the end of the re-warming period. All patients will be observed for signs of DVT or pulmonary embolism. Any such case will be recorded in the AE section of the eCRF and treated according to local standards.
- The risk of lesions of the femoral nerve is considered very low when the procedure of catheter placement is correctly followed, i.e., if venous blood can be drawn prior to insertion of the catheter into the femoral vein.

In some patients treated with therapeutic hypothermia for indications other than acute ischaemic stroke and to lower temperatures than proposed in the present trial, low blood pressure, bradycardia, cardiac arrhythmias, renal failure and elevated levels of the pancreatic enzymes, amylase and lipase, have been reported [Polderman 2009]. In the COOL AID, NOCSS and ICTuS-L trials, incidences of such events were comparable between experimental groups [De Georgia 2004, Weber 2008, Hemmen 2010].

Apart from pneumonia, no differences were observed in the COOL AID, NOCSS and ICTuS-L trials regarding the incidences of infections between the hypothermia and the normothermia treatment groups [De Georgia 2004, Weber 2008, Hemmen 2010, Piironen 2014]. It remains unclear, however, whether therapeutic hypothermia or the required anti-shivering regime is associated with an increased risk of pneumonia. In the ICTuS-L trial, 7 (25.0%) of 28 cooled patients and 2 of 30 (6.7%) of normothermic patients developed pneumonia [Hemmen 2010], and in the Helsinki trial 7 (39%) of 18 cooled patients and 2 (11%) of 18 normothermic patients [Piironen 2014]. No details on reporting criteria, severity and potential therapeutic consequences were given. By contrast, no difference in pneumonia rates between treatment groups were reported in the COOL AID and the NOCSS trials.

A possible explanation for the higher incidence of pneumonia in the hypothermia group of the ICTuS-L trial is the higher dose of pethidine administered in this trial. Patients received a mean (±SE) pethidine dose of 14.5±6.9mg/kg body weight over 24 hours. In the EuroHYP-1 trial, the pethidine dose administered over 24 hours will be limited to 500mg, which is the maximum daily dose recommended in Germany for the treatment of severe pain [Sanofi-Aventis Deutschland 2014].

Furthermore, all patients (i.e., in both treatment groups) will have their S_PO_2 levels continuously monitored through peripheral pulse oximetry for at least 24 hours. If in a patient receiving pethidine, S_PO_2 levels fall below 90% despite oxygen administration *via* a nasal cannula or if there is a decrease of ≥2 points on the GCS motor response subscale compared to the value at screening, no further pethidine doses will be administered until the patient has recovered to a S_PO_2 level ≥90% and the motor response has returned to the value at screening minus 1 point.

Another side-effect of pethidine is constipation, but this is not expected to pose a problem because its administration is limited to 24 hours.

Conceivably, infusion of large volumes of cold saline or Ringer's lactate could lead to volume overload, especially in patients with pre-existing heart failure. However, in several clinical trials, administration of ≥2l of cold vehicle solutions did not cause cardiac or other adverse events [Kim 2005, Kim 2007, Kollmar 2009]. If the cold saline or Ringer's lactate infusion cause volume overload in a patient, adequate doses of a fast acting diuretic will be administered in accordance with local guidelines. Moreover, patients with a NYHA score ≥III will not be enrolled into the trial.

Finally, the question arises whether therapeutic hypothermia may have an impact on thrombolysis with alteplase. This recombinant tissue-plasminogen activator has an extremely short plasma half-life of 4 to 5 minutes.

Only a few clinical data are available on the combination of therapeutic hypothermia and thrombolysis. In a subgroup of patients in the COOL AID and ICTuS-L trials, cooling was started with a considerable delay after termination of treatment with alteplase [De Georgia 2004, Hemmen 2010]. *In vitro* trials have shown that the fibrinolytic activity of alteplase is reduced at lower temperatures [Rijken 1990, Shaw 2007, Yenari 1995]: for each degree Celsius decrease in temperature the amount of *in vitro* clot lysis decreases by about 5% [Van der Worp 2010]. However, such *in vitro* systems are static in nature and may therefore not adequately reflect the situation in patients.

Experimental data in animals indicate that in comparison to thrombolysis alone, a combination of cooling to 34°C and thrombolysis by alteplase reduces both infarct size and parameters associated with the disruption of the blood brain barrier [Kollmar 2004]. Combination therapy did not change perfusion parameters as measured by perfusion-weighted imaging.

In accordance with the SmPC for Actilyse® [Boehringer Ingelheim Pharma 2011], the medicinal product containing alteplase, the compound will be administered i.v. over a period of 60 minutes. Therapeutic hypothermia will be started only after the end of alteplase administration. Given the pharmacokinetic properties of alteplase, its mode of action and the length of the time interval between start of alteplase administration and a reduction in body temperature, no clinically relevant impact of therapeutic hypothermia on thrombolysis is anticipated.

In conclusion, several risks associated with therapeutic hypothermia have been identified in previous clinical trials and appropriate, mostly preventive, counter-measures will be taken in the EuroHYP-1 clinical trial. Whether different risk levels exist inside the hypothermia group has not been investigated yet. Theoretically, patients may be exposed to different levels of risk depending on the exact set-up of their treatment, e.g., endovascular vs. surface cooling or additional use of the EMCOOLS Brain.Pad for induction of cooling.

Best medical treatment alone group

Patients randomised to best medical treatment alone receive the established SC and are not exposed to an increased risk.

3.3.2 Benefits

Next to reperfusion strategies, therapeutic hypothermia is the most promising novel therapeutic approach in acute ischaemic stroke with proof of concept (albeit in other indications) and a multimodal mechanism of action. Patients randomised to cooling may benefit from the intervention to a clinically relevant extent, as has been the case in experimental stroke models and in clinical trials conducted in patients after CPR and in newborns with HIE, potentially translating into lower rates of death or disability.

All patients who provide informed consent will be carefully monitored and undergo thorough neurological examination at several time points during the course of the trial.

If the clinical trial is able to demonstrate a beneficial effect of therapeutic cooling and best medical treatment over best medical treatment alone, an adaptation of national and international treatment guidelines for acute ischaemic stroke is anticipated. Such a change of the therapeutic paradigm will have a major and significant impact on the way stroke patients will be treated in the first days after symptom onset, on resources necessary for long-term provision of care, on relatives, carers and on society as a whole.

3.3.3 Risk-benefit balance

By its nature, acute ischaemic stroke is inherently associated with high rates of complications or long-term disability and a considerable risk of death. The burden it places on patients, relatives, carers and society is enormous. Therapeutic hypothermia currently constitutes the most promising novel approach with the potential of significantly reducing mortality or dependency. The benefits of therapeutic hypothermia have been impressively demonstrated in patients after CPR and in newborns with HIE.

The cooling procedure with its components of infusion of vehicle solution, catheter placement for endovascular cooling and medication for the prevention and treatment of shivering, carries specific risks which, however, appear manageable in awake patients and had no negative impact on long-term outcome data in the three clinical safety and feasibility trials quoted above. Moreover, a DSMC will closely monitor the patients' safety during the course of the trial.

Given the potential benefit of therapeutic cooling for trial participants, future stroke patients, their relatives, carers and society on one side and the limited, manageable risks to trial participants on the other side, the sponsor and the various committees involved in the conduct of the trial conclude on a risk-benefit balance clearly in favour of conducting this clinical trial.

4 CLINICAL TRIAL OBJECTIVES

4.1 Primary objective

To determine whether systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

4.2 Secondary objectives

- To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, in patients with acute ischaemic stroke on
  - mortality at 3 months.
  - neurological outcome at 3 months.
  - quality of life at 3 months.
  - cerebral infarct size at 48±24 hours.
- To determine the safety and tolerability of systemic cooling and best medical treatment in patients with acute ischaemic stroke.

4.3 Other objectives

To assess the effect of systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 12 hours, in patients with acute ischaemic stroke on

- selected biomarkers.
- other imaging parameters.
- cost-effectiveness parameters.

5 INVESTIGATIONAL PLAN

5.1 Overall clinical trial design

Multicentre, open-label, randomised, parallel-group, with blinded outcome assessment.

5.1.1 End of clinical trial

The end of the clinical trial will be defined as the last assessment of the last patient. Further follow-up through public registers and potential call-back for further clinical assessment will be considered.

5.2 Specific aspects of the clinical trial design

Therapeutic hypothermia represents the most promising intervention to improve long-term functional outcome in stroke patients. This clinical trial sets out to compare the effect of therapeutic hypothermia and best medical treatment with the effect of best medical treatment alone. Once informed consent has been obtained, patients will be randomised to either treatment arm in a 1:1 distribution.

The very nature of therapeutic hypothermia effectively precludes a double-blind trial design. The mRS score on Day 91 after onset of acute ischaemic stroke will be assessed by an outcome adjudication committee blinded to the patient's treatment assignment, thus ensuring the highest possible standard for the evaluation of clinical benefit of the intervention.

For ensuring adequate statistical power, 800 patients need to be enrolled into the clinical trial. In order to ensure timely recruitment of trial participants, the trial will be conducted as a multinational, multicentre clinical trial across the EU and in some non-EU countries.

A patient with acute ischaemic stroke is routinely treated in a specialised stroke unit. Best medical treatment is generally ensured through regular staff training on treatment algorithms according to local and national practice. While these algorithms follow national and international guidelines, small differences due to cultural influences or local conditions for the delivery of care may exist between trial sites. Since the relevant treatment algorithms will be applied to all trial patients at a trial site, these minor discrepancies are not expected to influence trial assessments.

Furthermore, in order to qualify for participation in the trial, investigators and their staff will undergo extensive training prior to recruiting patients into the trial. The training programme includes web-based training modules on cooling procedures for investigators and trial staff; mandatory training provided by manufacturers of cooling systems on their devices for investigators and trial staff prior to use of the respective systems; mandatory web-based certification on mRS and NIHSS assessment for investigators; video training on correct placement of cooling catheters for

investigators; and provision of written instructions to trial staff on trial-specific procedures such as serum sample storage and handling.

For patients to qualify for participation in the clinical trial, start of treatment must be deemed possible within 6 hours after onset of ischaemic stroke.

Prior to enrolment, patients may or may not receive thrombolytic treatment with alteplase. The decision on alteplase treatment will be taken by the treating physician in strict adherence to the local alteplase SmPC and guidelines, and will be guided by purely clinical considerations. The use of alteplase is therefore not related to the clinical trial and alteplase is not considered an IMP.

Alteplase treatment in patients deemed to be eligible for thrombolysis must be started within 4.5 hours after the onset of ischaemic stroke and must be administered within 60 minutes.

In principle, a patient may be enrolled into a clinical trial only once he "has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial" [art. 3.2.d of Directive 2001/20/EC].

Stroke patients with an NIHSS of ≥6, the study population planned to be enrolled into this clinical trial, however, are impaired to varying degrees in their ability to give consent due to the acute brain injury. Moreover, they find themselves in a new, frightening and often life-threatening situation. Such patients will be unable to reach a balanced view of the potential risks and benefits of participation in this trial within a time frame of less than one hour. For these reasons, all potential study participants must be classified as not being able to give consent.

The proof of safety and efficacy of therapeutic hypothermia in acute ischaemic stroke can thus only be obtained with patients unable to give consent. However, "such research is essential to validate data obtained … by other research methods" [i.e. in the case of EuroHYP-1 from animal studies and investigations of clinical conditions other than stroke] "and relates directly to a life-threatening or debilitating condition from which the incapacitated adult concerned suffers" [art. 5.d of Directive 2001/20/EC].

Provisions for the enrolment of patients who are unable to give informed consent can be found in the national legislation of all EU member states. Prior to trial start, approval by the competent authority and the ethics commission for the procedure to follow in the respective country must be obtained. In order to ensure that all national regulatory requirements are met, investigators are requested to follow country-specific written instructions provided by the sponsor that must be observed when enrolling a patient into the trial.

After enrolment, patients will be randomised to either therapeutic hypothermia and best medical treatment or to best medical treatment alone.

In patients randomised to therapeutic hypothermia, induction of cooling will be started by infusion of 4°C isotone saline or Ringer's lactate administered over a period of 30 to 60 minutes. Saline or Ringer's lactate are not used as drugs, but as vehicles for providing a rapid drop in body temperature (physical effect). The choice

of the agent is left at the discretion of the investigator, and the agent is not considered an IMP.

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking and are used in strict adherence to their intended use. The use of any other cooling device or system is prohibited during the course of the clinical trial. The choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly (except for the EMCOOLS Brain.Pad which may be used along with cold fluid infusion during induction of cooling) and may not be switched during treatment.

Apart from the EMCOOLS Brain.Pad, the EMCOOLS Flex.Pad and the BrainCool cooling pads, all cooling systems must be filled with saline, distilled or sterile water or tap water. Since patients will not be directly exposed to these fluids, they are not considered IMPs.

In order to overcome the thermoregulatory defence mechanism of the body and to minimise patient discomfort during cooling, a combination of pethidine i.v. and buspirone p.o. will be used in patients randomised to therapeutic hypothermia. Since these drugs are used off-label in this clinical trial, they are considered IMPs.

For the prevention and treatment of opioid-induced nausea and vomiting, 5-HT_3RAs may be used as support medication. In accordance with the relevant guidance [European Commission ENTR/CT1 2010], these medications are not considered IMPs.

Body temperature will be assessed according to local standard clinical practice by intermittent tympanic or rectal temperature measurements, or with continuous rectal or bladder thermometry. However, in patients randomised to therapeutic hypothermia body temperature will be monitored through bladder or rectal thermal probes from the start of treatment period [TP, beginning of Hour 1 until end of re-warming period].

In patients randomised to therapeutic hypothermia, a body temperature between 34.0 and 35.0°C will be targeted. Cooling procedures will be adapted to keep body temperature as close as possible to the target.

Patients randomised to therapeutic hypothermia should reach a body temperature of ≤35.0°C as soon as possible, but within 3 hours after induction of cooling at the latest. Patients who do not achieve this threshold in time may continue to be cooled to any body temperature level ≥34.0°C that they tolerate. They will remain in the ITT population, but be excluded from the PPS.

If a patient shows poor tolerance of cooling, i.e., through pronounced shivering, agitation or discomfort, that cannot be controlled by administration of pethidine and buspirone or by surface counter-warming, the target temperature may be raised at a rate controlled by the cooling device of 0.2°C/h, or carefully at a higher rate if necessary, until a body temperature is reached that the patient tolerates.

Patients who do not achieve at least 6 h of body temperature at a level of ≤35.0°C during the period from beginning of Hour 1 to the end of Hour 12 of cooling will be considered treatment failures. They will remain in the ITT population, but will be excluded from the PPS.

Patients considered treatment failures will not be discontinued from the trial, but will be followed up until outcome assessment [A7, Day 91±14 days].

Within the first 7 days after patient's enrolment, all instances of subfebrile body temperature or fever (together defined as a body temperature >37.5°C) will be treated in accordance with international and local guidelines and standards, if the patient is still admitted to the hospital.

Breast-feeding mothers will not be enrolled into the clinical trial. Females of child-bearing potential must undergo a urine pregnancy test at screening assessment [A1, within 90 minutes before the start of the treatment phase TP]. If the test indicates a pregnancy, the patient will not be enrolled into the clinical trial. Since the therapeutic intervention is limited to 12 hours, no further means of birth control are requested for female patients during the course of the trial.

A patient experiencing an AE/SAE should receive proper treatment for the AE/SAE, if required, but should not be discontinued from the trial.

5.2.1 Minimisation of discomfort and risks

Participation in the clinical trial may entail specific discomfort and risks for the patients.

- Study participants assigned to the control group initially have their vital parameters closely monitored and also come to the study site once at the end of the follow-up phase for a final examination. The discomfort for these patients is classified as minimal; there are no study-related risks for these patients.
- For study participants assigned to therapeutic hypothermia by the randomisation process, the following control mechanisms and counter-measures have been implemented to minimise discomfort and risks.

Discomfort:

Discomfort	Monitoring	Counter-measure
Discomfort and shivering	Medical history, clinical symptoms (Bedside Shivering Assessment Scale; assessment every 15 minutes until the end of hour 3, then every half hour until the end of re-warming).	Administration of pethidine and buspirone, for single doses and minimal intervals see Section 7.2.1.4, if necessary increase in target body temperature or termination of hypothermia.
Opioid-induced nausea	Medical history, clinical symptoms.	Administration of 5-HT3-receptor antagonists, dosage see Section 7.2.1.4.
Pain from application of cooling catheter (endovascular cooling)	Medical history, clinical symptoms.	Local anaesthesia at the puncture site, maximum 2 puncturing attempts.

Risks:

Risk	Monitoring	Counter-measure
Volume overload due to induction infusion (20 mL/kg BW)	Medical history, clinical symptoms.	Exclusion criterion NYHA ≥III, if necessary administration of a diuretic.
Pneumonia	S_pO_2 monitoring, control of body temperature every 15 minutes until end of hour 3, every half hour until end of re-warming and every 8 hours after end of cooling, medical history, clinical symptoms, physical examination, if necessary laboratory test, chest X-ray.	Antibiotic therapy, if necessary discontinuation of hypothermia.
Catheterisation of the femoral vein /VCI (endovascular cooling):		
Incorrect arterial puncture, haematoma, haemorrhaging, damage to the femoral nerve	Visual inspection of the puncture site, medical history, clinical symptoms.	Established technique (Seldinger) with previous video training, five-minute application of pressure after removing the catheter.
Deep vein thrombosis	Medical history, clinical symptoms.	Use of a heparin-coated cooling catheter
Respiratory depression caused by pethidine	S_pO_2 monitoring, control of consciousness (GCS motor response assessment prior to intended repeat pethidine administration).	Limit daily maximum dose to 500 mg (according to SmPC for Dolantin®), minimum interval of 30 minutes between individual doses, if necessary (S_pO_2 ≤90%, worsening of GCS motor response by ≥2 points), administration of O_2 and withdrawal of medication.

6 CLINICAL TRIAL POPULATION

The trial population consists of patients of both sexes, aged ≥18 years, with acute ischaemic stroke and a NIHSS score of at least 6 at screening [A1, within 90 minutes before the start of the treatment phase TP].

6.1 Selection of trial population

Patients will be recruited among patients who present themselves at the trial site because of acute ischaemic stroke. Only patients who fulfil all inclusion criteria and none of the exclusion criteria at the time of screening will be considered for enrolment. No other recruitment activities are intended.

6.1.1 Distribution of sexes

The prevalence of acute ischaemic stroke is similar in both sexes, and the distribution of sexes in the study is expected to reflect the distribution of sexes in the general population. However, because sex is a prognostic factor, measures are taken to ensure equal distribution of sexes between treatment and control groups.

6.2 Inclusion criteria

Only patients meeting all of the following inclusion criteria at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] will be considered for trial enrolment:

Inclusion Criteria	Rationale
1. Written informed consent obtained from the patient or his/her legally acceptable representative or under such other arrangements as may be legally established in participating countries (see Section 13.3.1).	Administrative
2. Patients of both sexes aged ≥18 years.	Administrative
3. Estimated body weight of 50 up to and including 120kg.	Efficacy
4. Diagnosis of acute ischaemic stroke.	Efficacy
5. Possibility to start therapeutic hypothermia within 6 hours after onset of stroke.	Efficacy
6. Possibility to start therapeutic hypothermia within 150 minutes after start of alteplase administration in patients receiving thrombolysis at the trial site or within 150 minutes after start of endovascular treatment, if this is later.	Efficacy

Inclusion Criteria	Rationale
7. Possibility to start therapeutic hypothermia within 150 minutes after admission to trial site in patients not receiving thrombolysis or in patients who have received thrombolysis at a different site.	Efficacy
8. mRS score ≤2 prior to onset of stroke.	Efficacy
9. NIHSS score ≥ 6.	Efficacy
10. GCS motor response subscale score ≥5.	Safety concern

6.3 Exclusion criteria

Patients having any of the following criteria at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] will not be included in the trial:

Exclusion Criteria	Rationale
1. Use of monoaminoxidase inhibitors in the 14 days prior to screening.	Safety concern
2. Current use of medication interacting with pethidine or buspirone, i.e., ritonavir, phenytoin, cimetidine, phenothiazines, opioids and partial opioid agonists (e.g., pentazocine, nalbuphine, buprenorphine).	Safety concern
3. Acute alcohol intoxication.	Safety concern
4. Opioid addiction.	Efficacy
5. Nursing mother or pregnant woman, as verified by a positive urine pregnancy test in females of childbearing potential.[1]	Safety concern
6. Known hypersensitivity to the IMPs or any of their formulation ingredients.	Safety concern
7. Patient who is imprisoned or is lawfully kept in an institution.	Administrative
8. Employee or direct relative of an employee of the CRO (if applicable), the department of the investigator, or the sponsor.	Administrative

[1] Childbearing potential is defined as NOT premenarche, permanently sterilized, or postmenopausal (i.e., 12 months with no menses without an alternative medical cause)

Exclusion Criteria	Rationale
9. Participation in an interventional clinical trial within the last 4 weeks, or be under the exclusion period from another trial.	Administrative
10. Prior participation in this trial.	Administrative
11. Any acutely life-threatening conditions other than acute ischaemic stroke.	Safety concern
12. Rapidly resolving stroke symptoms.	Efficacy
13. Evidence from CT or MRI of intracranial haemorrhage or tumour or encephalitis or any diagnosis likely to cause the present symptoms other than acute ischaemic stroke. Haemorrhagic transformation of the infarct is not an exclusion criterion, except when there is a parenchymal haematoma covering more than 30% of the infarcted area, with significant space-occupying effect, or when there is a bleeding remote from the infarcted area.	Efficacy
14. Known convulsive disorder, acute closed angle glaucoma, myasthenia gravis.	Safety concern
15. S_PO_2 <94% (as measured by pulse oximetry) under nasal oxygen administration.	Safety concern
16. Other severe respiratory disorder.	Safety concern
17. Bradycardia (<40 bpm).	Safety concern
18. Severe cardiac failure, defined as NYHA classification ≥III.	Safety concern
19. Myocardial infarction or angina pectoris in the 3 months prior to screening.	Safety concern
20. Vasospastic disorders (e.g., Raynaud's disease).	Safety concern
21. Haematological dyscrasia (e.g., sickle cell disease, cryoglobulinaemia).	Safety concern.
22. Known platelet count <100,000/mm^3.	Safety concern
23. Known INR >1.7.	Safety concern
24. Skin damage (e.g., inflammation, burns, injuries, ulcerations, hives, rash) at the sites intended to be used for cooling.	Safety concern
25. Clinical diagnosis of sepsis.	Safety concern

Exclusion Criteria	Rationale
26. Known severe hepatic impairment (serum ALAT and/or ASAT >3 times ULN).	Safety concern
27. Known renal impairment (serum creatinine >2mg/100ml).	Safety concern
28. Addison's disease.	Safety concern
29. Any other condition that may interfere with, or be aggravated by, therapeutic hypothermia.	Safety concern
30. Any condition that is thought to reduce the compliance to cooperate with the trial procedures.	Efficacy

6.4 Discontinuation of patients from treatment or assessment

6.4.1 Discontinuation of patients

In accordance with the Declaration of Helsinki and the informed consent form, the patient or his/her legally acceptable representative may discontinue the participation of the patient in the clinical trial at any time without any penalty or loss of benefits to which the patient is otherwise entitled (see Section 6.4.2.2). Both the date of discontinuation of participation in the trial and the reason(s) why participation was prematurely discontinued (if such reasons are given by the patient or his/her legally acceptable representative) must be recorded in the patient file and on the eCRF.

Clinical study protocol deviations or conditions arising from the exclusion criteria established in Section 6.3 may (but will not necessarily) lead to the patient's discontinuation. All such conditions should be properly documented.

No other circumstances except death warrant discontinuation of the patient. If for a patient in the hypothermia group, continuation of cooling appears no longer in the interest of the patient, the investigator may terminate hypothermia. The patient will be re-warmed in accordance with the procedure described in this protocol (see Section 7.3.1.2) and subsequently receive best medical treatment alone. The patient will, however, remain in the study and be followed up until outcome assessment [A7, Day 91±14 days].

Following discontinuation, the end of trial assessment [A8] should be performed as soon as possible for safety reasons. The investigator is required to make every effort to contact patients lost to follow-up, and all such efforts should be documented in the patient file (e.g., times and dates of telephone contact, copies of letters).

Active cooling should usually be terminated in case of any of the following circumstances occurring after randomisation, unless in the opinion of the local investigator the potential risks of termination of cooling exceed the potential risks of continuing cooling:

- The investigator becomes aware that the patient fulfils any of the exclusion criteria mentioned in Section 6.3 only after the patient has been randomised.
- Symptomatic intracranial haemorrhage.
- Life-threatening extracranial haemorrhage.
- Epileptic seizure.
- Acute decompensated heart failure.
- Any new cardiac arrhythmia that fulfils the criteria for an SAE.
- Respiratory rate <8/min that persists despite a reduction in the dose of pethidine.
- S_pO_2 <90% that persists despite the administration of oxygen.
- Platelet count <100,000/mm^3.
- Sepsis.
- Frost bites.
- Allergic reaction to pethidine, buspirone, ondansetron, granisetron, or a material of the cooling pads or cooling catheters.
- Any other condition that may be aggravated by therapeutic hypothermia.
- A request of the patient or his/her legal representative to terminate cooling.
- To the clinical judgement of the treating physician, continuation of cooling appears no longer in the interest of the patient.
- Any other event or occurrence which, in the view of the treating physician, provides reason for early discontinuation on the grounds of the safety of the patient.

The patient will be re-warmed in accordance with the procedure described in this protocol (see Section 7.3.1.2) and subsequently receive best medical treatment alone. The patient will, however, remain in the study and be followed up until outcome assessment [A7, Day 91±14 days].

6.4.2 Premature termination or suspension of the trial or a trial site

6.4.2.1 Premature termination of the trial or a trial site

The trial or a trial site can be prematurely terminated by the EuroHYP-1 steering committee. Reasons for termination of the trial or a trial site may include, but are not limited to, the following:

- Patient enrolment is unsatisfactory.
- The risks and benefits of continuing the trial have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs/SAEs constitutes a potential health hazard to the patients.
- New scientific data on the IMDs or IMPs do not justify continuation of the trial.

- The investigator or trial site exhibit serious and/or persistent non-adherence to the clinical trial protocol, the Declaration of Helsinki, ICH–GCP and/or applicable regulatory requirements.

Furthermore, the trial may be prematurely ended if the regulatory authority or the IEC/IRB has decided to terminate or suspend approval for the trial, the trial site or the investigator.

If the trial is prematurely terminated for any reason, the investigator must inform the patients still in the trial or their legally acceptable representatives and ensure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, trial sites, the IEC/IRB and regulatory authorities of the termination of the trial as well as provide reasons for the action.

6.4.2.2 Suspension of the trial

With respect to safety, the DSMC will conduct interim analyses after 50, 100, 200, 400, and 600 patients had their outcome assessment [A7/8] performed. With respect to efficacy, the DSMC will conduct interim analyses after 400 patients had their outcome assessment (A7/8) performed. DSMC members will receive all reports on fatal SAEs as well as unblinded aggregate summaries of data by treatment groups for review in closed meetings in accordance with the DSMC charter (see Section 2.3). Feedback, blind to treatment, will be provided in open meetings and in written conclusions to the sponsor, EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee.

After each data review, the DSMC will make one of the following recommendations:

1. Continue the trial according to the current protocol version.
2. Carry out an interim analysis of fully cleaned, adjudicated and locked dataset.
3. Alter the clinical trial protocol so that one or more categories of patients are no longer included (for safety at any time point, or efficacy after one of the two interim analyses).
4. Place recruitment on hold so that additional follow-up information may be obtained on existing enrolled patients (for safety at any time point, or efficacy after one of the two interim analyses).
5. Stop the whole trial (for safety at any time point, or efficacy after an interim analysis of a cleaned, adjudicated and locked dataset).

If recommendation 4 or 5 is made by the DSMC, the sponsor or sponsor's authorised representative will suspend enrolment into the study with immediate effect and inform competent authorities and ethics commissions within the legal timeframes about this decision.

If the DMSC recommends stopping the trial for safety reasons, cooling may not start or may have to be stopped in patients randomised to therapeutic hypothermia group who at that moment are in screening [A1, within 90 minutes before the start of treatment phase TP] or in treatment phase [TP, beginning of Hour 1 to end of

Rewarming]. However, all patients included in this trial will be followed up until outcome assessment [A7/8]. The investigator must inform the patients still in the trial or their legally acceptable representatives accordingly.

If indicated, enrolment into the study may resume only after

- an appropriate amendment has been made to the clinical trial protocol following consultations with the EuroHYP-1 DSMC, the EuroHYP-1 ethics board, the EuroHYP-1 scientific advisory board, the EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee.
- obtaining approval by competent authorities and ethics commissions after submission of
  - the results of the interim analysis of the DSMB with a detailed justification of the recommendation for study termination.
  - a report about the safety of the patients within the clinical trial with a list of all hitherto serious adverse events that occurred in both therapy groups.
  - an account of the proposed actions for improving safety based on which the continuation of the study is seen as medically justifiable.
  - a demonstration of efficacy from within the hitherto existing study, if available.

6.4.3 Provision of care for patients after trial discontinuation

After trial discontinuation, the patients will be treated by their physician according to local clinical standards.

7 TREATMENTS

7.1 Investigational medical devices

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking and are used in strict adherence to their intended use. The use of any other cooling device or system is prohibited during the course of the clinical trial. The choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly (except for the EMCOOLS Brain.Pad which may be used along with cold fluid infusion during induction of cooling) and may not be switched during treatment.

The cooling period is expected not to exceed 22 hours (12 hours of cooling to a core body temperature of between 34.0°C and 35.0°C and a re-warming period of up to 10 hours).

For further information on the IMDs please refer to the EuroHYP-1 IB.

7.1.1 EMCOOLS Brain.Pad and EMCOOLS Flex.Pad (EMCOOLS)

7.1.1.1 Intended use and general information of investigational medical device

EMCOOLS Brain.Pad and EMCOOLS Brain.Pad are mobile non-invasive surface cooling systems that are used for temperature reduction and/or induction of mild therapeutic hypothermia in patients of at least 35kg body weight, when local temperature reduction is medically indicated, e.g. in stroke patients and hyperthermic patients.

EMCOOLS Brain.Pad consists of two cooling elements enveloping the neck and two cooling elements for the shoulders.

An EMCOOLS Flex.Pad package consists of two individual cooling elements to be applied to the body surface. Each element weighs 0.55kg (±10%).

Manufacturer:	EMCOOLS Medical Cooling Systems AG, Vienna, Austria
Regulatory evidence:	Declaration of Conformity Certificate no. TÜV-A-MT-1/11/E118 (EMCOOLS Brain.Pad) Certificate no. TÜV-A-MT-1/14/Q071 (EMCOOLS Flex.Pad)
Regulatory class:	I (EMCOOLS Brain.Pad) IIa (EMCOOLS Flex.Pad)

EMCOOLS Brain.Pad and EMCOOLS Flex.Pad are intended for single use only.

7.1.1.2 Description of investigational medical device

Both the EMCOOLS Brain.Pad and the EMCOOLS Flex.Pad consist of individual pre-cooled pads that are attached to the surface of the patient's body. The EMCOOLS Brain.Pad and the EMCOOLS Flex.Pad product labels display brief diagrammatic instructions on the use of the EMCOOLS Brain.Pad and the EMCOOLS Flex.Pad, respectively. The borders to these brief instructions are coated with a colour indicator showing when the pads are ready for use. The pads are layered with a skin-friendly medical adhesive film and will stick onto the patient's skin until removed. After use the adhesive film will allow for easy removal of the pads.

Once cooled, the pads do not require any power supply during use. The cooling therapy and the number of individual pads used must be individually adapted to the patient.

The exterior of EMCOOLS Brain.Pad and the EMCOOLS Flex.Pad is made of thermoplastic polyurethane. The reverse side of the pads consists of a medical adhesive film suitable for medical products with direct skin contact such as operating sheets and bandages. The adhesive film is skin-friendly and dermatologically tested.

EMCOOLS Brain.Pad and EMCOOLS Flex.Pad contain HypoCarbon, a proprietary technology that generates an immediate energy transfer between the surface cooling system and the patient's body. In doing so, HypoCarbon withdraws the heat from the body immediately after initial contact with the patient's skin. HypoCarbon, a viscous liquid when thawed, is non-toxic and does not constitute a safety hazard or danger to the environment. There is no risk to the user, patient or third parties if the liquid is released in event of mechanical damage to the outside material. In the event of a leakage, the substance can be removed with soapy water.

7.1.1.3 Preparation for use and application of investigational medical device

For the purpose of induction of cooling, EMCOOLS Brain.Pad and EMCOOLS Flex.Pad may be used in addition to infusion of cold solution and concomitantly with the other cooling systems during the first hour of treatment [TP, Hour 1] at the discretion of the investigator.

The IMD may only be used by appropriately trained medical staff under the supervision of an investigator. It is the responsibility of the principal investigator at the respective trial site to verify and ensure that investigators and trial staff have undergone training, are familiar with the IMD and have ready access to its user manual at any time.

Before use, EMCOOLS Brain.Pad and EMCOOLS Flex.Pad are stored at –8°C to –11°C in a freezer. The pads must be left in the vacuum package. The freezer should display the temperature and have a cooling capacity of >14kg/24h. The pads must be stored horizontally during freezing. Prolonged storage must be out of the light (in the original transportation box or in the freezer).

When the colour indicator on the EMCOOLS Brain.Pad product and the EMCOOLS Flex.Pad labels turns blue, the pads are ready for use and can be applied to the

patient. The vacuum package is torn open at the notch. Immediately prior to application of each individual pad to the patient's skin, the protective film at the back is peeled away. The pad is then carefully pressed to the patient's body surface (neck and shoulders for EMCOOLS Brain.Pad, chest, abdomen, back and limbs for EMCOOLS Flex.Pad) for 3-5 seconds to allow for the adhesive film to fully adhere to the skin. It is the responsibility of the investigator to verify the correct application of the pads.

For EMCOOLS Brain.Pad, the use of the neck pad is optional, depending on the patient's neck size. If used, it may be applied vertically or horizontally.

In order to prevent skin injuries, the use of a pressure-relieving or pressure-reducing underlay is recommended for patients with sensitive skin, patients with poor tissue blood flow, peripheral arteriosclerosis or poor nutrition, diabetics, adipose patients and patients taking steroids or high-dose vasopressor therapy.

During the treatment phase [TP], EMCOOLS Brain.Pad and EMCOOLS Flex.Pad may be used until the HypoCarbon has thawed or for a maximum of 60 minutes until end of Hour 1, whichever occurs first. The pads are then slowly and gently removed from the patient's skin and disposed of (see Section 7.1.9).

7.1.2 Arctic Sun and ArcticGel Pads (Medivance/Bard)

7.1.2.1 Intended use and general information of investigational medical device

The Arctic Sun temperature management system is intended for monitoring and controlling patient temperature within a range of 32°C to 38.5°C. The indications for use include any condition where patient temperature control within a range covering mild hypothermia to normothermia is required. This includes, but is not limited to, medical, surgical, febrile and accidental hypothermia or heat stroke patients.

The Arctic Sun temperature management system is a surface cooling system that consists of a control module (either Arctic Sun 2000 with remote display or Arctic Sun 5000 with interactive touch screen), disposable ArcticGel Pads, fluid delivery line, cables and accessories.

Manufacturer: Medivance Inc., Louisville, USA

Arctic Sun 2000

Regulatory evidence: Declaration of Conformity
Certificate no. MV02

Regulatory class: IIb

Arctic Sun 5000

Regulatory evidence:	Declaration of Conformity Certificate no. MV05
Regulatory class:	IIb

ArcticGel Pads

Regulatory evidence:	Declaration of Conformity Certificate no. MV03
Regulatory class:	I

The ArcticGel Pads are intended for single use only.

7.1.2.2 Description of investigational medical device

The Arctic Sun temperature management system consists of two major components: a set of pads that covers portions of the patient's skin and a control module that circulates distilled or sterile temperature-controlled water. There are also accessories.

The ArcticGel Pads are non-sterile, thin, conformable foam pads that consist of 3 layers:

- an inner biocompatible hydrogel layer that adheres to the patient.
- a thin film which serves as a fluid barrier.
- an outer foam layer with water channels which prevents heat transfer to the environment.

The ArcticGel Pads have inlet and outlet lines which are connected to the pads by means of a pad manifold.

The inner surface lined with a hydrogel layer adheres to the patient's skin. The biocompatible hydrogel material consists of approximately 50% water and therefore is a good thermal conductor. The hydrogel can maintain its adhesion level over extended periods. The pads can be repositioned on the patient's skin as needed. The pads are available in several sizes to provide adequate body coverage.

The control module pulls temperature-controlled water (range between 4°C and 42°C) through the ArcticGel Pads under negative pressure by means of fluid delivery lines. Each pad has an inlet and an outlet connection that attaches to a fluid delivery line. The pads are designed so that water flows within internal pathways across their surface to provide even, efficient heat transfer between the skin and the water.

When a target temperature has been set for a given patient, a thermal probe inserted into the patient and connected to the control module provides feedback to an internal control algorithm. The temperature of the circulating water increases or decreases automatically to achieve the target temperature.

7.1.2.3 Preparation for use and application of investigational medical device

The IMDs may only be used by appropriately trained medical staff under the supervision of an investigator. It is the responsibility of the principal investigator at the respective trial site to verify and ensure that investigators and trial staff have undergone training, are familiar with the IMDs and have ready access to their user manuals at any time.

A bladder or rectal thermal probe must be inserted into the patient and connected to the control unit. After a short self-check of the control unit, parameters appropriate for the individual patient are set using the remote display or the interactive touch screen, respectively. Patients should be cooled in automatic mode to a target body temperature between 34.0 to 35.0°C within 3 hours after the start of induction of the cooling.

Next, the ArcticGel Pads are placed on the patient. The pads should be used immediately after opening the outer package. The patient's body surface available for pad placement dictates style, size and number of pads applied. The pads are placed on the frontal and dorsal torso as well as on both upper thighs and are then connected to the fluid delivery line manifold.

In order to prevent skin injuries, the use of a pressure-relieving or pressure-reducing underlay is recommended for patients with sensitive skin, patients with poor tissue blood flow, peripheral arteriosclerosis or poor nutrition, diabetics, adipose patients and patients taking steroids or high-dose vasopressor therapy. The skin under the pads should be checked for integrity at regular intervals.

The Arctic Sun temperature management system operates under negative pressure, which helps the pads to conform to the patient's body and minimizes the risk of leaks in the event of accidental puncture of a pad or accidental disconnection of the fluid delivery line. In order to ensure negative pressure on the pads at all times, the patient's bed surface should be placed 75-150cm above the floor.

The Arctic Sun temperature management system should be operated under the following conditions:

- Temperature range: 10ºC to 27ºC.
- Ambient humidity range: 5% to 70% relative humidity, non-condensing.

At operating temperatures higher than 27ºC, the refrigeration system's cooling capacity and therefore its ability to cool a patient is compromised.

During the treatment phase [TP], the Arctic Sun temperature management system may be used from the start of the induction of cooling [TP, beginning of Hour 1] until the end of the re-warming period [end of TP]. Prior to removal, the pad's fluid content must be purged. The pads are then slowly and gently removed from the patient's skin and disposed of (see Section 7.1.9).

7.1.3 BrainCool System and BrainCool cooling pads (BrainCool)

7.1.3.1 Intended use and general information of investigational medical device

The BrainCool System is is a thermoregulatory device intended for monitoring and controlling patient temperature within a range of 33°C to 38.5°C.

The BrainCool System consists of a refrigeration and control unit (ECU 100), a cooling agent (BC Cool), a data collection device (BC Stick), a filling pitcher for refilling BC Cool and stabilisation insulation units. The BrainCool cooling pads are applied to the patient's head/neck, torso and thigh areas.

Manufacturer: BrainCool AB, Lund, Sweden

BrainCool System

Regulatory evidence: Declaration of Conformity
Certificate no. G1 15 08 91368 002

Regulatory class: IIb

BrainCool cooling pads

Regulatory evidence: Declaration of Conformity
Certificate no. 6.6.1-2015-87945

Regulatory class: I

The BrainCool cooling pads and the stabilizing insulation are intended for single use only.

7.1.3.2 Description of investigational medical device

The BrainCool System consists of three major components: a set of pads that covers portios of the patient's skin, the insulation stabilisation kits and a refrigeration and control unit.

The BrainCool cooling pads are moulded non-sterile silicone pads. The pads are pre-filled, and no filling or purging is necessary before or after a treatment. The BC Cool in the BrainCool System and the cooling pads contains an anti-freeze agent that also minimizes bacterial growth in the fluid pathway. The system does not require any rinsing or cleaning of the fluid pathway before or after use.

The pads are designed without any adhesive connection between the pad and the patient's skin and can easily be lifted during treatment if required. The cooling pads are divided into three separate cooling areas, head/neck, torso and thigh, with two pads foreseen for each area. The pads for the torso and the thigh are available in several sizes to provide adequate body coverage.

The stabilisation insulation is made of moisture-absorbent neoprene insulating agains the ambient environment while at the same time counteracting condensation.

The refrigeration and control unit pushes temperature-controlled BC Cool, consisting of non-hazardous diluted monopropylene glycol, through the cooling pads at approximately 1.2 litre per minute per pad. The temperature ranges from 4°C to 28°C. The BrainCool System has three double connections. All cooling pads have a uniquely keyed (left/right) design with internal sensors to indicate if a cooling pad is connected. When both the left and the right side of the cooling pad are connected, a green light is shown.

When a target temperature has been set for a given patient, a thermal probe inserted into the patient and connected to the control module provides feedback to an internal control algorithm. The temperature of the circulating cooling agent increases or decreases automatically to achieve the target temperature.

7.1.3.3 Preparation for use and application of investigational medical device

The BrainCool System may only be operated by personnel who have been trained by BRAINCOOL or an authorised distributor in the use of the system according to the "Training of medical staff checklist". It is the responsibility of the principal investigator at the respective trial site to verify and ensure that investigators and trial staff have undergone training, are familiar with the IMDs and have ready access to their user manuals at any time.

A temperature probe must be inserted into the bladder or the rectum of the patient and connected to the PT1 connector of the control unit. As soon as one or more cooling pads are connected together with the patient temperature probe PT1, the treatment will start automatically.

The cooling pads are placed on the patient following the instructions in the user manual. The pads are placed on the frontal and dorsal torso, around both upper thighs and on the head/neck and are then connected to the fluid delivery line.

In order to protect from skin injury, pressure-relieving or pressure-reducing devices may be used under the patient for patients with poor tissue perfusion or poor skin integrity due to diabetes, peripheral vascular disease, poor nutritional status, steroid use or high-dose vasopressor therapy.

The BrainCool System should be operated under the following conditions:

- Temperature range: 18°C to 27°C
- Humidity range: 30% to 90% relative humidity
- Altitude: ≤2000m

During the treatment phase [TP], the BrainCool System may be used from the start fo the induction of cooling [TP, beginning of Hour 1] until the end of the re-warming period [end of TP]. The pads are then removed from the patient's skin and disposed of (see Section 7.1.9).

7.1.4 CritiCool and CureWrap 3500 (MTRE Advanced Technologies)

7.1.4.1 Intended use and general information of investigational medical device

The CritiCool system is a thermal regulating system, indicated for monitoring and controlling patient temperature.

The CritiCool temperature management system is a surface cooling system that consists of the CritiCool control module, the disposable single-piece CureWrap 3500, thermal probes, fluid delivery line, cables and accessories.

Manufacturer: MTRE Advanced Technologies Ltd., Rehovot, Israel

CritiCool

Regulatory evidence: Declaration of Conformity
EC certificate no. 759CE

Regulatory class: IIb

CureWrap 3500

Regulatory evidence: Declaration of Conformity
EC certificate no. 759CE

Regulatory class: IIa

Core sensor and surface sensor

Regulatory evidence: EC certificate no. 759CE

Regulatory class: not stated

The CureWrap 3500 is intended for single-use only.

7.1.4.2 Description of investigational medical device

The CritiCool temperature management system consists of two major components: a wrap that covers portions of the patient's skin and a control module that circulates temperature-controlled tap water.

The CureWrap 3500 is a flexible 3D single-piece design through which the water circulates. It is designed to be in close contact with a large area of the body to enhance energy transfer. The patient side is made of polypropylene, the exterior consists of brushed loop fabric.

The CureWrap 3500 has one inlet and two outlet connections integrated with a quick coupling connector. Inlet and outlet fluid delivery lines connect to the wrap, and the control unit ensures that the water flows between the components.

Each section of the wrap is separately wrapped around the appropriate area of the patient to ensure maximum body surface coverage.

The CritiCool device functions as a control unit with a cooling/heating pump that circulating temperature-controlled water (range between 13°C and 40°C) through the CureWrap 3500.

When a target temperature has been set for a given patient, a rectal thermal probe is inserted into the patient, and a surface thermal probe is attached. Both probes are then connected to the control module. The probes provide feedback to an internal control algorithm. The temperature of the circulating water is automatically adapted to achieve the target temperature.

7.1.4.3 Preparation for use and application of investigational medical device

Only trained medical staff, familiar with all the system operating procedures and certified by MTRE Advanced Technologies Ltd. or authorized agents of MTRE Advanced Technologies Ltd. are allowed to use the CritiCool temperature management system under the supervision of an investigator. All staff using the CritiCool temperature management system must complete the CritiCool training program. It is the responsibility of the principal investigator at the respective trial site to verify and ensure that investigators and trial staff have undergone training, are familiar with the IMD and have ready access to its user manual any time.

After a short self-check of the control unit, a rectal thermal probe is inserted into, and a surface thermal probe is attached to, the patient before both probes are connected to the control unit.

Next, the CureWrap 3500 is placed on the patient. The wrap should be used immediately after opening the outer package. The wrap is placed on the frontal and dorsal torso as well as on both upper arms and thighs. It is then connected to the fluid delivery lines which automatically fill the wrap.

Parameters appropriate for the individual patient are set on the control unit. Patients should be cooled in automatic mode to a targeted body temperature of between 34.0 and 35.0°C within 3 hours after the start of the induction of cooling.

In order to prevent skin injuries, the use of a pressure-relieving or pressure-reducing underlay is recommended for patients with sensitive skin, patients with poor tissue blood flow, peripheral arteriosclerosis or poor nutrition, diabetics, adipose patients and patients taking steroids or high-dose vasopressor therapy. The skin under the pads should be checked for integrity at regular intervals.

The CritiCool temperature management system should be operated at room temperatures ranging from 10°C to 40°C.

The wrap's duration of use is limited to 72 hours. If this period is exceeded, the wrap must be replaced by a new one.

During the treatment phase [TP], the CritiCool temperature management system may be used from the start of the induction of cooling [TP, beginning of Hour 1] until the end of the re-warming period [end of TP]. Prior to removal of the wrap, the wrap clamps must be closed to avoid water spill, and the wrap then slowly and gently removed from the patient's skin and disposed of (see Section 7.1.9).

7.1.5 Zoll intravascular temperature management system (Zoll)

7.1.5.1 Intended use and general information of investigational medical device

The ICY and Quattro catheters, in combination with the CoolGard 3000 or Thermogard XP control module, permit circulation of temperature-controlled saline through a heat exchanger to cool and re-warm the patient's blood in patients for whom the risks of a central line are warranted.

The Zoll IVTM system is an endovascular cooling system that consists of a control module (either CoolGard 3000 or Thermogard XP), a CoolGard start-up kit, an ICY catheter (either IC-3893 AE or IC-3893 CO) or a Quattro catheter (either IC-4593AE or IC-4593CO), a catheter convenience kit for catheter insertion (CO models only), thermal probes and cables.

Manufacturer: Zoll Medical Corporation, Chelmsford, USA

CoolGard 3000

Regulatory evidence: CE mark 2028431CE06

Regulatory class: IIb

Thermogard XP

Regulatory evidence: CE mark 2028431CE06

Regulatory class: IIb

CoolGard start-up kit

Regulatory evidence: CE mark 2028431CE06

Regulatory class: I, sterile

ICY and Quattro catheters and catheter convenience kit

Regulatory evidence: CE mark 2028431CE05

Regulatory class: III

The CoolGard start-up kit, the ICY and Quattro catheters and the catheter convenience kit are for single-use only.

7.1.5.2 Description of investigational medical device

The Zoll IVTM system consists of an endovascular catheter, a control and heat exchange unit and a start-up kit which provides the fluid delivery lines connecting the control unit to the catheter.

The ICY and Quattro catheters are sterile, flexible, single-use central venous lines placed in the IVC and doubling as cooling devices *via* a closed-loop balloon system filled with sterile isotone saline. They are made of radiopaque polyurethane, are Applause heparin-coated and available in the following presentations:

- IC-3893 AE 9.3 French, 3 lumen catheter, 38cm long, pack contains catheter convenience kit for catheter insertion.
- IC-3893 CO 9.3 French, 3 lumen catheter, 38cm long, pack contains no catheter convenience kit for catheter insertion.
- IC-4593 AE 9.3 French, 3 lumen catheter, 45cm long, pack contains catheter convenience kit for catheter insertion.
- IC-4593 CO 9.3 French, 3 lumen catheter, 45cm long, pack contains no catheter convenience kit for catheter insertion.

The catheter is placed in the IVC under strict aseptic conditions from an insertion site in the femoral vein using the Seldinger technique. Prior to insertion, the catheter is filled with sterile isotone saline *via* the balloon inflow.

The catheter is connected to the CoolGard start-up kit *via* two manifolds for saline inflow and outflow. The central part of the start-up kit has a coil which is placed into the heat exchange unit of the control module. Prior to the coil's placement in the heat exchange unit and its connection to the catheter, the start-up kit is primed with sterile isotone saline, and is expected to remain sterile. Unless there is a breach of the catheter balloon or manifold, there is no infection risk to the patient arising from the saline, as it does not enter the patient's circulation.

The control module (either Coolgard 3000 or Thermogard XP) functions as a control unit and a cooling/heating pump circulating temperature-controlled saline through the CoolGard starter kit and the ICY or Quattro catheter. The control module responds to the difference between the patient's temperature and the targeted temperature, and to the rate of change of the patient's temperature.

Information on core body temperature is provided to the control module through two thermal probes inserted into the patient: a bladder probe is used to provide feedback for temperature control, a rectal probe is used as back-up and fail-safe

mechanism. The temperature of the circulating saline is automatically adapted to achieve the target temperature. If the difference between the temperatures registered by the two probes exceeds 2°C, an alarm is set off and medical staff will then need to verify the correct position of the probes.

7.1.5.3 Preparation for use and application of investigational medical devices

The IMDs may only be used by appropriately trained medical staff under the supervision of an investigator. It is the responsibility of the principal investigator at the respective trial site to verify and ensure that investigators and trial staff have undergone training, are familiar with the IMDs and have ready access to their user manuals at any time.

Prior to insertion of the ICY or Quattro catheter into the patient's IVC, the catheter is filled with sterile isotone saline *via* the balloon inflow. After the catheter's insertion, the correct catheter tip position is confirmed by abdominal ultrasound. The catheter position should be re-checked if displacement is suspected. Immediately after insertion of the cooling catheter, the insertion site will be inspected for signs of bleeding. If bleeding is observed, manual pressure will be applied to the site until bleeding stops.

After a short self-check of the control module, the CoolGard start-up kit is primed with sterile isotone saline, the central coil is placed into the heat exchange unit of the control module and both ends of the start-up kit are connected to the balloon inflow and outflow manifolds of the ICY or Quattro catheter. Air trapped in the circuit must be removed prior to the start of saline circulation.

A bladder thermal probe and a rectal thermal probe are inserted into the patient and are connected to the control module to provide feedback on core body temperature. The target body temperature is then set on the control module and the cooling process started. Patients should be cooled in automatic mode to a target body temperature between of 34.0 and 35.0°C within 3 hours after the start of the induction of cooling.

During the treatment phase [TP], the Zoll IVTM system may be used from the start of the induction of cooling [TP, beginning of Hour 1] until end of the re-warming period [end of TP].

The Zoll IVTM system should be operated under the following conditions:

- Temperature range: 10ºC to 27ºC.
- Ambient humidity range: 30% to 75% relative humidity, non-condensing.

At the end of the re-warming period [end of TP], the IVTM system will be disconnected and removed from the patient. The balloon inflow and outflow manifolds of the ICY or Quattro catheter are disconnected from the CoolGard start-up kit and left open to allow the balloon system to be drained of fluid prior to removal. The catheter is then removed, and manual pressure will be applied for 5 minutes to the insertion site to avoid local haematoma formation.

The loose ends of the start-up kit should be cross-connected to avoid fluid spill during system removal. Both the catheter and the start-up kit are then disposed of (see Section 7.1.9).

From IMD set-up until disconnection and removal of the IVTM system, strict aseptic conditions must be observed where appropriate (e.g., for catheter insertion and priming of the system with sterile isotone saline). The catheter insertion site and the surrounding tissue will be visually inspected for detection of local haematoma every 3 hours during the cooling period until the end of the re-warming period [end of TP] and for 3 hours after cooling has stopped.

The duration of the use of the ICY or Quattro catheter and the CoolGard start-up kit are limited to 4 and 7 days, respectively, well beyond the expected duration of cooling and re-warming of up to 22 hours.

7.1.6 Packaging and labeling of investigational medical devices

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking. Only commercially available equipment will be used. Therefore, no trial-specific packaging and labelling are required.

7.1.7 Storage of investigational medical devices

EMCOOLS Brain.Pad and EMCOOLS Flex.Pad

EMCOOLS Brain.Pad and EMCOOLS Flex.Padmust be stored in a dark, dry environment at temperatures below 40°C.

Arctic Sun temperature management system

The Arctic Sun control units 2000 and 5000 should be stored under the following conditions:

- Temperature range: -30ºC to 50ºC.
- Ambient humidity range: 5% to 95% relative humidity, non-condensing.

Prior to use, the ArcticGel Pads should be stored at ambient temperature.

BrainCool System

The BrainCool System should be stored under the following conditions:

- Temperature range: -20°C to 50°C
- Humidity range: 30% to 90% relative humidity

CritiCool temperature management system

The CritiCool control unit should be stored in a clean, dry area under the following conditions:

- Temperature range: -40ºC to 70ºC.
- Ambient humidity range: 10% to 100% relative humidity.

Prior to use, the CureWrap 3500 should be stored at ambient temperature.

Zoll IVTM system

The CoolGard 3000 and the Thermogard XP control modules should be stored in a clean, dry area under the following conditions:

- Temperature range: -20ºC to 60ºC.
- Ambient humidity range: 10% to 90% relative humidity, non-condensing.

Prior to use, the ICY and Quattro catheters, the CoolGard start-up kits and the catheter convenience kits should be stored in a clean, dry area at room temperature ranging from 15°C to 40°C.

7.1.8 Accountability for investigational medical devices

For all re-usable IMDs such as control units, serial numbers will be recorded on the eCRF.

For all disposable, single-use IMDs, batch numbers will be recorded on the eCRF, where applicable.

7.1.9 Disposal of investigational medical devices

EMCOOLS Brain.Pad, EMCOOLS Flex.Pad, ArcticGel Pads, BrainCool cooling pads, CureWrap wraps, ICY and Quattro catheters, CoolGard start-up kits and the catheter convenience kits are single-use products. For hygienic reasons, disposal is required after application. Due to the risk of bacterial or viral contamination, the devices must be disposed of as contaminated medical waste in accordance with local regulatory requirements.

7.2 Investigational medicinal products

7.2.1 Description of investigational medicinal products

7.2.1.1 Pethidine hydrochloride (INN)

ATC-Code:	N02AB02
Presentation and route of administration:	Solution for injection
Qualitative and quantitative composition:	Pethidine hydrochloride One ampoule with 2ml solution for injection

	contains 100mg pethidine hydrochloride
List of excipients[2]:	Water for injections

The presentation of the IMP may differ between countries in formulation, strength, and excipients.

7.2.1.2 Buspirone hydrochloride (INN)

ATC-Code:	N05BE01
Presentation and route of administration:	Tablets for oral use
Qualitative and quantitative composition:	Buspirone hydrochloride One tablet contains 10mg buspirone hydrochloride
List of excipients[3]:	Calcium hydrogen phosphate dihydrate Cellulose, microcrystalline Lactose monohydrate Magnesium stearate (Ph.Eur.) Maize starch Carboxymethyl starch, sodium (type A) (Ph.Eur.) Colloidal silicon dioxide

The presentation of the IMP may differ between countries in formulation, strength and excipients.

7.2.1.3 Instructions for preparation

In the framework of this clinical trial, medicinal products containing pethidine will be used in their original packaging, as approved and marketed in the respective country.

As a controlled substance, pethidine hydrochloride is included in the list of drugs under Schedule 1 of the 1961 Single Convention on Narcotic Drugs. For storage and handling, specific local rules applicable to controlled drugs must be observed.

Pethidine hydrochloride will be delivered to the investigator or authorised staff from the local hospital pharmacy's stock of controlled drugs as requested by local regulations.

Pethidine will be drawn from the ampoule into a sterile syringe under observance of aseptic conditions. If pethidine is not immediately used, the opening of the syringe

[2] Exemplary list from German SmPC for Dolantin® 100mg-Injektionslösung.

[3] Exemplary list from German SmPC for Busp® 10mg tablets.

will be capped by a sterile needle protected by its cover and kept at the bedside of the patient.

In countries where buspirone is commercially available, it will be used in its original packaging, as approved and marketed in the respective country. In countries where buspirone is not or no longer commercialised, it will either be imported from another EU member state where it is approved and marketed or provided by sponsor. In any case, the trial site will obtain busprirone from the local hospital pharmacy.

No specific instructions for the preparation of buspirone are required.

7.2.1.4 Instructions for administration

The use of the IMPs are restricted to the treatment phase [TP] in patients randomised to therapeutic hypothermia.

Buspirone 10mg p.o. will be administered as tablets *via* the oral route to patients randomised to therapeutic hypothermia prior to induction of cooling and prior to administration of pethidine. Repeat doses of 10mg p.o. may be administered as long as a maximum dose of 30mg/24h is observed. Patients who have difficulties swallowing will not receive buspirone, unless they have a nasogastric tube. In such a case, the tablet must be pulverised in a mortar, suspended in 10ml of sterile water for injection and the suspension injected into the nasogastric tube. Before and after administration of the suspension, the nasogastric tube will be flashed with 10ml of tap water.

For the prevention of opioid-induced nausea and vomiting, the administration of a 5-HT_3RA as support medication is recommended. An i.v. bolus, slowly administered over at least 30 seconds, or an infusion over 15 minutes of either ondansetron (ATC-Code: A04AA01) 8mg or granisetron (ATC-Code: A04AA02) 3mg will be administered to patients randomised to therapeutic hypothermia prior to induction of cooling and prior to administration of pethidine. In accordance with the recommendations of the respective SmPC, repeat doses of the selected 5-HT_3RA may be administered for the prevention and treatment of nausea and vomiting during the cooling and re-warming periods as long as the minimum interval between subsequent injections is respected and the maximum daily dose is not exceeded.

For patients randomised to therapeutic hypothermia, a bolus of pethidine 50mg, injected i.v. over a period of about 2 minutes, will be administered prior to the induction of cooling. Subsequently, if the patient experiences discomfort or shivering, or other signs of poor tolerance of cooling become apparent or are anticipated, a bolus of pethidine 25mg i.v. may be given as long as an interval between pethidine injections of at least 30 minutes is respected and a maximum dose of 500mg/24h is not exceeded.

All patients (i.e., in both treatment groups) will have their S_PO_2 levels continuously monitored through peripheral pulse oximetry for at least 24h. If in a patient receiving pethidine, S_PO_2 levels fall below 90% despite oxygen administration *via* a nasal cannula or if there is a decrease of ≥2 points on the GCS motor response subscale compared to the value at the screening assessment [A1, within 90 minutes before the start of the treatment phase TP], no further pethidine doses will be

administered until the patient has recovered to a S_PO_2 level ≥90% and the motor response has returned to the value at the screening assessment minus 1 point.

All administration of anti-shivering and support medication will be recorded in the respective patient file and on the eCRF.

7.2.1.5 Packaging and labelling of investigational medicinal products

In the framework of this clinical trial, medicinal products containing pethidine will be used in their original packaging, as approved and marketed in the respective country. Labelling will be performed as required by local regulatory authorities.

Buspirone will be used in its original packaging, if it is commercially available in the respective country. In all other countries, buspirone will be labelled as required by local regulatory authorities.

7.2.2 Storage of, and accountability for, investigational medicinal products

Depending on the provisions of local legislation, it is the responsibility of the investigator and/or the hospital pharmacist to ensure that the IMPs are stored as requested by local regulations and that an updated record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the trial monitor and are open to inspection by an auditor appointed by the sponsor and by the regulatory authorities at any time.

If requested by national regulations, the competent authorities will be provided by the investigator and/or the hospital pharmacist with periodical reports on the amounts of pethidine locally used in the trial.

7.2.3 Destruction of investigational medicinal products

Any pethidine already drawn into a syringe, but unused at the end of the treatment phase [end of TP], will be destroyed as requested by local regulations. The time and the amount of drug destroyed will be recorded in the drug accountability form filed in the investigator site file.

Buspirone will be disposed of at trial sites in accordance with applicable local regulations and rules.

7.3 Treatments administered

Because of the complexity of the therapeutic intervention, a 24h/7d trial hotline is established at the Malmö and Bispebjerg university hospitals. The hotline will provide help on all therapeutic cooling-related questions. It will be staffed by health care providers experienced in therapeutic hypothermia. The hotline is projected to be available for 30 months after the initiation of the first trial site. By that time the overall experience with therapeutic cooling among the trial sites is expected to be sufficient.

When a patient has been randomised, the EuroHYP-1 hotline telephone number and email address will automatically be delivered to the respective trial site. The physician on duty at the hotline will simultaneously be informed by email and/or SMS about the randomisation.

Contact between the respective trial site and the EuroHYP-1 hotline may be initiated by both sides. All contact episodes will be noted in the coaching log kept at the Malmö and Bispebjerg university hospitals.

7.3.1 Clinical trial assessments

7.3.1.1 Screening [A1, within 90 minutes before the start of the treatment phase TP]

Prior to enrolment, patients may or may not receive thrombolytic treatment with alteplase. The decision on alteplase treatment will be taken by the treating physician in strict adherence to the local guidelines and will be guided by purely clinical considerations. Alteplase treatment in patients deemed to be eligible for thrombolysis must be started within 4.5 hours after the onset of ischaemic stroke and must be administered within 60 minutes.

All potential study participants must be classified as not being able to give consent. In order to ensure that all national regulatory requirements are met, investigators are requested to follow country-specific written instructions provided by the sponsor that must be observed when enrolling a patient into the trial. For details see Section 13.3.1.

After enrolment patients will be randomised to either therapeutic hypothermia and best medical treatment or to best medical treatment alone. For the method of randomisation see Section 7.3.2.

After enrolment blood samples for analysis of biomarkers will be collected between beginning of screening assessment [A1, within 90 minutes before the start of the treatment phase TP] and 60 minutes after start of the treatment phase TP. For further details see Section 8.1.2. For the list of further tasks and assessments at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] see Section 8.2.

7.3.1.2 The treatment phase [TP, beginning of Hour 1 to end of re-warming period]

Therapeutic hypothermia and best medical treatment group

Start of TP, beginning of Hour 1, is defined as the time of randomisation. The start of cooling is defined as the start of infusion of cold saline or Ringer's lactate. Therapeutic hypothermia will be performed for a period of 12 hours, followed by the re-warming period. TP will end when the patient has been re-warmed to a body temperature of 36.0°C and cooling devices have been removed.

In order to overcome the thermoregulatory defence mechanisms of the body and to minimise patient discomfort during cooling, a combination of pethidine i.v. and buspirone p.o. will be used in patients randomised to therapeutic hypothermia. Loading doses of buspirone 10mg p.o. and pethidine 50mg i.v. will be administered prior to induction of cooling. Patients who have difficulties swallowing will not receive buspirone, unless they have a nasogastric tube. For further details see Section 7.2.1.4.

For the prevention of opioid-induced nausea and vomiting, the administration of a 5-HT_3RA as support medication is recommended. An i.v. bolus, slowly injected over at least 30 seconds, or an infusion over 15 minutes of either ondansetron 8mg or granisetron 3mg will be administered to patients randomised to therapeutic hypothermia prior to induction of cooling and prior to administration of pethidine. In accordance with the recommendations of the respective SmPC, repeat doses of the selected 5-HT_3RA may be administered for the prevention and treatment of nausea and vomiting during the cooling and re-warming periods as long as the minimum interval between subsequent injections is respected and the maximum daily dose is not exceeded.

Induction of cooling will be started by infusion of 20ml/kg estimated body weight of 4°C isotone saline or Ringer's lactate administered over a period of 30 to 60 minutes.

In addition to infusion of cold solution, surface cooling to the neck and shoulders with the EMCOOLS Brain.Pad may be performed during the first hour of treatment [TP, Hour 1]. The use of the neck pad is optional, depending on the patient's neck size. If used, it may be applied vertically or horizontally.

- In patients receiving thrombolysis at the trial site, induction of cooling will be started after the end of alteplase administration, but not later than 150 minutes after the start of thrombolysis or 150 minutes after the start of endovascular treatment, if this is later. All preparations for the start of cooling, including the administration of anti-shivering medication, may be performed while alteplase is still being given.
- In patients not receiving thrombolysis and in patients who have received thrombolysis at a different site, induction of cooling will be started within 150 minutes after admission to the trial site.

If induction of cooling in a patient has not been started within 6 hours after onset of stroke, the patient may or may not receive therapeutic hypothermia, but will always receive best medical treatment and will continue to be assessed throughout the clinical trial. They will remain in the ITT-analysis group, but be excluded from the PPS analysis group.

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking and are used in strict adherence to their intended use. The use of any other cooling device or system is prohibited during the course of the clinical trial. The choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly (except for the EMCOOLS Brain.Pad which may be used along with cold fluid infusion during induction of cooling) and may not be switched during treatment. For further information on the IMDs see Section 7.1 and the EuroHYP-1 IB.

For therapeutic hypothermia maintained by endovascular cooling, a catheter will be inserted into the IVC *via* one of the femoral veins using the Seldinger technique. After catheter insertion, the correct catheter tip position is confirmed through abdominal ultrasound. The catheter position should be re-checked if displacement is suspected. Right after insertion of the cooling catheter, the insertion site will be inspected for signs of bleeding. If bleeding is observed, manual pressure will be applied to the site until bleeding stops.

If therapeutic hypothermia is induced and maintained by use of surface cooling devices, urine, anti-bacterial solutions and other fluids must not be allowed to accumulate underneath the device. They could mix with the adhesive film used on the devices, thereby reducing the adhesion of the device to the patient's skin or, in rare cases, leading to chemical burns.

As soon as possible after induction of cooling by infusion of cold solution, either surface or endovascular cooling will be started. Regardless of the cooling method used, the body temperature targeted is between 34.0 and 35.0°C. Body temperature will be monitored through bladder or rectal thermal probes from the start of treatment period [TP, beginning of Hour 1] until end of re-warming period, and cooling procedures will be adapted to keep body temperature as close as possible to the target.

If during therapeutic hypothermia, the patient experiences discomfort or shivering, or other signs of poor tolerance of cooling become apparent or are anticipated, further doses of the anti-shivering medication may be administered as long as the minimum intervals between administrations are respected and the maximum doses/24h are not exceeded. Patients who have difficulties swallowing will not receive buspirone, unless they have a nasogastric tube. For details see 7.2.1.4.

All patients (i.e., in both treatment groups) will have their S_PO_2 levels continuously monitored through peripheral pulse oximetry for at least 24h. If in a patient receiving pethidine, S_PO_2 levels fall below 90% despite oxygen administration *via* a nasal cannula or if there is a decrease of ≥2 points on the GCS motor response subscale compared to the value at the screening assessment [A1, within 90 minutes before the start of the treatment phase TP], no further pethidine doses will be administered until the patient has recovered to a S_PO_2 level ≥90% and the motor response has returned to the value at the screening assessment minus 1 point.

Patients randomised to therapeutic hypothermia should reach a body temperature of ≤35.0°C within 3 hours after induction of cooling. Patients who do not achieve at least 6 h of body temperature at a level of ≤35.0°C during the period from beginning of Hour 1 to the end of Hour 12 of cooling will be considered treatment failures. They will remain in the ITT population, but will be excluded from the PPS.

If a patient shows poor tolerance of cooling, i.e., through pronounced shivering, agitation or complains about discomfort, the target temperature may be raised up to a maximum of 35.0°C. If even this target temperature is not tolerated, patients will have their body temperature level raised at a rate controlled by the cooling device of 0.2°C/h, or at a higher rate if necessary, until a body temperature is reached that the patient tolerates.

Patients considered treatment failures will not be discontinued from the trial, but will be followed up until outcome assessment [A7, Day 91±14 days].

At the end of the cooling period, patients will be passively re-warmed at a rate controlled by the cooling device of 0.2°C/h until the patient's rectal or bladder temperature reaches 36.0°C. The cooling device will then be disconnected and removed from the patient.

If endovascular cooling is performed, the catheter insertion site and the surrounding tissue will be visually inspected for detection of local haematoma every 3 hours during the cooling period until the end of the re-warming period [end of TP] and for 3 hours afterwards. After removal of the catheter, manual pressure will be applied for 5 minutes to the insertion site.

As well as therapeutic hypothermia, patients in this group will also receive best medical treatment until discharge from hospital in accordance with published guidelines for the treatment of acute ischaemic stroke [Adams 2007, ESO Guidelines 2008] and for secondary prevention [ESO Guidelines 2008, Furie 2011].

For the list of further tasks and assessments at the treatment phase [TP] see Section 8.2.

Best medical treatment alone group

In all patients, TP, beginning of Hour 1, is defined as the time of randomisation. End of the treatment phase [end of TP] is defined as end of Hour 22. This timepoint has been seletected because in cooled patients, the end of TP may range from Hour 17 to 22, depending on the body temperature in Hour 12.

Patients randomised to the normothermic group will receive best medical treatment until discharge from hospital in accordance with published guidelines for the treatment of acute ischaemic stroke [Adams 2007, ESO Guidelines 2008] and for secondary prevention [ESO Guidelines 2008, Furie 2011]. It may be that local investigators wish to use e.g. pethidine, buspirone, or ondansetron in non-cooled patients as part of SC; this is allowed.

For the list of further tasks and assessments at the treatment phase [TP] see Section 8.2.

7.3.1.3 Assessment 2 [A2, Hour 24±2 hours]

At assessment 2 [A2, End of Hour 24±2], the patient´s NIHSS will be assessed. At the same time, blood samples for analysis of biomarkers will be collected. For further details see Section 8.1.2.

For the list of further tasks and assessments at assessment 2 [A2, Hour 24±4 hours] see Section 8.2.

7.3.1.4 Assessment 3 [A3, Hour 48±4 hours]

During assessment 3 [A3, Hour 48±4 hours], the patient's NIHSS will be assessed.

For the list of further tasks and assessments at assessment 3 [A3, Hour 48±4 hours] see Section 8.2.

7.3.1.5 Imaging assessment [A4, Hour 48±24 hours]

During the imaging assessment [A4, Hour 48±24 hours], a brain CT or MRI will be performed. The imaging method used may be different from the one used at screening assessment [A1, within 90 minutes before the start of the treatment phase TP]. This examination is not a trial-specific measure, but part of the clinical routine at all trial sites.

For the list of further tasks and assessments at imaging assessment [A4, Hour 48±24 hours] see Section 8.2.

7.3.1.6 Assessment 5 [A5, Hour 72±4 hours]

During assessment 5 [A5, Hour 72±4 hours], blood samples for analysis of biomarkers will be collected. For further details see Section 8.1.2. For the list of further tasks and assessments at assessment 5 [A5, Hour 72±4 hours] see Section 8.2.

7.3.1.7 Assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first]

During assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] which marks the end of the acute phase of stroke treatment, patients will undergo a series of tests and questionnaires. The assessment is scheduled on Day 8 or the day of discharge from hospital, whichever occurs first.

For the list of further tasks and assessments at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] see Section 8.2.

7.3.1.8 Outcome assessment [A7, Day 91±14 days]

During outcome assessment, the mRS and the NIHSS will be used as measures for the patient's long-term functional and neurological outcomes, respectively. The mRS assessment will be recorded using a digital video camera. The digital recordings will be transferred to the EuroHYP-1 outcome adjudication web portal.

For all patients who terminate the trial according to the protocol, the outcome assessment [A7, Day 91±14 days] replaces the end-of-trial assessment [A8].

For the list of further tasks and assessments at outcome assessment [A7, Day 91±14 days] see Section 8.2.

7.3.1.9 End of trial assessment [A8]

End of trial is performed only in patients who prematurely terminate the trial. For the list of tasks and assessments at end of trial assessment [A8] see Section 8.2.

7.3.1.10 Body temperature management during hospital stay

Within the first 7 days after the patient's enrolment, all instances of subfebrile body temperature and fever (together defined as a body temperature >37.5°C) will be treated in accordance with international and local guidelines and standards, if the patient is still admitted to the hospital.

7.3.2 Methods for assigning patients to treatment groups

After enrolment patients will be allocated to their respective treatment group. Allocation to treatment groups will be based on proportional minimisation through a web-based allocation service hosted at the University of Edinburgh.

Treatment allocation will be stratified by country and will include the following minimisation factors: intention to give alteplase; intended method of cooling (surface *vs*. endovascular); sex; stroke severity (NIHSS 6-12 *vs*. 13 or higher); age (≤65 years *vs*. >65 years); visibility of a relevant ischaemic lesion on the first brain imaging (yes *vs*. no) and time since symptom onset (≤4 hours *vs*. 4–6 hours). The patient will be allocated to the treatment which minimizes differences between groups within that stratification with a probability of 0.8. There is a probability of 0.2 that they will be allocated to the alternate group. Treatment allocation will be recorded along with the date and time of randomisation in the eCRF.

Patients discontinued from the trial will not be replaced.

7.3.3 Selection of investigational medical devices and of doses of investigational medicinal products in the trial

All cooling devices approved by the sponsor for use in this clinical trial bear the CE marking and are used in strict adherence to their intended use. The use of any other cooling device or system is prohibited during the course of the clinical trial. The choice of the cooling system is left at the discretion of the investigator. Cooling systems may not be used concomitantly (except for the EMCOOLS Brain.Pad which may be used along with cold fluid infusion during induction of cooling) and may not be switched during treatment.

Patients randomised to therapeutic hypothermia will receive a combination of pethidine i.v. and buspirone p.o. For the prevention and treatment of opioid-induced nausea and vomiting, a 5-HT_3RA may be administered as support medication. The cumulative doses/24h are limited in accordance with the instruction in the relevant SmPCs. For details see Section 7.2.1.4.

7.3.4 Selection and timing of doses of investigational medicinal products for each patient

In order to overcome the thermoregulatory defence mechanism of the body and to minimise patient discomfort during cooling, a combination of pethidine i.v. and buspirone p.o. will be used in patients randomised to therapeutic hypothermia. Patients will receive loading doses of the medication prior to the induction of cooling, followed by further administrations on an as-needed basis up to 24-hour maximum doses which are in line with current dosing recommendations in the EU for both compounds. Patients who have difficulties swallowing will not receive buspirone, unless they have a nasogastric tube. For further details see Section 7.2.1.

If in a patient receiving pethidine, S_PO_2 levels fall below 90% despite oxygen administration *via* a nasal cannula or if there is a decrease of ≥2 points on the GCS motor response subscale compared to the value at the screening assessment [A1, within 90 minutes before the start of the treatment phase TP], no further pethidine doses will be administered until the patient has recovered to a S_PO_2 level ≥90% and the motor response has returned to the value at the screening assessment [A1, within 90 minutes before the start of the treatment phase TP] minus 1 point. For details see Section 7.2.1.4.

7.3.5 Duration of treatment per patient

- Patients randomised to the therapeutic hypothermia and best medical treatment group are expected to undergo cooling for 12 hours from start of induction of hypothermia until the start of re-warming. Patients will be passively re-warmed at a rate controlled by the cooling device of 0.2°C/h until the patient's rectal or bladder temperature reaches 36.0°C. The cooling device will then be disconnected and removed from the patient. Thereafter, the patient will continue receiving best medical treatment until discharge from hospital.

- Patients randomised to the best medical treatment alone group will receive best medical treatment until discharge from hospital.

During follow-up, patients will receive local standard treatment as appropriate for their clinical condition. Outcome assessment [A7] will be performed on Day 91±14 days after stroke onset.

7.3.6 Treatment compliance

Not applicable.

7.3.7 Treatment of overdose of investigational medicinal products

As treatment with anti-shivering medication is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this trial is estimated to be low.

An overdose of pethidine is defined as a single i.v. dose of >50mg or an i.v. 24-hour dose >500mg. In case of pethidine overdose, the patient must have his/her vital parameters carefully monitored, especially respiratory function (respiratory rate, S_PO_2 by pulse oximetry). The action of pethidine can be abolished by administration of an opioid receptor antagonist (e.g., naloxone). The opioid receptor antagonist may have to be administered repeatedly, since the action of pethidine may outlast the action of the antagonist. Further treatment options include tracheal intubation and mechanical ventilation of the patient until symptoms of opioid intoxication subside.

An overdose of buspirone is defined as a single p.o. dose of >30mg or a p.o. 24-hour dose of >60mg. For buspirone, no antidote has been identified to date. The investigator is advised to use best clinical judgment in the unlikely event of a buspirone overdose. Treatment options include gastric lavage and monitoring of vital parameters.

Any overdose must be recorded on the eCRF. Any case of overdose leading to a SAE must be reported to the SAE adjudication committee in an expedited manner using the appropriate reporting form (see Section 9.2).

7.4 Previous and concomitant therapies

Prior to enrolment, the patient's medical history should include a detailed list of all medications the patient is currently taking. The record should include the drug name (trademark or generic), route of administration (e.g., i.v., oral), total daily dose/unit (expressed in mg, ml or IU) and indication for each medication.

The use of a monoaminoxidase inhibitor in the 14 days prior to screening constitutes an exclusion criterion.

The use of ritonavir, phenytoin, cimetidine, phenothiazines, opioids and partial opioid agonists (e.g., pentazocine, nalbuphine, buprenorphine) at the time of screening constitutes an exclusion criterion. Their use is forbidden during and until 24 hours after administration of anti-shivering medication.

In patients who underwent thrombolysis with alteplase, the use of anti-thrombotic prophylaxis with drugs such as aspirin, clopidogrel or heparin is forbidden until 24 hours have elapsed.

The concomitant use of all other medications is permitted during the trial for all patients. However, caution is advised when strong inhibitors of CYP2B6 and CYP3A4 are administered concomitantly.

All other non-drug therapies are permitted during the trial for all patients. Patients allocated to the best medical treatment alone group will be able to participate in early mobilization exercises. Patients randomised to the therapeutic hypothermia and best medical treatment group will not be able to participate to the same extent in early mobilisation exercises during the period of active cooling and re-warming until disconnection and removal of the cooling device.

Therapy changes (including changes of regimen) during the treatment phase of the trial are to be documented in the patient file and in the eCRF.

7.5 Blinding

The very nature of therapeutic hypothermia effectively precludes a double-blind trial design. The mRS score at outcome assessment [A7, Day 91±14 days] will be assessed not only by the local investigator, but also by an outcome adjudication committee blind to the patient's treatment assignment. The scores of the committee will become the primary efficacy variable. This will ensure the highest possible standard for the evaluation of clinical benefit of the intervention. See Section 8.1.1.2 for more details.

A DSMC will assess the patient safety and efficacy data throughout the trial (see Section 11.5.2.2). Special care will be exercised to safeguard the trial team from unblinding to treatment groups. Procedures for the evaluation of safety and efficacy data and unblinding by the DSMC are documented in the DSMC charter.

7.5.1 Emergency envelopes

Not applicable.

7.5.2 Unblinding procedures

After the SAP has been finalized and the database has been locked, pseudonymised, cleaned and validated data, masked to intervention, will be delivered from the data management work package to The Copenhagen Trial Unit for analysis. The results of these analyses reported to the EuroHYP-1 steering committee will be blinded to intervention. Unblinding will only happen after all analyses are finalised and two unbiased conclusions have been written, one assuming that one group is the hypothermia and best medical treatment group and the other assuming that the same group is the best medical treatment alone group.

8 TRIAL EVALUATIONS AND ASSESSMENT SCHEDULE

8.1 Trial evaluations

8.1.1 Clinical evaluations

8.1.1.1 Patient and treatment characteristics

At the beginning of the trial, the patient's demographic data, medical history, vascular risk factors and all current medications will be recorded. A review of this information will allow the investigator to assess whether the patient should be enrolled. Other data will be collected as required, including information obtained from physical examinations and radiological procedures as well as information on concurrent medication including thrombolytic treatment with alteplase and non-drug therapies.

All time points relevant for the conduct of the trial and the evaluation of parameters will be recorded. They include, but are not limited to, the following:

- Time of onset of stroke symptoms.
- Time of admission to hospital.
- Time of start of alteplase administration (if applicable).
- Time of randomisation.
- Time of collection of blood samples for routine blood and biomarker analyses.
- Time of end of alteplase administration (if applicable).
- Time of start of therapeutic hypothermia (if applicable).
- Time of administration of IMDs (if applicable).
- Time of administration of IMPs and concomitant medication (if applicable).
- Time of start and end of the re-warming period (if applicable).
- Time of assessment of parameters.

Furthermore, the type, serial number (if applicable) and batch number (if applicable) of IMDs used as well as the batch number of IMPs administered will be recorded.

8.1.1.2 Modified Rankin Scale

The modified Rankin Scale (mRS) [Van Swieten 1988] is the preferred disability outcome variable for clinical stroke trials [Roberts 1998]. For further details see Section 16.1.1.

The mRS is a 7-point ordinal hierarchical scale describing the range of disability encountered post stroke by scores ranging from 0 to 6, with higher scores indicating more severe disability, and with death assigned a score of 6.

Each Rankin score encompasses a broad range of potential outcomes, and boundaries between grades are poorly defined relative to other outcome assessment instruments [Wolfe 1991]. This lack of structure is reflected by a certain degree of inter-observer variability seen when the mRS is applied in clinical practice.

In order to improve mRS scoring consistency, investigators will undergo a multimedia mRS training system process [Quinn 2007] developed at the University of Glasgow/UK and available online. Investigators must successfully pass certification in mRS assessment as a pre-requisite for their participation in the trial. The certificate will be delivered by the Outcomes Coordinating Centre, Western Infirmary, Glasgow, UK.

The mRS assessments will be performed in a standardised fashion according to each centre's normal practice. During the interview process, investigators may use a structured format or other format as recommended by the outcomes adjudication committee in their training materials. The presence of a carer or family member is welcome even for communicative patients, since their participation can assist with interpretation of answers. The investigator will assign a mRS score which will be recorded on the trial eCRF website including a comment on whether there is significant dysarthria or dysphasia.

At outcome assessment [A7, Day 91±14 days], the mRS assessment will be recorded using a digital video camera. During this recording, no reference to clinical events that could give clues as to treatment allocation will be made. The digital recordings will then be transferred to the EuroHYP-1 outcome adjudication web portal *via* the inbuilt internet USB 2 connection on a FLIP device. The clip can be uploaded from within the trial eCRF website. Central archiving and storage of copies of clips will be as for other trial-related data.

Editing of the clip may be necessary to disallow patient identification and to ensure assessment blinded to treatment allocation. If any editing has occurred, the nature of the editing will be recorded on the EuroHYP-1 trial website. However, the original clip will be maintained except for the parts of the clip that allow patient identification. The edited clip will be the one used for review by the members of the EuroHYP-1 outcome adjudication committee.

In order to improve accurateness of point estimates and statistical power for the primary efficacy variable of this trial, digital recordings will be reviewed by at least 4 members the EuroHYP-1 outcome adjudication committee, coordinated at the Western Infirmary Acute Stroke Unit, Glasgow, UK, following a protocol laid down in the committee's charter. Recordings will be adjudicated by native speakers or by English-speaking reviewers after translation into English by native speakers. For more information on the committee see Section 2.3.6. For the review of a given clip, the committee members involved will be selected from a pool according to availability and will be notified by email.

If the reviewers deem a clip's quality sufficient for mRS assessment, the review process will be performed and a mRS score will be assigned. Each reviewer will perform his/her assessment of the clip independently from other reviewers and without knowledge of the score assigned by the investigator and by co-reviewers.

The score assigned by each reviewer will be entered into the web portal. For final assignment of a patient's mRS score, the median of the scores assigned by the reviewers will be retained. The adjudication committee may also review cases in which there are discrepant scores among blinded reviewers and assign a final score after committee discussion. All original scores will be retained and the statistical analysis plan will describe the handling of the adjudicated scores.

Technically unsatisfactory clips will be identified and notified to the investigator within a few days of upload to facilitate replacement. In this case, missing information from the interview may be replaced *via* questions relayed to the interviewer by email, or patients may be invited to another outcome assessment.

In case of death in the course of the trial, the patient will be assigned a mRS score of 6.

The mRS will be assessed by the investigator at screening assessment [A1. within 90 minutes before the start of the treatment phase TP] as pre-stroke score in the medical history, at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days]. In addition, the mRS will be assessed by the 4 reviewers of the EuroHYP-1 outcome adjudication committee at outcome assessment [A7, Day 91±14 days].

8.1.1.3 National Institutes of Health Stroke Scale

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance [Brott 1989]. Scores range from 0 to 42, with higher scores indicating a more severe deficit. For further details see Section 16.1.2.

A web-based training programme and certification procedure using video clips is available at http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx *via* a dedicated EuroHYP-1 trial campus. Investigators must successfully pass certification in NIHSS assessment as a pre-requisite for their participation in the trial.

The NIHSS will be assessed by the investigator at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], at assessment 2 [A2, End of Hour 24±2], at assessment 3 [A3, Hour 48±4 hours], at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

8.1.1.4 Assessment of body temperature

Body temperature is defined as the temperature measured in degrees Celsius. Body temperature will be assessed according to local standard clinical practice by intermittent tympanic or rectal temperature measurements, or with continuous rectal or bladder thermometry. During treatment phase [TP], the method and timepoints of body temperature assessment differ between treatment groups:

- In patients randomised to therapeutic hypothermia, body temperature will be monitored through bladder or rectal thermal probes from the start of treatment period [TP, beginning of Hour 1] until end of re-warming period. It will be

assessed once at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], subsequently during the treatment phase [TP] every 15 minutes during the first 3 hours (except at timepoints t=0min and t=15min, when body temperature will not be assessed) and every 60 minutes thereafter until end of re-warming period.

- In patients randomised to best medical treatment alone, body temperature will be assessed every 60 minutes (except at timepoint t=0min, when body temperature will not be assessed) until end of treatment phase [TP] according to local standard clinical practice.

Following the end of the treatment phase [TP], body temperature will be assessed at 8-hour intervals according to local standard clinical practice until assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first].

Body temperature measurements will be performed by an investigator or a trial nurse. The results of the measurements will be recorded in the patient's chart and in the eCRF from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] until assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first].

8.1.1.5 Timing and dose of antipyretic medication

Timing and dose of any antipyretic medication administered will be recorded in the patient's chart and on the eCRF from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] until assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first].

8.1.1.6 Glasgow Coma Scale motor response subscale

The GCS is a neurological scale aiming at providing a reliable, objective way of recording the level of consciousness of a person [Teasdale 1974]. The best motor response is assessed with a 6-point ordinal hierarchical scale. Scores range from 1 to 6. For further details see Section 16.1.3.

For the purpose of this trial, the GCS motor response is used as a means to monitor the patient's alertness/sedation levels in patients undergoing therapeutic hypothermia. The GCS motor response will be assessed by the investigator or a trial nurse once at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] and prior to any intended repeat pethidine administration thereafter, and recorded on the eCRF.

8.1.1.7 Timing and dose of investigational medicinal products and support medication

For anti-shivering and support medication, timing and dose of each administration will be recorded during the treatment phase [TP] in patients undergoing therapeutic hypothermia.

8.1.1.8 *Bedside Shivering Assessment Scale*

The BSAS is a 4-point ordinal hierarchical scale to assist in the monitoring and control of shivering. Scores range from 0 to 3 [Badjatia 2008]. For further details see Section 16.1.4.

The BSAS will be recorded from patients undergoing therapeutic hypothermia during the treatment phase [TP] every 15 minutes during the first 3 hours (except at timepoints t=0min and t=15min, when the BSAS will not be assessed) and every 60 minutes thereafter.

8.1.1.9 *Brain infarct size*

Brain infarct size and other key baseline and follow-up imaging parameters will be determined from CT or MRI imaging by the imaging evaluation team based at the University of Edinburgh, Edinburgh, UK.

Prior to initiation of a trial site, written instructions for minimum scan quality standards, timing and formats will be delivered to the respective neuroradiological department *via* the local investigator. Each trial site will be requested to send a test scan, of every type of scan intended to be used, *via* the image data submission mechanisms, prior to enrolment of the first patient at the site. This enables imaging quality assurance tests and ensures that site trial staff are familiar with data transfer protocols prior to trial start.

CT or MRI imaging will be performed as part of routine clinical care before enrolment and at imaging assessment [A4, Hour 48±24 hours]. Both scans must be sent to Edinburgh for evaluation.

For infarct size and volume assessment, a CT brain scan, preferably volume acquisition, or a MR T2 or a MR FLAIR series, performed at imaging assessment [A4, Hour 48±24 hours], must be submitted to the imaging evaluation team. All images must be axial, not coronal. Details of slice parameters, sequence details and other requirements are provided in a separate document.

Pseudonymised brain scan images will be electronically transferred to the EuroHYP-1 imaging website by either sending an encrypted CD or DVD by mail or by using secure web uploading.

Image review will be done *via* the Systematic Image Review System, a web-based, largely browser-independent, very rapid image presentation tool. The image data remain on the EuroHYP-1 imaging server and are transferred in the jpeg format. Expert review will include qualitative scan rating of ischaemic lesion extent, swelling, haemorrhagic transformation, hyperattenuated artery and background brain changes (atrophy, leukoaraiosis, old stroke lesions) using validated methods and quantitative measures. Reviewers will be told whether the respective scan had been performed during the screening assessment [A1, within 90 minutes before the start of the treatment phase TP] or imaging assessment [A4, Hour 48±24 hours], but will remain blinded to the patient's clinical details and treatment group.

The final infarct size will be determined using validated quantitative scores which are described in detail in a separate document. Where scan quality allows this, the infarct volume will be measured either by manual outlining the lesion on the scan images, multiplying the lesion area by slice thickness to obtain the lesion volume on each slide and then summing up the slice volumes to obtain the total lesion volume [van der Worp 2001] or based on diameter measures.

Ischaemic tissue is defined on CT as brain tissue hypoattenuation with respect to contralateral normal tissue attenuation, and on MRI as T2 or FLAIR hyperintensity within the affected brain region. Patients with no visible lesion will have infarct size recorded as zero. A subset of 5% of datasets will be double-measured for quality assurance purposes.

A dedicated email address has been established for queries by investigators and their affiliated neuroradiologists regarding imaging CT and MRI imaging issues (eurohyp.imaging@ed.ac.uk).

8.1.1.10 Other imaging parameters

CT or MRI scans will be performed during screening assessment [A1, within 90 minutes before the start of the treatment phase TP] and during imaging assessment [A4, Hour 48±24 hours]. Specific written instructions to:

- trial site investigators and neuroradiologists on acquisition parameters and the timing and format of scan data are provided in a separate document.
- to biostatisticians on parameters for statistical analysis (scoring and classification of images) are provided in the SAP.

The CT or MRI scan performed before enrolment will additionally be used for verification of inclusion and exclusion criteria and for characterisation of the trial population. Finally, their predictive value regarding the patient's response to therapeutic hypothermia in the presence or absence of alteplase will be evaluated.

In this context, the presence, location and extent of any visible infarct, early infarct swelling, hyperdense artery, leukoaraiosis, atrophy and prior infarct on the scan performed before enrolment will be tested for any interaction with early (infarct swelling, haemorrhagic transformation, neurological deterioration, death) and late (NIHSS and mRS scores, death) neurological and functional outcome variables at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

8.1.1.11 Date of discharge from hospital

The date of discharge from hospital will be recorded by the investigator or a trial nurse after assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] had been performed.

8.1.1.12 Death

Patients will be categorised as "alive" (mRS score ≤5) or "dead" (mRS score = 6) at outcome assessment [A7, Day 91±14 days].

8.1.1.13 Patient experience survey

The patient experience survey consists of 2 parts to be administered at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days], respectively, if a version is available in a language the patient understands. It is available in two slightly different versions to be applied to patients depending on the treatment group they have been randomised to. For details see Sections, 16.1.8, 16.1.9 and 16.1.10. In some cases, the patient will not be able to complete the questionnaire because of severe aphasia (defined as a score >1 on item 9 on the NIHSS) or cognitive disorders (defined as a score >0 on at least one of the items 1a, 1b, or 1c on the NIHSS).

Part I consists of a 24-item questionnaire on the patient's experience with the respective treatment. Responses to each question will be scored on a scale ranging from 1 to 7 except for the last 3 questions where patients are asked to provide free-text answers. For some questions, a box may be ticked, if the patient has no recollection of the item.

Part II consists of a 6-item questionnaire which is identical for both treatment groups. Responses to each question will be scored on a scale ranging from 1 to 7.

8.1.1.14 Transcranial ultrasound sub-study

The transcranial ultrasound sub-study aims to assess the effect of therapeutic hypothermia on reperfusion after acute ischaemic stroke. It will be performed in a subset of patients treated at selected trial sites. Patients participating in this sub-study will have to meet a number of additional inclusion and exclusion criteria.

The transcranial ultrasound sub-study will use transcranial colour-coded sonography. The assessment will be performed by an investigator specifically qualified for the method during screening assessment [A1, within 90 minutes before the start of the treatment phase TP] and at several time points during the treatment phase [TP]. Full details of all aspects of the sub-study will be provided in a separate supplementary clinical trial protocol which will be submitted for approval to competent authorities and IRBs/IECs prior to enrolment of the first patient into the sub-study.

8.1.2 Laboratory evaluations

8.1.2.1 Clinical and research laboratory evaluations

For routine laboratory evaluations see Section 9.6.6.

For the assessment of biomarkers in the blood that potentially mirror the pathophysiology of acute ischaemic stroke, venous blood samples with a volume of

about 25ml each will be drawn at baseline [between beginning of screening assessment A1, within 90 minutes before the start of the treatment phase TP, and 60 minutes after start of the treatment phase TP], at assessment 2 [A2, End of Hour 24±2] and at assessment 5 [A5, Hour 72±4 hours].

Proteomics and genomics will be performed on the samples to identify new biomarkers related to the safety and efficacy of hypothermia. The assessments by the biomarker team will include the following biomarkers:

- MMPs including gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8 and MMP-13) and stromelysines (MMP-3 and MMP-10) using multiplex ELISA [SearchLight technology].
- MMP endogen inhibitors (TIMP-1 and TIMP-2) using multiplex ELISA [SearchLight technology].
- H-FABP, UFD-1, RNABP, NDKA, GSTP-1 and Pro-BNP using standard ELISA.
- Cerebral Array I & II containing BDNF, GFAP, NSE, NGAL, sTNFRI, D-dimer and CRP using biochip analysers [Randox].
- Pro-ANP, Copeptin, IL6, IL8, IL10, mannose-binding lectin (MBL), mHLA-DR, monocytotic cytokin-secretion ex vivo stimulation, C5a in plasma, ultrasensitive PCT, lipopolysaccharide-binding protein (LBP).

8.1.2.2 Specimen preparation, handling, storage and shipping

Blood samples for routine clinical chemistry, haematology and coagulation will be taken, prepared, handled and sent to the local trial site laboratory for analysis.

For the purpose of biomarker assessment, web-based training as well as specific written instructions for specimen preparation, handling, storage and shipping will be laid down in a separate document which will be provided to the trial site prior to their participation in the trial. Each blood withdrawal comprises 2 serum separation tubes, 2 plasma EDTA separation tubes and one Tempus Blood RNA stabilisation tube. Only the specially prepared tubes supplied by the biomarkers team will be used to obtain the samples intended for biomarkers evaluation in order to avoid any pre-analytical variation.

Pseudonymised samples will be sent to the biomarker assessment team at Hospital Vall d'Hebron, Barcelona, Spain. Part of the blood samples will be forwarded for specific analyses to Randox Testing Services (Crumlin, UK), Proteome Sciences (Cobham, UK) or Charité - Universitätsmedizin Berlin (Berlin, Germany).

Other analyses than those listed in Section 8.1.2.1 may be performed on the patient's blood samples if new insights become available during the course of the trial or after its completion. All of these analyses will also be performed on pseudonymised samples. Any blood sample remaining after analyses will be destroyed within 15 years after completion of EuroHYP-1.

8.1.3 Economic evaluations

8.1.3.1 Investigational medical devices

The type and number of disposable IMD items used during the treatment phase [TP] and the re-warming period will be recorded on the eCRF by the investigator or trial staff.

8.1.3.2 Patient location during stay in hospital

The location of the patient will be assessed and recorded by the investigator or a trial nurse at 12:00 hours on each day the patient spends in hospital during his/her initial stay after onset of acute ischaemic stroke. The location of the patient will be recorded as falling in one of the following 5 categories:

- Neurological intensive care unit.
- Intensive care unit.
- Intermediate care unit/high dependency unit.
- Stroke unit.
- Normal ward.

8.1.3.3 Destination after discharge from hospital

The patient's destination after discharge from hospital will be recorded by the investigator or a trial nurse on assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] as falling into one of the following 5 categories:

- The patient's or a relative's home.
- Other hospital.
- Rehabilitation center.
- Chronic nursing facility (24h/7d medically assisted facility).
- Retirement home (medical support via general practitioner).

8.1.3.4 World Health Organization Disability Assessment Schedule

The WHODAS 2.0 is an ordinal hierarchical scale used as a general measure of functioning and disability in 6 major life domains [Üstün 2010a, Üstün 2010b]. Responses to each of the 36 domain questions are scored on a 5-point scale. Summary scores range from 36 to 180. In some cases, the patient will not be able to complete the questionnaire because of severe aphasia (defined as a score >1 on item 9 on the NIHSS) or cognitive disorders (defined as a score >0 on at least one of the items 1a, 1b, or 1c on the NIHSS). In case the patient cannot participate in the

interview, due to severe aphasia or cognitive disorders, the patient's relative/carer will be interviewed instead of the patient.

The WHODAS 2.0 will be filled in by the investigator at outcome assessment [A7, Day 91±14 days], if a validated version is available in a language the patient or his/her relative/carer understands. For further details see Section 16.1.5.

8.1.3.5 EuroQoL 5-dimensions 5-level questionnaire

EQ-5D-5L is a standardised measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal [Herdman 2011]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

EQ-5D-5L is designed for self-completion by respondents and is suited for use in postal surveys, in clinics and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

- If the patient is impaired in his/her handwriting capacity, the EQ-5D-5L will be filled in by the patient's relative/carer or the trial nurse as instructed by the patient.
- If the patient will not be able to complete the questionnaire because of aphasia or cognitive impairment, the patient's relative/carer will fill in the EQ-5D-5L instead of the patient.

The EQ-5D-5L will be filled in by the patient or his/her relative/carer at outcome assessment [A7, Day 91±14 days], if a validated version is available in a language the patient or his/her relative/carer understands. For further details see Section 16.1.6.

8.1.3.6 Sections 6 and 7 of the Health Recovery Guide and Diary

At discharge from hospital [A6], a health recovery guide and diary will be handed out to the patient or his/her relative/carer, if a version is available in a language both the patient and his/her relative/carer understands. The document contains the following sections:

- Information about me and my hospital.
- Recovering from stroke.
- Useful contact information.
- Preventing another stroke.
- Keeping track of my medications.
- My rehabilitation diary.
- Stroke recovery scorecard.

- Blood pressure measurement.
- Finding your Stroke Support Organisation.
- The EuroHYP-1 trial: purpose and useful information about the trial.
- Impressum.
- My questions to my doctors and nurses.

For further details see Section 16.1.7.

The patient or his/her relative/carer is requested to hand the document over to the investigator at the outcome assessment [A7, Day 91±14 days]. Sections 6 and 7 of the document will be removed from the diary and incorporated into the patient's chart, where it will serve as source documentation. The remaining document will be checked for instances of changes to concomitant medication and of AEs to be recorded in the patient's chart. The document will then be handed back to the patient or his/her relative/carer. All values relevant for the statistical analysis will be recorded in the eCRF by the investigator or the trial nurse.

Section 6

In Section 6 of the document ("My rehabilitation diary"), the following items are recorded:

- Visits to physicians, other health care professionals and/or hospital and the respective date.
- Home time defined as the number of nights that a patient spends back in his/her own home or a relative's home out of the first 90 days from stroke onset [Quinn 2008].
- Overall well-being day by day.

Only the first two items will be subject to statistical analysis.

The patient is requested to fill in this section of the document every day from discharge from hospital [A6] until outcome assessment [A7, Day 91±14 days]. The relative/carer may fill in the section if the patient is not able to do so for whichever reason.

Section 7

The Section 7 of the document ("Stroke recovery scorecard") is identical to the 12-item version, proxy-administered, of the WHODAS 2.0.

The relative/carer is requested to fill in Section 7 of the document just prior to the outcome assessment [A7, Day 91±14 days].

8.2 Assessment schedule

The purpose of the screening assessment is to determine patient eligibility for trial participation. The screening assessment must be completed prior to randomisation. The final trial assessment will occur at Day 91±14 days.

The trial activities and assessment schedule are shown in Table 2.

Table 2 Overview of clinical trial activities/assessment schedule

Yellow rows: hypothermia group only

	A1	TP				A2	A3	A4	A5	A6	A7/8
	Screening					**End of Hour 24**		**Imaging**			**Outcome**
Day										**8 or discharge**	**91±14 or End of trial**
Time	Period of 90min prior to start of TP	t=0	Hour 1-3: every 15min[18]	Hour 4-12: every 60min	Re-warming: every 60min[1]	Hour 24±2	Hour 48±4	Hour 48±24	Hour 72±4		
CT or MRI (standard of care; may be performed longer than 90 minutes before start of treatment)	X							X			
Patient enrolment[16]	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history	X										
Previous/concomitant medication[2]	X										
Physical examination	X					X	X		X	X	X
Body weight and height (estimate)	X										
12-lead ECG	X										
Laboratory testing[3]	X										
Pregnancy test (females of childbearing potential only)	X										
Vital signs (blood pressure,	X		X[19]	X	X[1]	X	X		X	X	X

	A1	TP				A2	A3	A4	A5	A6	A7/8
	Screening					**End of Hour 24**		**Imaging**			**Outcome**
Day										**8 or discharge**	**91±14 or End of trial**
Time	Period of 90min prior to start of TP	t=0	Hour 1-3: every 15min[18]	Hour 4-12: every 60min	Re-warming: every 60min[1]	Hour 24±2	Hour 48±4	Hour 48±24	Hour 72±4		
heart rate, respiratory rate)											
Oxygen saturation	X		X[19]	X	X[1]	X					
Body temperature[4]	X		X	X	X[1]		X				
Modified Rankin Scale	X									X	X[5]
NIHSS	X					X[17]	X			X	X
Randomisation		X									
Anti-shivering medication[6]		X	X								
Induction of cooling[7]		X									
Application of IMDs[8]		X									
Drug accountability		X									
Inspection of insertion site[9]		X									
Bedside Shivering Assessment Scale			X	X	X						
Patient survey										X	X
Monitoring for pneumonia[10]	X										
Assessment of antipyretic medication	X										
GCS motor response subscale	X	X[20]									
Patient location during stay in hospital[11]	X										

	A1	TP				A2	A3	A4	A5	A6	A7/8
	Screening					**End of Hour 24**		**Imaging**			**Outcome**
Day										**8 or discharge**	**91±14 or End of trial**
Time	Period of 90min prior to start of TP	t=0	Hour 1-3: every 15min[18]	Hour 4-12: every 60min	Re-warming: every 60min[1]	Hour 24±2	Hour 48±4	Hour 48±24	Hour 72±4		
Date/destination of discharge										X	
WHODAS 2.0											X[12]
EQ-5D-5L											X[12]
Health Recovery Guide and Diary											X[13]
AE/SAE assessment	X										
Blood sampling for biomarker[14]	X					X			X		
Transcranial ultrasound[15]	X	X									

1 Re-warming: hypothermia group only
2 Previous medication including alteplase
3 Includes sodium, potassium, magnesium, creatinine, urea, gamma-glutamyl transpeptidase, ASAT, ALAT, alkaline phosphatase, blood glucose; haemoglobin, haematocrit, erythrocytes, leukocytes, platelets, INR. Further samples may be taken throughout the study at the discretion of the investigator
4 Body temperature will be assessed according to local clinical practice with tympanic, bladder, or rectal temperature measurement, except in patients randomised to therapeutic hypothermia from start of treatment phase [TP, beginning of Hour 1] until end of re-warming period, when bladder or rectal thermal probes will be used. During TP, body temperature will be assessed every 15min during the first 3 hours (except at timepoints t=0min and t=15min) and every 60min thereafterin patients randomised to therapeutic hypothermia, every 60min (except at timepoint t=0min) in patients randomised to best medical treatment alone, subsequently in all patients at 8-hour intervals until A6 [Day 8 or day of discharge from hospital, whichever occurs first]
5 The mRS assessment at outcome assessment [A7] will be recorded using a digital video camera. The clip will then be transferred to the EuroHYP-1 outcome adjudication web portal
6 Anti-shivering medication: induction: buspirone 10mg p.o./pethidine 50mg i.v. (2min); repeat doses of 10mg buspirone p.o. may be administered as long as a maximum dose of 30mg/24h is respected; a bolus of pethidine 25mg i.v. may be given as long as an interval of at least 30min is respected and a maximum dose of 500mg/24h is not exceeded. 24h-doses include induction bolus. For the prevention and treatment of opioid-induced nausea and vomiting, a $5HT_3RA$ may be administered as support medication
7 Induction of cooling: 20ml/kg estimated bodyweight 4°C isotone saline or Ringer´s lactate over a period of 30-60min; EMCOOLS Brain.Pad, if available

8 IMDs permitted for cooling: EMCOOLS Brain.Pad (for induction of cooling only); Medivance/Bard Arctic Sun temperature management system with heat exchange control unit Arctic Sun 2000 or Arctic Sun 5000 and ArcticGel Pads; MTRE CritiCool temperature management system with heat exchange control unit CritiCool, accessoires and CureWrap; Zoll IVTM system with heat exchange control unit CoolGard 3000 or Thermogard XP, CoolGard start-up kit and intravascular temperature management catheters ICYy 3893 AE or ICY 3893 CO
9 If endovascular cooling is performed, the catheter insertion site must be visually inspected for detection of bleeding/haematoma in 3-hour intervals during TP and once 3 hours after removal of the intravascular catheter
10 Monitoring for pneumonia includes monitoring of oxygen saturation and body temperature, physical examination (auscultation, percussion) and, if clinically indicated, chest X-ray. Monitoring for signs of pneumonia must be performed from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] until A6 [Day 8 or day of discharge from hospital, whichever occurs first]
11 Patient location during stay in hospital must be assessed at 12:00 hours on each day in hospital
12 WHODAS 2.0 questionnaire and EQ-5D questionnaire must be filled in by the patient or his/her relative/carer at outcome assessment [A7]
13 Health Recovery Guide and Diary: Section 6: filled in by the patient every day from discharge to V7; Section 7: filled in by the carer/relative prior to V7
14 For participation in the biomarker sub-study a special ICF must be filled in by the patient or his/her legal representative. Baseline samples to be collected between beginning of A1, within 90 minutes before start of treatment period TP, and 60 minutes after start of treatment period TP. Assessment at End of Hour 24±2 hours
15 Only selected study sites
16 Informed consent will be obtained in accordance with national regulatory requirements
17 NIHSS assessment at End of Hour 24±2 hours
18 Starting at t=30min
19 Every 60 minutes only
20 Prior to intended repeat administration of pethidine

9 SAFETY

9.1 Definition of an adverse event

An AE is any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the trial, having been absent at baseline, or if present at baseline, appears to worsen, whether or not related to an IMD or an IMP, in a patient, user or any other person involved in the clinical trial. For users or other persons, this definition is restricted to events related to IMDs.

The period of observation for an AE extends from the time of patient enrolment until outcome assessment [A7, Day 91±14 days] or end of trial assessment [A8], respectively, has been performed. Any medical occurrence that happens between the time of patient enrolment and the first treatment with an IMD or the first administration of an IMP is an AE and has to be documented in the patient's file and on the eCRF AE report form. New AEs reported to the investigator during the follow-up period after the last treatment with an IMD and the last administration of an IMP must be documented, treated and followed up like all other AEs.

AEs will not be followed up after the outcome assessment [A7, Day 91±14 days] has been performed.

Pre-existing conditions that do not worsen during the course of the trial are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the patient at screening assessment [A1, within 90 minutes before the start of the treatment phase TP]. Abnormal laboratory values obtained at screening assessment will only meet AE criteria if newly detected.

In patients randomised to therapeutic hypothermia, shivering occurring during the cooling and re-warming periods represents a physiological reaction to the lowering of body temperature and will therefore not be recorded as an AE.

Data pertaining to AEs will be collected during each trial assessment based on the patient's or relative's/carer's spontaneous description, through investigator inquiry or discovered in the course of examinations done during the assessment. The investigator will assess and record any AE in detail in the patient file and on the eCRF AE report form. The following information must be recorded:

- AE diagnosis or main symptom.
- Date of onset.
- Time of onset.
- Date of worsening.
- Time of worsening.
- Intensity (maximum observed; see Section 9.1.1).
- Causal relationship (not related; related).
- Serious (yes; no).

- Outcome (see Section 9.1.4).
- Action taken with IMPs or action taken with an IMD (see Section 9.1.4).
- AE leading to discontinuation of the patient from the clinical trial (yes; no).
- Stop date and time.

After completion of all scheduled assessments the investigator must document any AEs arising from these assessments.

In case of an SAE,the investigator must additionally complete an SAE report form and report it to the sponsor immediately, as described in Section 9.2.

Treatment of overdose with IMPs is described in Section 7.3.7.

9.1.1 Definition of intensity

The clinical intensity of an AE will be classified as:

Mild:	Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the patient is distracted.
Moderate:	Signs and symptoms that cause discomfort and interfere with normal functioning, but are tolerable. They cannot be ignored and do not disappear when the patient is distracted.
Severe:	Signs and symptoms that affect usual daily activity and incapacitate the patient, thereby interrupting his/her daily activities.
Life-threatening:	Life-threatening consequences, urgent intervention indicated.
Fatal:	Death related to AE.

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the eCRF AE report form). In such situations, the investigator should make a judgment based on personal experience.

9.1.2 Definition of causal relationship with investigational medical devices and investigational medicinal products

An AE is considered to be related/possibly related to an IMD or related to an IMP if a causal relationship between the IMD or the IMP and an AE is at least a reasonable possibility. In this case the event is considered an adverse device effect/adverse reaction. If the event is serious (see below), it is a serious adverse device effect/adverse reaction.

The expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline). Otherwise, the relationship should be considered as not related.

9.1.3 Definition of expectedness

Expected/anticipated AEs are those listed in the current SmPC/IB or the latter's appendices (e.g., operator's manual, user guide). An unexpected/unanticipated AE is an experience not previously reported in nature, severity or incidence in the current SmPC/IB or the latter's appendices.

9.1.4 Categories of actions taken and outcome

Action(s) taken with IMD(s)/IMP(s):

- Drug withdrawn/treatment suspended.
- Dose reduced.
- Dose increased.
- Dose not changed.
- Unknown.
- Not applicable.

The reportable outcomes and/or sequelae of an AE are as follows:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered/resolved with sequelae.
- Fatal.
- Unknown.

In case of death and more than one AE, only the AE leading to death will be attributed with a fatal outcome.

9.2 Definition of a serious adverse event

An SAE is an AE that

- Led, might have led, or could lead to a death.
- Led, might have led, or could lead to a serious deterioration in the health of the patient that
  - resulted in a life-threatening[4] illness or injury.

[4] The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- resulted in a permanent or significant impairment of a body structure or a body function.
- required in-patient hospitalization or prolongation of existing hospitalization.
- resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function or consists of any other medically important condition.[5]

➢ Led, might have led or could lead to foetal distress, foetal death, or a congenital abnormality or birth defect.

In case of death, an autopsy report should be submitted (if available). The date and cause of death should be recorded.

All SAEs that occur during the trial period, whether considered to be related to an IMD or to an IMP or not, must be reported by the investigator by telefax within 24 hours of knowledge of the event.

SAE report forms are provided in the eCRF. Completed reports must be printed out, signed by the investigator and transferred by telefax to the EuroHYP-1 SAE adjudication committee, the institution designated by the sponsor for this purpose. In addition, the eCRF will automatically inform the SAE adjudication committee that a SAE has occurred. Further reporting details will be outlined in the SMP.

The address for SAE reporting is:

Renate Vogler, MD
Chair, EuroHYP-1 SAE adjudication committee
Center for Clinical Studies (CCS Erlangen)
University Hospital Erlangen
Krankenhausstr. 12
91054 Erlangen
Germany
Telephone: +49 9131 85 47023
Telefax: +49 9131 85 35120
Email: renate.vogler@uk-erlangen.de
ams.ccs@uk-erlangen.de

Although all information required for completion of a SAE report form may not be available within the specified time period, an initial report should be submitted if the following minimal information is available:

➢ An identifiable patient (number, initials).

➢ An identifiable reporting source (investigator/trial site identification).

[5] According to ICH E2A, CPMP/ICH/377/95: "Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient/patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse."

- An event or outcome that can be identified as serious.

The EuroHYP-1 SAE adjudication committee is commissioned by the sponsor to review and assess all SAE reports and to ensure expedited reporting of relevant reports to regulatory authorities and IECs/IRBs in accordance with all applicable regulatory requirements.

Once the review process is completed, the EuroHYP-1 SAE adjudication committee will forward the SAE report and all other relevant documentation to the CCS Erlangen for queries, follow-up and data collection in the SAE database. Details will be outlined in the SMP.

The investigator must supply further supporting information within 3 days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information. Follow-up reports should be sent without delay to the EuroHYP-1 SAE adjudication committee as an SAE report form (marked as a follow-up report) and accompanied by appropriate supporting documentation (e.g., hospital discharge letters). The SAE has to be followed up until a final outcome and date are available.

SAEs occurring after the end of the follow-up period need only be reported if the investigator considers the event to be related to an IMD or an IMP. In general, these reports will not be entered into the trial database, but will be added to the clinical study report and reported to the regulatory authorities and IECs/IRBs, if applicable.

9.3 Pregnancy

Each pregnancy that starts during the trial must be reported by the investigator to the EuroHYP-1 SAE adjudication committee within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on a pregnancy monitoring form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to an IMD or an IMP. Each pregnancy has to be reported as a non-serious AE (device/drug exposure before or during pregnancy) as well.

9.4 Device deficiency

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, user errors and inadequate labeling.

The investigator will assess and record any device deficiency in detail on the eCRF device deficiency form. Reporting of a device deficiency to the manufacturer or the competent authority will follow national legislation.

9.5 Incident

An incident is any device deficiency that led, might have led or could lead to death or a serious deterioration in the health of a patient, user or any other person involved in the clinical trial.

The investigator must report any incident to the manufacturer or the competent authority as required by national legislation. Reports must be printed out, signed by the investigator and transferred by telefax to the EuroHYP-1 SAE adjudication committee. For address details see Section 9.2.

In case of an incident that fulfils the definition of a SAE, the investigator is additionally requested to complete, print out, sign and transfer by telefax a SAE report form to the EuroHYP-1 SAE adjudication committee immediately. For address details see Section 9.2.

9.6 Other safety variables

9.6.1 Diagnosis of pneumonia

Pneumonia will be diagnosed if CDC radiological AND clinical/laboratory criteria have been met:

Radiological criteria

Two or more serial chest radiographs with at least one of the following:

- New or progressive and persistent infiltrate.
- Consolidation.
- Cavitation.

NOTE: In patients without underlying pulmonary or cardiac disease (e.g. respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.

Clinical and laboratory criteria

At least one of the following:

- Fever (>38°C) with no other recognized cause.
- Leukopenia (<4,000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3).
- For adults >70 years old: altered mental status with no other recognized cause.

AND at least two of the following:

- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements.
- New onset or worsening cough, or dyspnea, or tachypnea.

- Rales or bronchial breath sounds.
- Worsening gas exchange (e.g. O_2 desaturations (e.g., P_aO_2/FiO_2 <240), increased oxygen requirements, or increased ventilator demand).

9.6.2 Vital signs

Blood pressure, heart rate and respiratory rate will be recorded once at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], subsequently during treatment phase [TP] every 60 minutes (except at timepoint t=0min, when vital signs will not be recorded), at assessment 2 [A2, End of Hour 24±2], at assessment 3 [A3, Hour 48±4 hours], at assessment 5 [A5, Hour 72±4 hours], at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

Body weight will be estimated at screening assessment [A1, within 90 minutes before the start of the treatment phase TP] as the basis for the calculation of the volume of cold solution to be administered for induction of hypothermia.

9.6.3 Pulse oximetry

S_PO_2 levels will be recorded once at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], subsequently during treatment phase [TP] every 60 minutes (except at timepoint t=0min, when S_PO_2 levels will not be recorded).

9.6.4 Physical examination

The investigator will perform a physical examination, which includes auscultation of the heart and lungs and percussion of the chest, at screening assessment [A1, within 90 minutes before the start of the treatment phase TP], at assessment 2 [A2, End of Hour 24±2], at assessment 3 [A3, Hour 48±4 hours], at assessment 5 [A5, Hour 72±4 hours], at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days]. However, results will be recorded in the eCRF only, if

- the finding constitutes an AE or
- the finding leads to a change in concomitant medication or non-drug therapy or
- the finding is judged clinically relevant by the investigator.

9.6.5 Electrocardiography

A standard 12-lead ECG will be performed for all patients at screening assessment [A1, within 90 minutes before the start of the treatment phase TP]. The ECG must be recorded by a qualified physician, nurse or technician. The ECG will be reviewed by the investigator or an authorized representative who is experienced in the evaluation of ECGs

9.6.6 Clinical chemistry, haematology and coagulation

Blood samples for routine clinical chemistry, haematology and coagulation will be analysed in the local trial site lab and the values recorded on the eCRF at screening assessment [A1, within 90 minutes before the start of the treatment phase TP]. Further samples may be taken throughout the trial at the discretion of the investigator, e.g., a urine sample may be taken, if a urinary tract infection is suspected. However, values will be recorded on the eCRF only, if

- the laboratory value constitutes an AE or
- the laboratory value leads to a change in concomitant medication or non-drug therapy or
- the laboratory value is judged clinically relevant by the investigator.

The routine clinical chemistry, haematology and coagulation analyses will include evaluation of the following parameters: sodium, potassium, magnesium, creatinine, urea/blood urea nitrogen, gamma-glutamyl transpeptidase, ASAT, ALAT, alkaline phosphatase, blood glucose; haemoglobin, haematocrit, erythrocytes, leukocytes, platelets; INR.

10 DATA QUALITY ASSURANCE

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of trial. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit trial-related monitoring, audits, reviews by the IEC/IRB and/or regulatory authorities, and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

10.1 Standard operating procedures

Standard operating procedures will be implemented to ensure accurate, consistent, complete and reliable data, including methods to ensure standard practice among sites (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations and validation methods).

This trial will be monitored regularly by a qualified monitor from the sponsor or an organisation commissioned by the sponsor, according to GCP guidelines and the respective SOPs (see Section 10.4).

10.2 Source documentation requirements

All data collected from a patient during the course of the clinical trial shall be entered and/or filed in the respective patient file. This includes a copy of the letter sent to the patient's primary physician about the patient's participation in the trial (provided the patient has a primary physician and has agreed to the primary physician being informed).

The following data will be entered directly on the eCRF and are considered to be source data:

- mRS score adjudicated by the reviewers of the EuroHYP-1 outcome adjudication committee based on video clips recorded by the investigator at outcome assessment [A7, Day 91±14 days] (see Section 8.1.1.2). Reviewers will enter their scores directly onto the outcome adjudication portal, from where the data will be transferred onto the eCRF.
- Brain infarct size and other imaging variables assessed by the reviewers of the imaging evaluation team based on CT or MRI scans performed before enrolment and at the imaging assessment [A4, Hour 48±24 hours] (see Sections 8.1.1.9 and 8.1.1.10).
- Biomarkers assessed by the biomarker assessment team in blood samples drawn between beginning of screening assessment [A1, within 90 minutes before the start of the treatment phase TP] and 60 minutes after beginning of the treatment phase TP, at assessment 2 [A2, End of Hour 24±2] and at assessment 5 [A5, Hour 72±4 hours] (see Section 8.1.2.1).

If the site is using a validated computer system including audit trail with a separate access for the monitor (i.e., the monitor can only access the data of the trial patients), then no signed paper print-outs are required.

If a trial site is using an electronic system for documenting source data without a separate access for the monitor, then a member of the site staff must print out the source data after each assessment. The paper print-outs must be overlapping, if possible (i.e., must contain at least the last row of data from the patient's previous assessment). If it is not possible to obtain overlapping paper print-outs, the completeness of source data must be ensured by other suitable means. The print-out must be signed and dated by a member of the site staff who can confirm the accuracy and completeness of data in the paper print-out. The monitor should also sign and date after verifying the source data. The paper print-out should be stored in the patient's file. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initialled and dated. The same applies to any corrections of original data.

10.3 Data management

Investigators and/or persons with delegated authority will enter the information required by the protocol onto eCRFs developed for the trial by the data management work package and stored on a validated web-based database. Computers used to collate the data will have limited access measures *via* user names and passwords. The web pages for mRS rating and for uploading CT or MRI scans will only be accessible using SSL communication, which will utilize a validation certificate created especially for a particular server in the trial site's specific domain. This will enable authentication from the server to the user's browser and will encrypt all traffic between their computer and the authenticated host server.

All data will be collected and stored on firewall-protected, high-volume servers with preventative system maintenance policies in place to ensure uninterrupted service. These web servers are secured by VeriSign, the BT Trust Services Global Server Certificate programme. In addition, extensive data security procedures including virus detection and removal, daily backups, routine transaction logging and both on-site and off-site fire-proof storage of backups will further secure the data. Access to the trial data will be restricted to those who are part of the trial team. Various levels of access will be assigned to maintain masking of assessors to investigators' scores and to treatment group.

Data collection and management will comply with the UK Data Protection Act and international laws as appropriate, in accordance with legal and regulatory guidelines. The ISO 9001:2000-accredited data management centre has extensive experience of managing data in the context of privacy and data protection legislation, including the Data Protection Act 1998 and EU Data Protection Directive 95/46/EC. Plausibility checks will be performed according to a DVP. Inconsistencies in the data will be queried to the investigators; changes to the data will be documented on data clarification forms.

After all data are entered and all queries are solved, the database will be closed. In case of any changes to the data after database close, these changes will be documented according to the procedures and SOP of The Copenhagen Trial Unit.

All data and video recordings (in the format available at data lock) collected by the Robertson Centre for Biostatistics at the University of Glasgow on behalf of the outcome adjudication committee will be archived for a period of at least 10 years after the end of the trial (see Section 12.2 for more details).

10.4 Monitoring

This trial will be monitored regularly by a qualified monitor from the sponsor or an organisation commissioned by the sponsor according to GCP guidelines and the respective SOPs. Monitoring procedures include a site initiation visit designed to clarify all prerequisites before the trial commences at the site. Interim site monitoring visits will take place on a regular basis according to a mutually agreed schedule, but at least once per year. During these visits, the monitor will check for:

- evaluation of study progress.
- existence of an ICF duly dated and signed by the patient or his/her legal representative and the investigator.
- patient eligibility.
- completeness of the entries onto the eCRFs.
- the agreement of the source data with the eCRF entries.
- the correct documentation and timely reporting of AEs and SAEs.
- the correct storage of the IMPs and IMDs and the corresponding drug and device inventory records.
- compliance with the clinical trial protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.
- discussion of problems including AEs.

Monitoring will also be aimed at detecting any misconduct or fraud.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring assessments. In addition, the investigator is required to:

- have all data properly recorded on the eCRF and patient files prior to each monitoring assessment.
- have the source documentation available at the monitoring assessments.

All patients who are screened, but not entered into the trial, will be listed on the patient screening log.

Further details of monitoring activities will be outlined in the monitoring manual.

10.5 Auditing

Audits will be performed according to the corresponding audit plan, including the possibility that a member of the sponsor's quality assurance team may arrange to visit the investigator in order to audit the performance of the trial at the trial site, as well as all trial documents originating there. Auditors conduct their work independently of the clinical trial and its performance.

Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance team will agree with the contract auditor regarding the timing and extent of the audit(s). In the case of audits at the investigational site, the monitor will usually accompany the auditor(s).

11 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of trial planning. Further details on the statistical and analytical aspects will be presented in the SAP. which should include the statistical analysis system, e.g., SAS version number.

Any deviations from the planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close or unblinding will be described in amendments to the clinical trial protocol or the SAP. All deviations and/or alterations will be summarised in the clinical trial report.

11.1 Determination of sample size

The sample size calculations are based not only on evidence from the limited literature, but also on considerations of what size of clinical benefit would be sufficient to change clinical practice. We consider that, for a relatively complex intervention such as cooling, an absolute reduction in the risk of poor outcome of less than 7% would not be sufficient to change practice, and the trial is therefore powered to detect this 7% effect. This corresponds to approximately two thirds of the benefit from intravenous thrombolysis with alteplase within three hours of treatment onset [Lees 2010] and is equivalent to a NNT of 14. Our primary analysis will use an ordinal (shift) analysis of the mRS rather than the conventional dichotomous analysis [Bath 2012, Lees 2012].

Recent statistical research on ordinal analysis of the mRS and similar work on the Glasgow Outcome Scale shows that the use of ordinal analysis together with covariate adjustment can substantially increase the statistical efficiency [Murray 2005, Bath 2007, McHugh 2010].

The analysis is based on the proportional odds assumption, namely the assumption that wherever the mRS is dichotomised, the odds ratio for treatment *vs*. control will be the same – the 'common odds ratio'. The analysis retains validity with modest deviations from the proportional odds assumption, provided that the impact of treatment is to shift the entire distribution of mRS in the same direction. The analysis would only be inappropriate in a situation where a treatment might improve outcome in most patients but be harmful in those with severe disease.

The ordinal analysis of the mRS and of the Glasgow Outcome Scale has been accepted as valid by the drug regulatory authorities, has been recommended by the European Stroke Organisation Outcomes Working Group [Bath 2012], and is being increasingly adopted for the primary analysis of pivotal trials in stroke and head injury, including for instance the Scandinavian Candesartan Acute Stroke Trial (SCAST) [Sandset 2010].

The table below shows the required sample size based on the following assumptions. We are aiming for 80% power at a 5% significance level (2-sided), with patients randomised 1:1 to cooling *vs*. control. Recent pivotal trials in patients with acute ischaemic stroke had similar power [Sandercock 2012; Berkhemer 2015; Saver 2015]. For modelling purposes we have assumed an overall distribution of the mRS

from 0 (full recovery) to 6 (dead) as observed in our meta-analysis of existing trials of cooling in acute stroke: mRS 0 - 9%; mRS 1 - 13%; mRS 2 - 15%; mRS 3 - 21%, mRS 4 - 18%; mRS 5 - 7%; mRS 6 (dead) - 17%. This corresponds to an overall risk of unfavourable outcome (mRS ≥3) of 63%; a 7% absolute reduction in the risk of a poor outcome therefore corresponds to risks of a poor outcome of 66.5% in the control group and 59.5% in the treatment group, resulting in an odds ratio of 0.74.

The sample size calculation is based on the method of Whitehead [1993] which is designed for shift analyses based on ordinal logistic regression. We have conservatively allowed for 3% loss to follow up, although every effort will be taken to achieve a lower proportion. The table also illustrates the impact on the required sample size with a 20% efficiency gain as a result of covariate adjustment. Analysis of data of previous stroke trials has demonstrated that adjusting for prognostic baseline factors can reduce sample size by 20% to 30% for a given power [Gray 2009]. Such adjustment addresses imbalances in baseline factors between the treatment groups and increases in the precision of the estimated treatment effect. Covariate adjustment is now also recommended for other neurological diseases, for example traumatic brain injury [Bath 2012].

Central adjudication of mRS assessments as performed in EuroHYP-1 improves the reliability of the outcomes and can therefore reduce the required sample size by 19 to 24% [McArthur 2013]. In this trial, we conservatively estimate the reduction in sample size through central outcome adjudication as 15%.

In Table 3 we also model, for the sake of completness, sample sizes requires for the midpoints of the estimated benefits (25% and 21.5%) and the maxima of the estimated benefits (30% and 24%)

Table 3 Sample size estimates based on ordinal analysis of the ordered categorical modified Rankin Scale, with incorporation of covariate adjustment and greater precision in MRS determination, at 90% and 80% power.

ARR	Common OR	90% power						
		Group size	Total	3% loss to follow up	Covariate adjustment (20%)	Covariate adjustment (20%) plus MRS central adjudication (15%)	Covariate adjustment (25%) plus MRS central adjudication (21.5%)	Covariate adjustment (30%) plus MRS central adjudication (24%)
5	0.81	1403	2806	2893	2314	1967	1703	1498
6	0.78	974	1948	2008	1607	1366	1182	1040
7	0.74	715	1430	1474	1179	1002	868	764
8	0.71	547	1094	1128	902	767	664	584
9	0.67	432	864	891	713	606	524	461
10	0.63	349	698	720	576	489	424	373

ARR	Common OR	80% power						
		Group size	Total	3% loss to follow up	Covariate adjustment (20%)	Covariate adjustment (20%) plus MRS central adjudication (15%)	Covariate adjustment (25%) plus MRS central adjudication (21.5%)	Covariate adjustment (30%) plus MRS central adjudication (24%)
5	0.81	1048	2096	2161	1729	1469	1272	1119
6	0.78	728	1456	1501	1201	1021	884	778
7	0.74	535	1070	1103	882	750	649	571
8	0.71	409	818	843	675	573	496	437
9	0.67	323	646	666	533	453	392	345
10	0.63	262	524	540	432	367	318	280

Based on these figures we shall target a total sample size of 800 randomised patients. This comes from rounding up the total of 750 patients required to detect an absolute risk reduction of 7% (corresponding to an odds ratio of 0.74), and allowing for a 3% loss to follow up.

11.2 Analysis sets

The analysis populations for the statistical analyses of this trial are:

11.2.1 The intention-to-treat population of patients

The ITT population is defined as all included patients classified according to the intervention to which they were randomised (intervention groups).

11.2.2 Per-protocol population of patients

The per-protocol population, called the PPS, is the subset of all included patients without major protocol violations and classified according to the intervention to which they were randomised (intervention groups).

Major protocol deviations will be defined by the EuroHYP-1 steering committee before the detailed SAP is written.

11.3 Analysis types

An analysis of a specified variable in a population is a comparison of its distributions between the population's two intervention groups.

11.3.1 Complete case analysis

If the data are analysed only using data obtained from patients without any values of the variable(s) in question missing, then the analysis is a complete case analysis.

11.3.2 Analysis of data augmented by multiple imputation

The data may also be augmented by additional data generated by a multiple imputation prior to the analysis. Multiple imputations will be used if the p-value of Little's test is ≤0.05, indicating that the criterion 'missingness completely at random' (MCAR) is not fulfilled, i.e., the complete case sample is not a random sample of the ITT population. If the p value of Little's test is >0.05, there is no evidence that the MCAR is not fulfilled [Schafer 1999], and no multiple imputations will be used.

11.4 Variables for analysis

The primary and secondary outcomes and the primary safety variable will be analysed using the ITT population.

Exploratory analyses which include additional variables as well as the above variables, but using the per protocol population, will be conducted and the results discussed and contrasted to the primary results.

11.4.1 Values to be used in the primary analyses

11.4.1.1 Efficacy variables

11.4.1.1.1 Primary outcome measure

Score on the mRS at outcome assessment [A7, Day 91±14 days], as analysed with ordinal logistic regression and expressed as a common odds ratio.

11.4.1.1.2 Secondary outcome measures

- Death or dependency, defined as a score on the mRS >2 at outcome assessment [A7, Day 91±14 days].
- Death at outcome assessment [A7, Day 91±14 days].
- Score on NIHSS at outcome assessment [A7, Day 91±14 days].
- Brain infarct size at imaging assessment [A4, Hour 48±24 hours].
- WHODAS 2.0 score at outcome assessment [A7, Day 91±14 days].
- EQ-5D-5L score at outcome assessment [A7, Day 91±14 days].

11.4.1.2 Primary safety variable

- Occurrence of SAEs until outcome assessment [A7, Day 91±14 days].

11.4.2 Variables for explorative analyses

The analyses of the primary and secondary outcomes will be repeated using the per protocol population (PPS). In addition, the variables defined below will be subjected to analyses using the ITT as well as the PPS.

11.4.2.1 Intervention variables

- Time until achievement of target temperature, duration of active cooling , duration of therapeutic hypothermia, total dose of anti-shivering and support medications, distribution of IMDs used for cooling purposes, and BSAS during the treatment phase [TP] (hypothermia group only).
- Patient experience at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

11.4.2.2 Economic variables

- Distribution of patients' location in hospital at 12:00 hours from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Length of hospital stay after stroke onset, defined as interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Patients' destination at day of discharge from hospital.
- Number of visits to health care professionals and hospital, and home time at outcome assessment [A7, Day 91±14 days].
- Total length of stay and total healthcare resource use during interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to outcome assessment [A7, Day 91±14 days].
- Costs of primary hospital admission, defined as interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to day of discharge from hospital.
- Total costs of stroke during interval between screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to outcome assessment [A7, Day 91±14 days].

11.4.2.3 Safety variables

- Incidence of pneumonia from screening assessment [A1, within 90 minutes before the start of the treatment phase TP] to assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first].

- Occurrence of AEs and SAEs related to the administration of IMPs or treatment with an IMD.

The following variables will be evaluated for supportive safety purposes:

- Values of blood pressure, heart rate and respiratory rate during the treatment phase [TP], at assessment 2 [A2, End of Hour 24±2], at assessment 3 [A3, Hour 48±4 hours], at assessment 5 [A5, Hour 72±4 hours], at assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first] and at outcome assessment [A7, Day 91±14 days].

11.4.2.4 Other variables

- Change in biomarker concentrations from baseline [samples collected between beginning of screening assessment A1, within 90 minutes before the start of the treatment phase TP, and 60 minutes after beginning of the treatment phase TP] to assessment 2 [A2, End of Hour 24±2], and to assessment 5 [A5, Hour 72±4 hours].

Further variables for analysis include patient disposition, frequencies of protocol deviations, concomitant therapies, and the results of the patient survey.

11.5 Statistical analysis methods

Final statistical analyses will be carried out by statisticians at The Copenhagen Trial Unit. The Copenhagen Trial Unit is independent of the DSMC and will perform the final statistical analysis once the sample size has been reached or when the EuroHYP-1 steering committee stops the trial.

Pseudonymised, cleaned and validated data, masked to intervention, will be delivered by the data management work package to The Copenhagen Trial Unit for analysis. The results reported to the EuroHYP-1 steering committee will be blind to the intervention. Unblinding will only happen after all analyses are finalised and two unbiased conclusions have been written, one assuming that one group is the hypothermia group and the other assuming that the same group is the normothermia group.

11.5.1 Efficacy, safety and economic variables

All analyses will be based primarily on the ITT population and additionally, for sensitivity purposes, on the PPS.

11.5.1.1 Primary outcome measure

The primary efficacy variable, the score on the mRS at the outcome assessment [A7, Day 91±14 days], will be determined with multi-level, ordinal logistic regression. If the assumption of the ordinal regression analysis model is not fulfilled, the groups will be compared using non-parametric method (Mann Whitney) and the result will be the primary result. If the assumption of the model is fulfilled, the result of an

adjusted analysis will be the primary result. The adjusting variables will include the following minimisation factors:

- Intention to perform thrombolysis (yes *vs*. no).
- Method of cooling (surface *vs*. endovascular).
- Sex (male *vs*. female).
- Stroke severity (NIHSS 6-12 *vs*. 13 or higher).
- Age (≤65 years *vs*. >65 years).
- Visibility of a relevant ischaemic lesion on the first brain imaging (yes *vs*. no).
- Time since symptom onset (≤4 hours *vs*. 4–6 hours).

The primary efficacy variable is a candidate for an analysis using multiple imputations (see criterion defined above). If the variable is subjected to such an analysis the result will be the primary result.

11.5.1.2 Secondary outcome measures and safety variables

Logistic regression with and without adjustment (see above) and the general linear univariate model with or without adjustment will be used as appropriate. If the assumptions of the general linear univariate model cannot be fulfilled, a non-parametric test will be used (Mann Whitney).

11.5.2 Special statistical/analytical issues

11.5.2.1 Interim analyses

The DSMC will monitor the safety of the patients in the EuroHYP-1 trial by reviewing the available clinical data after 50, 100, 200, 400, and 600 patients have been recruited and followed up until outcome assessment [A7, Day 91±14 days] and *ad hoc* as needed. With respect to efficacy and hazard, the committee will conduct interim analyses on partially cleaned data after outcome assessment [A7, Day 91±14 days] of the first 400 patients. Details on procedures and threshold values are defined in the DSMC charter.

11.5.2.2 Data and safety monitoring committee

An independent DSMC has been established to oversee the safety of patients and the efficacy of the interventions in the trial under a contract with the sponsor. The DSMC comprises experts in stroke, cooling and biostatistics and is chaired by a person with extensive experience with DSMCs. It is supported by an independent biostatistician who will perform unblinded analyses of relevant data.

The DSMC will work in accordance with a charter developed by the DSMC members and agreed upon with the sponsor, EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee. The charter will describe the DSMC's scope of work and its modus operandi. A copy signed by the chairperson of

the DSMC and the representative of the sponsor or a person authorised by the sponsor will be kept in a separate file together with the list of DSMC members. The DSMC will follow processes recommended by the DAMOCLES statement.

With respect to safety, the DSMC will conduct interim analyses after 50, 100, 200, 400, and 600 patients had their outcome assessment [A7/8] performed. With respect to efficacy, the DSMC will conduct interim analyses after 400 patients had their outcome assessment (A7/8) performed. DSMC members will receive all reports on fatal SAEs as well as unblinded aggregate summaries of data by treatment groups for review in closed meetings in accordance with the DSMC charter (see Section 2.3). Feedback, blind to treatment, will be provided in open meetings and in written conclusions to the sponsor, EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee.

After each data review, the DSMC will make one of the following recommendations:

1. Continue the trial according to the current protocol version.
2. Carry out an interim analysis of fully cleaned, adjudicated and locked dataset.
3. Alter the clinical trial protocol so that one or more categories of patients are no longer included (for safety at any time point, or efficacy after one of the two interim analyses).
4. Place recruitment on hold so that additional follow-up information may be obtained on existing enrolled patients (for safety at any time point, or efficacy after one of the two interim analyses).
5. Stop the whole trial (for safety at any time point, or efficacy after an interim analysis of a cleaned, adjudicated and locked dataset).

If recommendation 4 or 5 is made by the DSMC, the sponsor or sponsor's authorised representative will suspend enrolment into the study with immediate effect and inform competent authorities and ethics commissions within the legal timeframes about this decision.

If the DMSC recommends stopping the trial for safety reasons, cooling may not start or may have to be stopped in patients randomised to therapeutic hypothermia group who at that moment are in screening [A1, within 90 minutes before the start of treatment phase TP] or in treatment phase [TP, beginning of Hour 1 to end of Rewarming]. However, all patients included in this trial will be followed up until outcome assessment [A7/8]. The investigator must inform the patients still in the trial or their legally acceptable representatives accordingly.

If indicated, enrolment into the study may resume only after

- an appropriate amendment has been made to the clinical trial protocol following consultations with the EuroHYP-1 DSMC, the EuroHYP-1 ethics board, the EuroHYP-1 scientific advisory board, the EuroHYP-1 executive committee members and the chairperson of the EuroHYP-1 steering committee.
- having obtained approval by competent authorities and ethics commissions after submission of

- the results of the interim analysis of the DSMB with a detailed justification of the recommendation for study termination.
- a report about the safety of the patients within the study with a list of all hitherto serious adverse events that occurred in both therapy groups.
- an account of the proposed actions for improving safety based on which the continuation of the study is seen as medically justifiable.
- a demonstration of efficacy from within the hitherto existing study, if available.

12 DATA HANDLING AND RECORD KEEPING

12.1 Corrections to data

All data required by this clinical trial protocol are to be entered into an internet-based validated database of eCRFs. However, unless otherwise specified in Section 10.2, direct entries are not allowed; data must be transcribed from the source (e.g., patient file) to the eCRF.

If corrections in the patient scales are necessary, the patient should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The patient should date the correction but not initial it. The investigator should not make any changes to these documents.

Data management will be responsible for data processing in accordance with the relevant SOPs. Database close will occur only after quality assurance procedures have been completed.

12.2 Record keeping

Essential documents (as defined by ICH-GCP guidelines, Section 8) shall be retained and archived for at least 10 years after the end of the trial. However, the documents shall be retained for a longer period if required by applicable regulatory requirements.

Essential documents at the trial site include (but are not limited to):

- patient files.
- patient identification code list which identifies the patient by number, name and date of birth.
- a signed copy of the final clinical trial protocol and any amendment.
- data clarification forms and any associated patient-related source data (or, where applicable, authorised copies of source data).
- signed informed consent forms.
- copies of trial site investigators' curricula vitae and trial site staff named on the trial delegation list.
- copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies), if applicable.
- copies of laboratory normal ranges and methods.
- copies of trial supply receipt forms and drug inventory forms.
- copies of all correspondence between the investigator and the monitor as well as between the investigator and the sponsor.
- copies of safety information reported during the trial and provided by the sponsor.

12.3 Destruction of trial documents

Trial documents may not be destroyed by trial site personnel prior to the end of the retention period specified above without the prior written consent of the sponsor. The PI and/or the institution must inform the sponsor in due time if the PI leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board

The following documents must be submitted to the responsible IEC/IRB and approval obtained before the trial begins:

- the clinical trial protocol.
- the IB.
- patient leaflets and informed consent forms.
- a description of all planned patient recruitment procedures and any advertisement used to recruit patients (if applicable).
- any other required documents.

If applicable, and in accordance with local legal requirements, the above documents may also be submitted to the respective regulatory authority(ies) for separate approval.

The same applies to all amendments made to the clinical trial protocol that are not solely of an administrative nature and to patient leaflets and informed consent forms.

13.2 Ethical conduct of the trial

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with ICH-GCP and applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during and after the conduct of the trial.

13.3 Patient information and informed consent

13.3.1 Procedure for obtaining informed consent

In principle, a patient may be enrolled into a clinical trial only once he "has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial" [art. 3.2.d of Directive 2001/20/EC].

Stroke patients with an NIHSS of ≥6, the study population planned to be enrolled into this clinical trial, however, are impaired to varying degrees in their ability to give consent due to the acute brain injury. Moreover, they find themselves in a new, frightening and often life-threatening situation. Such patients will be unable to reach a balanced view of the potential risks and benefits of participation in this trial within a time frame of less than one hour. For these reasons, all potential study participants must be classified as not being able to give consent.

The proof of safety and efficacy of therapeutic hypothermia in acute ischaemic stroke can thus only be obtained with patients unable to give consent. However, "such research is essential to validate data obtained … by other research methods" [i.e. in the case of EuroHYP-1 from animal studies and investigations of clinical conditions other than stroke] "and relates directly to a life-threatening or debilitating condition from which the incapacitated adult concerned suffers" [art. 5.d of Directive 2001/20/EC].

Provisions for the enrolment of patients who are unable to give informed consent can be found in the national legislation of all EU member states. Prior to trial start, approval by the competent authority and the ethics commission for the procedure to follow in the respective country must be obtained. In order to ensure that all national regulatory requirements are met, investigators are requested to follow country-specific written instructions provided by the sponsor that must be observed when enrolling a patient into the trial.

The procedure of obtaining informed consent will be performed once the patient is deemed by the investigator to be able to fully understand the implications of his/her participation in the clinical trial or once a legal representative has been appointed. The consent must be confirmed by the investigator who conducted the informed consent briefings. The informed consent process must be traceable from the available documentation. At a minimum, this documentation shall include information about when the patient was first informed about the trial and who supplied the information.

During the course of the trial, the patient or his/her legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The patient or his/her legally acceptable representative is free to withdraw consent at any time and for any reason, whether expressed or not.

If the patient or his/her legal representative object to the patient's further participation in the clinical trial, the patient will immediately be discontinued from the trial and undergo his/her trial termination assessment [A8]. However, data generated for the trial purpose up to this moment will be kept for analysis, and patients and/or their legal representatives will be informed accordingly.

The patient or his/her legally acceptable representative will be given an original of the signed and dated written informed consent form as well as all consent form updates (if applicable).

13.3.2 Patient card

A patient card will be given to all patients, who will be instructed to keep it in their possession at all times. The patient card will contain the following printed information:

- The name, address, and telephone number of the sponsor.
- Clinical trial short title.
- Clinical trial full title.

- EudraCT number.
- Patient identity number.
- Patient name.
- Date of patient enrolment.
- Short clinical trial design.
- The name, address and telephone of the investigator or institution, as the main contact for trial information.
- A 24-hour hotline number for emergencies.

13.3.3 Post-trial treatment

After the end of the trial, the patients will be treated by their physician according to local clinical standards.

13.3.4 Patient privacy

The patient or his/her legally acceptable representative will be informed of procedures to protect patient privacy. Although recorded data will be passed on in a coded version, re-identification by the investigator (e.g., in case of emergencies) will be possible by the patient identity number assigned to the patient (see Section 7.3.2). Access to non-coded data will be allowed solely to check validity, and such access will be limited strictly to authorised individuals (e.g., the members of IECs/IRBs [if applicable]) who have been bound to confidentiality. When the results of the trial are published, the patient's identity will remain confidential.

13.3.5 Contact point

All patients will be provided with a contact address where they may obtain further information regarding clinical trials.

13.4 Insurance

From the beginning of the trial until its termination, each patient will be insured against any health impairment occurring as a result of participation in the trial in accordance with the laws and regulations of the country in which the trial is performed.

The patient or his/her legally acceptable representative will be informed by the investigator and through the patient's informed consent form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the patient or his/her legally acceptable representative, if requested or if required by local law.

Any medical deviation from the clinical trial protocol that is deemed to have occurred through the patient's own fault is not covered by this insurance.

The sponsor is not liable for injuries/cases of death that occur solely as a consequence of the patient's underlying disease or condition or from diagnostic or therapeutic measures not specifically required by the agreed clinical trial protocol. The sponsor is also not liable for events resulting from negligence of the investigator and clinical trial staff, including failure to act according to ICH-GCP principles or to comply strictly with the agreed clinical trial protocol.

13.5 Funding

The trial is funded by the Seventh Framework Programme (FP7) of the European Union (Grant Agreement no. 278709). The pre-funding phase has been supported by an unrestricted grant provided by Professor Werner Hacke, Neurologische Klinik, Universität Heidelberg, Germany.

The financial aspects of the trial will be documented in an agreement between the sponsor and each investigator or any other involved party and must be confirmed in writing before the trial commences.

14 PUBLICATION POLICY

The trial will be registered in a public clinical trials registry prior to the enrolment of the first patient. The results will be posted in the registry within one year after the end of the trial.

Publications are the responsibility of EuroHYP-1 steering committee. The EuroHYP-1 steering committee may decide to share data earlier, e.g., for the purpose of meta-analyses.

Data ownership

Ownership of the data arising from the trial resides with the EuroHYP-1 steering committee and the investigators. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared in accordance with the principles of ICH guidelines. Within 1.5 years after trial completion, anonymised data from the trial will be uploaded to a public repository.

Clinical trial report

The EuroHYP-1 steering committee will prepare a clinical trial report within one year after the end of the trial. The DSMC is requested to confirm the findings in the clinical trial report prior to its public use, e.g., for communications to the scientific or lay community, presentations at congresses, or submission of manuscripts for publication.

Authorship policy

Authorship policy follows the guidelines of the International Committee of Medical Journal Editors.

Publication

The clinical trial report will be used for publication and presentation at scientific meetings. The trial results will be published in the name of the EuroHYP-1 investigators, with the EuroHYP-1 executive committee drafting manuscripts which will be approved by the EuroHYP-1 steering committee prior to submission for publication. Any additional analyses must be approved by the EuroHYP-1 steering committee prior to their conduct and will also be published in the name of the EuroHYP-1 investigators. Before submission of any manuscript, all members of the EuroHYP-1 steering committee will have the opportunity to comment on the manuscript. Summaries of results will also be made available to investigators for dissemination within their clinical workplace (where appropriate and at their discretion).

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16 ADDENDA

16.1 Description of outcome variables

16.1.1 Modified Rankin Scale

The mRS is an ordinal hierarchical scale describing the range of disability encountered post stroke by scores ranging from 0 to 6.

0= No symptoms.

1= No significant disability. Able to carry out all usual activities despite some symptoms.

2= Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3= Moderate disability. Requires some help, but able to walk unassisted.

4= Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted.

5= Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6= Dead.

16.1.2 National Institutes of Health Stroke Scale

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance. Scores range from 0 to 42 and include the following dimensions and respective grades:

1a	Level of consciousness	0=	Alert; keenly responsive.
		1=	Not alert; but arousable by minor stimulation to obey, answer or respond.
		2=	Not alert; requires repeated stimulation to attend or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).
		3=	Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b	Level of consciousness questions	0=	Answers both questions correctly.
	Based on material provided	1=	Answers one question correctly.
		2=	Answers neither question correctly.

1c	Level of consciousness commands	0=	Performs both tasks correctly.
	Based on material provided	1=	Performs one task correctly.
		2=	Performs neither task correctly.
2	Best gaze	0=	Normal.
		1=	Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
		2=	Forced deviation or total gaze paresis not overcome by the oculocephalic manoeuvre.
3	Visual	0=	No visual loss.
		1=	Partial hemianopia.
		2=	Complete hemianopia.
		3=	Bilateral hemianopia (blind including cortical blindness).
4	Facial palsy	0=	Normal symmetrical movements.
		1=	Minor paralysis (flattened nasolabial fold, asymmetry on smiling),
		2=	Partial paralysis (total or near-total paralysis of the lower face).
		3=	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5	Motor arm	0=	No drift; limb holds 90 (or 45) degrees for full 10 seconds.
5a	Left arm		
5b	Right arm	1=	Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
		2=	Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
		3=	No effort against gravity; limb falls.
		4=	No movement.
		UN=	Amputation or joint fusion.
6	Motor leg	0=	No drift; leg holds 30-degree position for full 5 seconds.
6a	Left leg		
6b	Right leg	1=	Drift; leg falls by the end of the 5-second period, but does not hit bed.

		2=	Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.
		3=	No effort against gravity; leg falls to bed immediately.
		4=	No movement.
		UN	Amputation or joint fusion.
7	Limb ataxia	0=	Absent.
		1=	Present in one limb.
		2=	Present in two limbs.
		UN	Amputation or joint fusion.
8	Sensory	0=	Normal; no sensory loss.
		1=	Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick, but patient is aware of being touched.
		2=	Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg.
9	Best language	0=	No aphasia; normal.
		1=	Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided material, examiner can identify picture or naming card content from patient's response.
		2=	Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient's response.
		3=	Mute, global aphasia; no usable speech or auditory comprehension.

10	Dysarthria	0=	Normal.
		1=	Mild to moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.
		2=	Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia or is mute/anarthric.
		UN	Intubated or other physical barrier.
11	Extinction and inattention	0=	No abnormality.
		1=	Visual, tactile, auditory, spatial or personal inattention or extinction of bilateral simultaneous stimulation in one of the sensory modalities.
		2=	Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side in space.

16.1.3 Glasgow Coma Scale motor response subscale

The GCS is a neurological scale aiming at providing a reliable, objective way of recording the conscious state of a person. The motor response subscale registers the best motor response on a 6-point ordinal hierarchical scale. Scores range from 1 to 6.

1= No motor response.

2= Extension to pain (abduction of arm, external rotation of shoulder, supination of forearm, extension of wrist; *decerebrate response*).

3= Abnormal flexion to pain (adduction of arm, internal rotation of shoulder, pronation of forearm, flexion of wrist; *decorticate response*).

4= Flexion/withdrawal to pain (flexion of elbow, supination of forearm, flexion of wrist when supraorbital pressure is applied, pulling part of body away when nailbed is pinched).

5= Localises to pain (purposeful movement towards painful stimuli, e.g. hand crosses mid-line and gets above clavicle when supraorbital pressure is applied).

6= Obeys commands (the patient does simple things when asked).

16.1.4 Bedside Shivering Assessment Scale

The BSAS is a 4-point ordinal hierarchical scale to assist in the monitoring and control of shivering. Scores range from 0 to 3.

0=	None	No shivering noted on palpation of the masseter, neck or chest wall.
1=	Mild	Shivering localised to the neck and/or thorax only.
2=	Moderate	Shivering involves gross movement of the upper extremities (in addition to neck and thorax).
3=	Severe	Shivering involves gross movements of the trunk and upper and lower extremities.

16.1.5 World Health Organization Disability Assessment Schedule

The WHODAS 2.0 is an ordinal hierarchical scale used as a general measure of functioning and disability in 6 major life domains.

Domain	Domain question
1: Cognition	**In the last 30 days, how much difficulty did you have in:**
1.1	Concentrating on doing something for 10 minutes.
1.2	Remembering to do important things.
1.3	Analysing and finding solutions to problems in day-to-day life.
1.4	Learning a new task, e.g., learning how to get to a new place.
1.5	Generally understanding what people say.
1.6	Starting and maintaining a conversation.
2: Mobility	**In the last 30 days, how much difficulty did you have in:**
2.1	Standing for long periods such as 30 minutes.
2.2	Standing up from sitting down.
2.3	Moving around inside your home.
2.4	Getting out of your home.
2.5	Walking a long distance such as a kilometre (or equivalent).
3: Self-care	**In the last 30 days, how much difficulty did you have in:**
3.1	Washing your whole body.
3.2	Getting dressed.
3.3	Eating.
3.4	Staying by yourself for a few days.
4: Getting along	**In the last 30 days, how much difficulty did you have in:**
4.1	Dealing with people you do not know.
4.2	Maintaining a friendship.
4.3	Getting along with people who are close to you.

4.4	Making new friends.
4.5	Sexual activities.
5: Life activities	**In the last 30 days, how much difficulty did you have in:**
5.1	Taking care of your household responsibilities.
5.2	Doing most important household tasks well.
5.3	Getting all the household work done that you needed to do.
5.4	Getting your household work done as quickly as needed.
5.5	Your day-to-day work.
5.6	Doing your most important work tasks well.
5.7	Getting done all the work that you needed to do.
5.8	Getting your work done as quickly as needed.
6: Participation	**How much of a problem do you have:**
6.1	Joining in community activities.
6.2	Because of barriers or hindrances in the world.
6.3	Living with dignity.
6.4	From time spent on health condition.
6.5	Feeling emotionally affected.
6.6	Because health is a drain on your financial resources.
6.7	With your family facing difficulties due to your health.
6.8	Doing things for relaxation or pleasure by yourself.

Responses to each of the 36 domain questions are scored on a 5-point Likert scale. Summary scores range from 36 to 180.

1= None.

2= Mild.

3= Moderate.

4= Severe.

5= Extreme.

16.1.6 EuroQoL 5-dimensions 5-level questionnaire

The EQ-5D-5L is a quality of life questionnaire which will be filled out by the patient or his/her carer.

By ticking one box in each group below, the patient or his/her carer will indicate which statements best describe the patient's health state.

Mobility	➢ I have no problems in walking about. ➢ I have slight problems in walking about. ➢ I have moderate problems in walking about. ➢ I have severe problems in walking about. ➢ I am unable to walk about.
Self-care	➢ I have no problems washing or dressing myself. ➢ I have slight problems washing or dressing myself. ➢ I have moderate problems washing or dressing myself. ➢ I have severe problems washing or dressing myself. ➢ I am unable to wash or dress myself.
Usual activities (e.g., work, study, housework, family or leisure activities)	➢ I have no problems doing my usual activities. ➢ I have slight problems doing my usual activities. ➢ I have moderate problems doing my usual activities. ➢ I have severe problems doing my usual activities. ➢ I am unable to do my usual activities.
Pain/discomfort	➢ I have no pain or discomfort. ➢ I have slight pain or discomfort. ➢ I have moderate pain or discomfort. ➢ I have severe pain or discomfort. ➢ I have extreme pain or discomfort.
Anxiety/depression	➢ I am not anxious or depressed. ➢ I am slightly anxious or depressed. ➢ I am moderately anxious or depressed. ➢ I am severely anxious or depressed. ➢ I am extremely anxious or depressed.

Moreover, the patient or his/her carer is requested to assess and indicate the patient's current health state using a visual analogue scale where 0 means the worst health imaginable and 100 means the best health imaginable.

16.1.7 Sections 6 and 7 of the health recovery guide and diary

The patient or his/her relative/carer is requested to hand the Health Recovery Guide and Diary over to the investigator at the outcome assessment [A7,

Day 91±14 days]. Sections 6 and 7 of the document will be removed from the diary and incorporated into the patient's patient chart, where it will serve as source documentation. The remaining document will be checked for instances of changes of concomitant medication and for AEs to be recorded in the patient's patient chart. The document will then be handed back to the patient or his/her carer. All values relevant for the statistical analysis will be recorded in the eCRF by the investigator or the trial nurse.

Section 6

The patient is requested to fill in this section of the document every day from day of discharge from hospital [A6] until outcome assessment [A7, Day 91±14 days]. The relative/carer may fill in the section, if the patient is not able to do so for whatever reason.

Date

Visits - doctors and/or other health care professionals & hospital visits:	➢ General practitioner. ➢ Home care nurse. ➢ Physiotherapist. ➢ Occupational therapist. ➢ Hospital visit. ➢ Other professional(s).
I go to sleep at:	➢ Home. ➢ Institution/rehabilitation centre. ➢ Hospital.

Section 7

Section 7 of the document ("Stroke recovery scorecard") is identical to the 12-item version, proxy-administered, of the WHODAS 2.0.

The carer is requested to fill in Section 7 of the document just prior to the outcome assessment [A7, 91±14 days].

H4	Relationship to relative	➢ Husband or wife. ➢ Parent. ➢ Son or daughter. ➢ Brother or sister. ➢ Other relative. ➢ Friend. ➢ Professional carer. ➢ Other.

In the last 30 days, how much difficulty did your relative have in

S1 Standing for long periods such as 30 minutes?

S2 Taking care of his or her household responsibilities?

S3 Learning a new task, for example, how to get to a new place?

S4 How much of a problem did your relative have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?

S5 How much has your relative been emotionally affected by his or her health condition?

S6 Concentrating on doing something for ten minutes?

S7 Walking a long distance such as a kilometre (or equivalent)?

S8 Washing his or her whole body?

S9 Getting dressed?

S10 Dealing with people he or she does not know?

S11 Maintaining a friendship?

S12 His or her day-to-day work?

H1	Overall, in the past 30 days, how many days were these difficulties present?	Record number of days.
H2	In the past 30 days, for how many days was your relative totally unable to carry out his or her usual activities or work because of any health condition?	Record number of days.
H3	In the past 30 days, not counting the days that your relative was totally unable, for how many days did your relative cut back or reduce his or her usual activities or work because of any health condition?	Record number of days.

Responses to each of the questions S1 to S12 are scored on a 5-point Likert scale. Summary scores range from 12 to 60.

1= None.

2= Mild.

3= Moderate.

4= Severe.

5= Extreme or cannot do.

16.1.8 Patient experience survey for the therapeutic hypothermia and best medical treatment group, Part I

At Assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first], patients will be asked to fill in a 24-item questionnaire on the treatment experience, if necessary assisted by a trial nurse. Responses to each question will be scored on a scale ranging from 1 to 7 except for the last three questions where patients are asked to provide free-text answers. For some questions, a box may be ticked if the patient has no recollection of the item.

1. How well do you remember receiving the patient information booklet about EuroHYP-1?
   1 = No, I do not remember receiving the EuroHYP-1 booklet.
   7 = Yes, I remember extremely well receiving the EuroHYP-1 booklet.

2. How useful was the EuroHYP-1 information booklet in helping you (and your family members) to decide to join the study?
   1 = Not useful at all.
   7 = Extremely useful.

3. How well do you remember making the decision to participate in the EuroHYP-1 study?
   1 = I do not remember the decision.
   7 = I remember the decision extremely well.
   Default option: I did not make the decision myself about joining the trial.

4. How much information were you given about the EuroHYP-1 study when you were asked to join in?
   1 = Far too little.
   7 = Far too much.
   Default option: I do not remember receiving any information.

5. How well do you think the description of the cooling treatment in the Patient Information Booklet represents your real experiences of body cooling?
   1 = Very poorly.
   7 = Very well.
   Default option: I do not remember the description in the Patient Information Booklet.

6a. How did you feel when the cooling started with the ice cold saline drip?
   1 = It was unbearable.
   7 = I felt okay.
   Default option: I do not remember the start of the treatment.
   Default option: Cold saline has not been used to start the cooling.

6b. *In case EMCOOLS Brain.Pad was additionally used for induction of cooling:*
How did you feel when the cooling started with the cooling pads placed on your neck and shoulders?
1 = It was unbearable.
7 = I felt okay.
Default option: I do not remember the start of the treatment.
Default option: The EMCOOLS Brain.Pad was not used for induction of cooling.

7. Did you experience any pain when the cooling started?
1 = No pain.
7 = Extremely painful.
Default option: I do not remember the start of the cooling.

8. Were you aware of being cold at the beginning of the cooling process (during the first 3-6 hours)?
1 = No, I was not aware of being cold.
7 = Yes, I felt extremely cold.
Default option: I do not remember what happened.

9. If you were aware of being cold, how unpleasant was it?
1 = It was unbearable.
7 = It felt okay.

10a. *In case of surface cooling with pads:*
How did you find having the cooling pads placed onto your body?
1 = It was unbearable.
7 = It felt okay.
Default option: I do not remember cooling pads being placed onto my body.

10b. *In case of cooling with catheter:*
Do you remember feeling any discomfort related to the placement of the cooling catheter?
1 = Extreme discomfort.
7 = No discomfort.
Default option: I do not remember the placement of the cooling catheter.

11, *Complete this question if body warming interventions were used such as a warming blanket and/or woollen socks.*
How did you find the body warming?
1 = It was unbearable.
7 = It felt pleasant.
Default option: I do not remember body warming.
Default option: Warming interventions were not used.

12. How aware were you of shivering during the cooling?
1 = Completely unaware; I do not remember any shivering.
7 = Completely aware; I remember very clearly.

13. If you did experience shivering, how unpleasant was it?
1 = It was unbearable.
7 = It was okay.

14. Do you remember having nausea or vomiting during the cooling period?
1 = No, I do not remember any nausea or vomiting.
7 = I remember very strong nausea and vomiting.

15. Do you remember having anxiety or fear during the cooling period?
    1 = My anxiety was unbearable.
    7 = I felt no anxiety.

16. How safe did you feel during the cooling period?
    1 = Very unsafe.
    7 = completely safe.

17. Do you remember asking for help from your doctors and nurses during the cooling treatment?
    1 = No, I do not remember asking for help.
    7 = Yes, I remember asking for help.

18. Do you remember receiving help from your doctors and nurses during the cooling treatment?
    1 = No, I do not remember receiving help.
    7 = Yes, I remember receiving help.

19. Did you think there were enough doctors and nurses taking care of you during the cooling treatment?
    1 = No, there were too few.
    7 = Yes, the numbers were sufficient.

20. Considering all aspects, how would you rate your cooling experience?
    1 = It was unbearable.
    7 = It was okay.
    Default option: I do not remember the experience.

21. Considering all aspects of therapeutic cooling, how likely would you be to recommend this treatment to other patients?
    1 = I would not recommend therapeutic cooling.
    7 = I am extremely likely to recommend therapeutic cooling.

22. Were there any other aspects of the treatment which you found to be unpleasant?

23. Can you think of anything we could do to improve the experience of being cooled?

24. Can you think of anything that would have improved your experience of being involved in the EuroHYP-1 trial?

16.1.9 Patient experience survey for the best medical treatment alone group, Part I

At Assessment 6 [A6, Day 8 or day of discharge from hospital, whichever occurs first], patients will be asked to fill in a 24-item questionnaire on the treatment experience, if necessary assisted by a trial nurse. Responses to each question will be scored on a scale ranging from 1 to 7 except for the last 3 questions where patients are asked to provide free-text answers. For some questions, a box may be ticked, if the patient has no recollection of the item.

1. How well do you remember receiving the patient information booklet about EuroHYP-1?
   1 = No, I do not remember receiving the EuroHYP-1 booklet.
   7 = Yes, I remember extremely well receiving the EuroHYP-1 booklet.
2. How useful was the EuroHYP-1 information booklet in helping you (and your family members) to decide to join the study?
   1 = Not useful at all.
   7 = Extremely useful.
3. How well do you remember making the decision to participate in the EuroHYP-1 study?
   1 = I do not remember the decision.
   7 = I remember the decision extremely well.
   Default option: I did not make the decision myself about joining the trial.
4. How much information were you given about the EuroHYP-1 study when you were asked to join in?
   1 = Far too little.
   7 = Far too much.
   Default option: I do not remember receiving any information.
5. How well do you think the description of the treatment in the Patient Information Booklet represents your real experiences associated with the treatment?
   1 = Very poorly.
   7 = Very well.
   Default option: I do not remember the description in the Patient Information Booklet.
6. How did you feel when the treatment started?
   1 = It was unbearable.
   7 = I felt okay.
   Default option: I do not remember the start of the treatment.
7. Did you experience any pain when the treatment started?
   1 = No pain.
   7 = Extremely painful.
   Default option: I do not remember the start of the treatment.
8. Were you aware of being cold at the beginning of the treatment process (during the first 3-6 hours)?
   1 = No, I was not aware of being cold.
   7 = Yes, I felt extremely cold.
   Default option: I do not remember what happened.
9. If you were aware of being cold, how unpleasant was it?
   1 = It was unbearable.
   7 = It felt okay.
10. Do you remember feeling any discomfort related to the start of the treatment?
    1 = Extreme discomfort.
    7 = No discomfort.
    Default option: I do not remember the start of the treatment.

11. *Complete this question if body warming interventions were used such as a warming blanket and/or woollen socks.*
How did you find the body warming?
1 = It was unbearable.
7 = It felt pleasant.
Default option: I do not remember body warming.
Default option: Warming interventions were not used.

12. How aware were you of shivering during the first 36 hours of the treatment?
1 = Completely unaware; I do not remember any shivering.
7 = Completely aware; I remember very clearly.

13. If you did experience shivering, how unpleasant was it?
1 = It was unbearable.
7 = It was okay.

14. Do you remember having nausea or vomiting during the first 36 hours of the treatment?
1 = No, I do not remember any nausea or vomiting.
7 = I remember very strong nausea and vomiting.

15. Do you remember having anxiety or fear during the first 36 hours of the treatment?
1 = My anxiety was unbearable.
7 = I felt no anxiety.
Default option: I do not remember having any anxiety or fear.

16. Did you feel safe during the first 36 hours of the treatment?
1 = No, I did not feel safe during the first 36 hours of the treatment.
7 = Yes, I felt safe during the first 36 hours of the treatment.

17. Do you remember asking for help from your doctors and nurses during the first 36 hours of the treatment?
1 = No, I do not remember asking for help.
7 = Yes, I remember asking for help.

18. Do you remember receiving help from your doctors and nurses during the first 36 hours of the treatment?
1 = No, I do not remember receiving help.
7 = Yes, I remember receiving help.

19. Did you think there were enough doctors and nurses taking care of you during the first 36 hours of your treatment?
1 = No, there were too few doctors and nurses.
7 = Yes, there were sufficient doctors and nurses.

20. Considering all aspects, how would you rate your treatment experience?
1 = It was unbearable.
7 = It was okay.
Default option: I do not remember the experience.

21. Considering all aspects of the treatment, how likely would you be to recommend this treatment to other patients?
1 = I would not recommend the treatment.
7 = I am extremely likely to recommend the treatment.

22. Were there any other aspects of the treatment which you found to be unpleasant?

23. Can you think of anything we could do to improve the treatment experience?

24. Can you think of anything that would have improved your experience of being involved in the EuroHYP-1 trial?

16.1.10 Patient experience survey, Part II

At Assessment 7 [A7, Day 91±14 days], patients will be asked to fill in a 6-item questionnaire on the treatment experience, if necessary assisted by a trial nurse. Responses to each question will be scored on a scale ranging from 1 to 7.

Did you receive therapeutic cooling as part of the EuroHYP-1 trial?
Yes. (Please begin at question 25)
No. (Please begin at question 26)

25 How unpleasant was it to receive the cooling treatment after your stroke?
1 = It was unbearable.
7 = It was OK.

26. How much recovery do you feel you have made since your stroke?
1 = I have made no recovery.
7 = I have made a full recovery.

27. How satisfied are you with the amount of information you received throughout the three-month period about the EuroHYP-1 trial?
1 = Completely unsatisfied. There was not enough information.
7 = Completely satisfied. I felt fully informed.

28. How useful did you find the Health Recovery Guide and Diary?
1 = Useless. I did not use it at all.
7 = Invaluable. I referred to it throughout the three months.

29. Overall, how would you rate your experience in the EuroHYP-1 trial?
1 = An extremely negative experience.
7 = An extremely positive experience.

30. Can you think of anything that would have improved your experience of being involved in the EuroHYP-1 trial during the whole three-month period?

17 AMENDMENTS

See attachment 1 to clinical trial protocol v5.0 24-May-2016.

STATEMENT OF COMPLIANCE

Investigational Sites

I have thoroughly read and reviewed the clinical trial protocol. Having understood the requirements and conditions of the clinical trial protocol, I agree to perform the clinical trial according to the clinical trial protocol, the case report form, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

I have received the current investigator's brochure. Having been adequately informed about the IMDs and the IMPs, I also agree to:

- Sign this clinical trial protocol before the trial formally starts.
- Wait until I have received approval from the appropriate ethics committee (EC) and competent regulatory authority (if applicable) before enrolling any patient in this trial.
- Obtain informed consent for all patients prior to any trial-related action performed.
- Start the trial only after all legal requirements in my country have been fulfilled.
- Permit trial-related monitoring, audits, EC review, and regulatory inspections.
- Provide direct access to all trial-related records, source documents, and patient files for the monitor, auditor, EC, or regulatory authority upon request.
- Use the IMDs and IMPs and all trial materials only as specified in the IB, manuals, user guides and special trainings.
- Report to the responsible drug safety officer, within 24 hours, any adverse event (AE) that is serious, whether considered treatment related or not.
- Report to the responsible drug safety officer, within 24 hours, any AE of special interest as defined in the clinical trial protocol, whether considered treatment-related or not.

Furthermore, I understand that:

- Changes to the clinical trial protocol must be made in the form of an amendment that has the prior written approval of the sponsor and – as applicable – of the appropriate EC and regulatory authority.
- The content of the clinical trial protocol is proprietary to the EuroHYP-1 executive committee.
- Any deviation from the clinical trial protocol may lead to early termination of the trial site.

Principal investigator	Date	Signature
		Print Name
<Delete item if not applicable> Investigator/Sub-investigator	Date	Signature
		Print Name
<Delete item if not applicable> Qualified physician	Date	Signature
		Print Name
<Investigational site stamp:>		