CLINICAL TRIAL PROTOCOL

SPACE 2

Stent-protected Angioplasty

in Asymptomatic Carotid Artery Stenosis

vs. Endarterectomy

Two two-arm Clinical Trials

Clinical Trial Code:	SPACE 2
ISRCTN number:	ISRCTN 78592017
Clinical Phase:	Therapeutic confirmatory (Phase III)
Version:	**Final** (10.10.2008) **Including Amendment 1** (25.09.2012)

CLINICAL TRIAL PROTOCOL SUMMARY

Title:
SPACE 2: Stent-protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy. Two two-arm clinical trials

Phase: III

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Financing / Status of the Sponsor:
BMBF/DFG (HA 1394/5-1)
Co-financing by pharmaceutical industry

Indication:
Asymptomatic carotid artery stenosis (I65.2)

Trial Population:
Key inclusion criteria:

- Sonographic identification of a ≥ 70% stenosis of the extracranial carotid

artery in a patient without stroke or stroke-like symptoms attributable to the target stenosis within the previous 180 days.
- Written informed consent
- For women with childbearing potential, adequate contraception

Key exclusion criteria:
- Non-atherosclerotic origin of stenosis
- Stenosis related neurological symptoms within the previous 180 days

Objectives:
The trial has a 30-day safety endpoint and a composite primary efficacy endpoint (periprocedural and long-term events):
OLD: SPACE-2a: The primary hypothesis is the superiority of carotid artery stenting (CAS) and carotid endarterectomy (CEA) as compared to best medical treatment alone (BMT) with respect to the composite primary endpoint.
SPACE-2b: The primary hypothesis is that stent-protected angioplasty is not inferior to carotid endarterectomy with respect to the composite primary endpoint.
NEW: Two separate superiority-trials of interventions versus best medical treatment (BMT) are designed. The decision for one type of intervention is made (CEA = SPACE2a or CAS = SPACE2b) prior randomization. In both studies - SPACE2a and SPACE2b - the interventional treatment-groups (CEA and CAS) will be compared with BMT separately. In addition data from the CEA and CAS-groups will be compared in an explorative manner.

Trial Design :
OLD: Randomized, controlled, open, multi-centre, 3 parallel groups
NEW: Two parallel studies with a randomized, controlled, open, multi-centre design with two arms each

Sample Size:
OLD: To be allocated to trial (n = 3,640); To be analyzed (ITT) (n = 3,640)
NEW: To be allocated and analyzed in the overall trial (n = 3,272); to be allocated to SPACE2a (n=1,636) and to SPACE2b (n=1,636)

Statistical Analysis:
The primary analysis will be intention-to-treat (ITT). In addition, a per-protocol (PP) analysis will also be performed after exclusion of patients who did not finish therapy or other serious protocol violations

Safety**:** A non-inferiority design with a non-inferiority-margin of 1.5% will be used (following the strategy of second level of the efficacy endpoint).
Efficacy**:**

OLD: A hierarchical testing procedure is used to test both efficacy hypotheses.
Its first level consists of two tests on differences in event rates (Space-2a: CAS versus BMT and CEA versus BMT). Rates are compared by Chi²-test or a z-test (if losses to follow-up require the calculation of event rates and their standard errors by Kaplan-Meier-techniques).
If both tests show a significant result, the second level of the hierarchical testing procedure assesses non-inferiority of the event rates in the CAS/CEA groups (Space-2b) based on a one-sided 97.5% confidence interval under H0 for the rate difference (H_0: $rate_{CAS}$-$rate_{CEA}$ >/= 0.025). The non-inferiority margin is set to 2.5%.
NEW: The primary analysis consists in testing the difference between intervention (CEA or CAS) and BMT with respect to the composite primary end point (Section

2.3). The comparison will use the Cox-PH model. The tests are performed on a 5% level. In addition an explorative comparison of the event rates in the CEA and the CAS groups will be done (Calculating a 95% confidence interval of the hazard rate for the primary endpoint between both treatments). In order to analyze the effect between these two interventional methods, an indirect treatment comparison will be performed.

Trial Duration and Dates:
Follow-up per patient: 5 years
First patient in to last patient out: 8 years (3-year-recruiting phase, 5-year-follow-up)
Total trial duration 9 years
Duration of treatment per patient: Stent-protected angioplasty and carotid endarterectomy are performed within 4 weeks of randomization. Best medical treatment continues throughout the follow-up period.

ABBREVIATIONS

AE	Adverse Event
BDSG	Bundesdatenschutzgesetz
BMBF	Bundesministerium für Bildung und Forschung
BMT	Best medical treatment
CAS	Carotid artery stenting
CEA	Carotid endarterectomy
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Curriculum Vitae
DBL	Data Base Lock
DFG	Deutsche Forschungsgemeinschaft
DMC	Data Monitoring Committee
DVP	Data Validation Plan
EC	Ethics Committee
EEC	Endpoint Evaluation Committee
ExC	Executive Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISF	Investigator Site File
ISRCTN	International Standard Randomized Controlled Trial Number
ITT	Intention To Treat
KKS	Coordination Center for Clinical Trials (Koordinierungszentrum für Klinische Studien)
LKP	Coordinating Investigator according to German law (Leiter der Klinischen Prüfung)
n.a.	not applicable
OE	Outcome Event
SAE	Serious Adverse Event
SC	Steering Committee
SDV	Source Data Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

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FLOW CHART / TRIAL SCHEDULE

Figure 1: Trial flow chart and visit plan (Old)

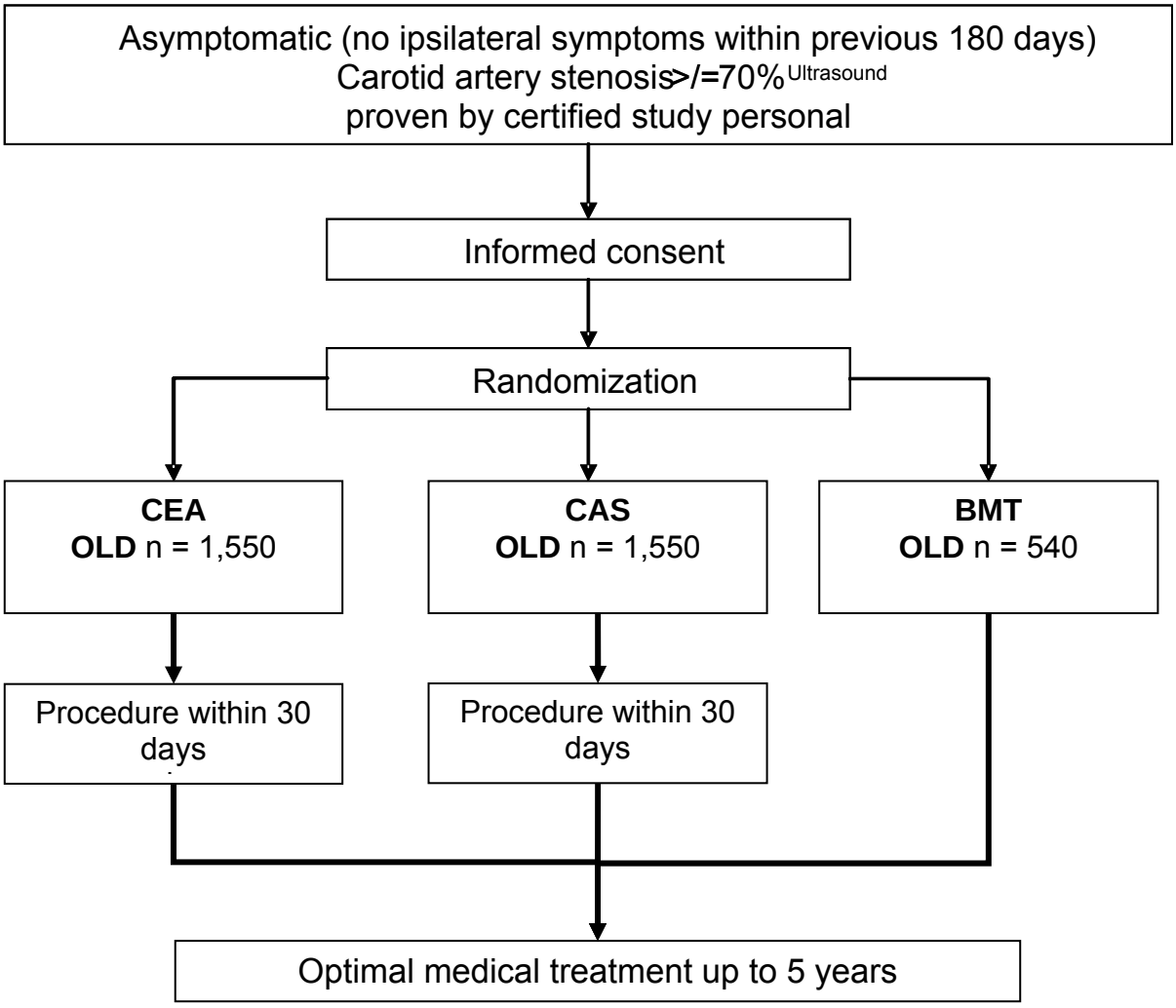
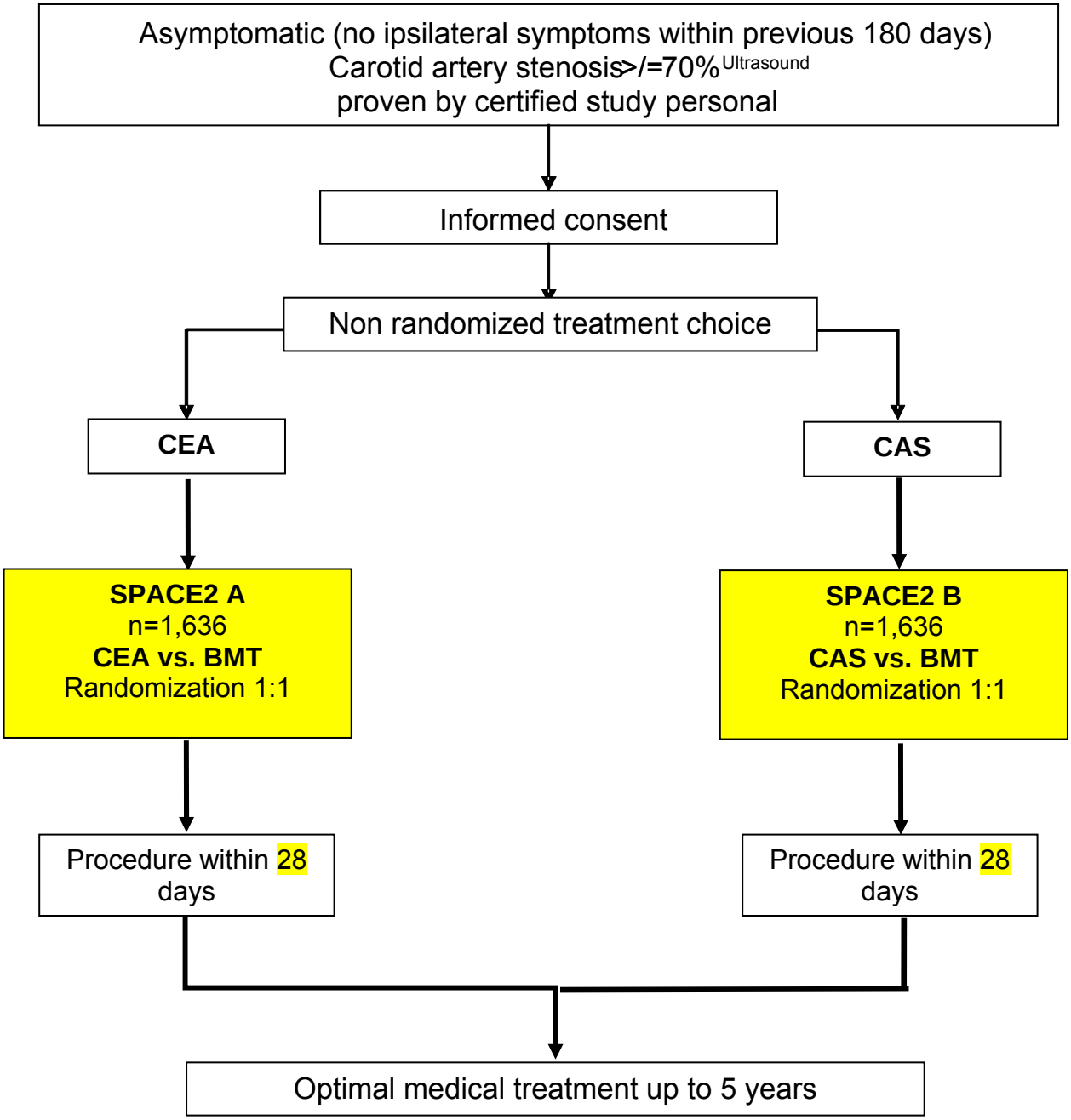


Figure 1: Trial flow chart and visit plan (**NEW**)



	Screening	Randomization	CAS/CEA	D1 [b]	D30	M6	A1	A2	A3	A4	A5
Informed consent	X	X									
Ultrasound	X			X	X	X	X	X	X	X	X
ECG	X			X							
Risk factor screening using a standardized questionnaire	X			X	X	X	X	X	X	X	X
Modified Rankin Score	X			a	a	a	a	a	a	a	a
NIH Stroke Scale	X			a	a	a	a	a	a	a	a
Co-medication	X			X	X	X	X	X	X	X	X
Event-Screening:	X			X	X	X	X	X	X	X	X
• Any stroke				X	X		X		X		X
• Ipsilateral ischemic stroke				X	X	X	X	X	X	X	X
• Death from any cause					X		X		X		X
• Vascular death					X		X		X		X
• Myocardial infarction					X						
• Technical failure			X								
Adverse Events			X	X	X	X	X	X	X	X	X

a: only in case of outcome events; b: only if randomized to CEA or CAS

1 INTRODUCTION

1.1 Scientific background

Treatment of individuals with asymptomatic carotid artery stenosis is handled controversially. Surgery for asymptomatic and symptomatic carotid artery bifurcation stenosis ranks among the most frequent surgical procedures worldwide. For Germany about 25,000 procedures are performed every year. The superiority of carotid endarterectomy (CEA) compared to medical treatment in symptomatic carotid disease (in patients, who already had stroke or TIA on the side of the stenosis) is established, provided that the surgical procedure can be done with a perioperative morbidity and mortality of less than 6% [6]. The advantage of CEA for asymptomatic patients (those, who did not have a previous cerebrovascular ipsilateral event) is less well established. There is a mild superiority of this intervention compared with standard medical therapy, provided that the operation can be done with the perioperative morbidity and mortality of less than 3%. Even then, about 20 patients have to be treated to prevent one stroke over a period of 5 years, which also causes doubts about the cost effectiveness of this intervention [8].

Recently, for both symptomatic and asymptomatic carotid artery stenoses, an alternative treatment, carotid stenting (stent-protected angioplasty, CAS) has been developed. This treatment is used frequently in both, symptomatic and asymptomatic patients. However, up to today, no prove of superiority or non-inferiority of carotid artery stenting for symptomatic stenosis has been demonstrated [20, 22].

In the last decade, major advantages in medical primary prevention of cerebrovascular and cardiovascular disease have been accomplished. Specifically, treatment of hypertension with modern antihypertensive drugs such ACE inhibitors or ARBs, partially in combination with diuretics and the use of statins have shown significant risk reduction for both cerebrovascular and cardiovascular events [1, 14]. In addition, life style modification, smoking cessation and individualized antiplatelet therapy may also have an impact on the event rate in so far asymptomatic patients. The control groups in the large trials for asymptomatic carotid artery disease (ACAS and ACST) originate from more than a decade ago and, for the major part, have not received a medical primary prevention strategy that would now be considered standard according to current national and international guidelines [18]. Therefore, for asymptomatic carotid artery

disease, it seems adequate and timely, to compare state of the art medical prevention with the interventional therapies. For that reason initially a three-arm trial with a hierarchical design was chosen. On the first level, a superiority trial of intervention (CAS or CEA) versus state of the art conservative treatment is designed. In case of superiority of the interventions, a non-inferiority endpoint will be tested between CAS and CEA. After some years problems with this study design became obvious, thus the design was modified to two parallel two-arm trials.

1.1.1 Evidence

Asymptomatic carotid artery stenosis, per definition, can be found only in the context of screening examinations. Due to the lack of systematic screening examinations valid data about prevalence is not known. It is estimated that the prevalence of asymptomatic carotid artery stenoses >/=50% is around 2-8%, and of stenoses >/=80% around 1-2% [9]. Moderate to severe (>/=70%) asymptomatic stenosis of the extracranial carotid artery leads to an increased rate of stroke of approximately 11% in five years [8, 12]. Patients with asymptomatic carotid stenosis, however, are at also higher risk of non-stroke vascular events. The estimated annual risks of such events in patients with asymptomatic stenosis are 7% for coronary ischemic event and 4-7% for overall mortality [15].

1.1.2 Role of conservative treatment

Medical management of patients with asymptomatic carotid stenoses consists of risk factor modification, antiplatelet medication and careful monitoring of progression or hemodynamic relevance by ultrasound. Although no primary prevention trials specifically focusing on patients with asymptomatic carotid stenosis have been done, these treatment regimens have been the standard therapy for asymptomatic carotid stenoses in the past and many treatment guidelines still recommend them as therapy of choice if surgical treatment cannot be provided with morbidity and mortality-rates below 3% [6].

1.1.3 Role of carotid endarterectomy

The Asymptomatic Carotid Surgery Trial (ACST) and the smaller Asymptomatic Carotid Atherosclerosis Study (ACAS) studied the role of CEA in nearly 5,000 patients with asymptomatic carotid stenoses (no stroke or stroke-like symptoms within the previous 6 months) [7-8]. A recent metaanalysis included three trials with a total of 5,223 patients. In these trials, the overall risk of perioperative stroke or death was 2.9%. For the

outcome of perioperative stroke or death or any subsequent stroke, patients undergoing CEA fared better than those treated medically (relative risk (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83). Similarly, for the outcome of perioperative stroke or death or subsequent ipsilateral stroke, there was benefit for the surgical group (RR 0.71, 95% CI 0.55 to 0.90). For the outcome of any stroke or death, there was a non-significant trend towards fewer events in the surgical group (RR 0.92, 95% CI 0.83 to 1.02)[4]. The general applicability of these findings has been questioned because morbidity and mortality rates exceeding 3% have been reported in general surgical practice under non-trial.

1.1.4 Role of carotid artery stenting

During the past decade, stent-protected angioplasty has been introduced as an alternative treatment for carotid stenoses. Several studies have investigated its efficacy in preventing further strokes in symptomatic carotid stenoses [3, 16], information on its efficacy in asymptomatic carotid stenosis was limited to self-reported uncontrolled case-series and registries [20, 22]. Recently the CREST trial has been published, including a substantial proportion of asymptomatic patients [2]. For the entire proportion of 2.502 patients there was no difference between CAS and CEA regarding the primary composite end point stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. This was not influenced by the symptomatic-status. However the subgroup analysis for asymptomatic patients was not powered to proof the equivalence of CAS and CEA in those patients and CREST did not have a medical arm.

1.2 Trial rationale/ justification

There is substantial and ongoing uncertainty in the choice of treatment for patients with asymptomatic carotid stenoses. Although a benefit has been demonstrated for surgery under well-controlled trial conditions, the applicability of these findings to the general population is an ongoing controversy [4]. Specifically two major criticisms exist: Firstly, the absolute and relative risk reduction of CEA over conservative treatment is rather small. Consequently, the numbers needed to treat (NNT) are high. Secondly, the majority of conservatively treated patients in ACAS and ACST was included more than 10 years ago and was not treated according to today's recommendations and guidelines. It has been argued that these trials should be repeated in the light of recent advances in medical treatment [5].

Only limited information on safety and efficacy of CAS is available for asymptomatic stenoses. Most of the data derive from the SAPPHIRE study, which included less than 150 asymptomatic patients per study arm. The results suggesting superiority of CAS over CEA are driven by the cardiovascular contribution to the endpoint, not by stroke. Potential advantages of stenting are shorter target vessel occlusion times, lack of wound healing problems, shorter hospital stay and usually the procedure is performed without general anesthesia. Despite the lack of evidence several thousand procedures are done every year. To clarify the role of CAS compared to CEA and modern medical treatment a large-scale randomized trial is clearly needed. The European Stroke Initiative (EUSI) Recommendations for Stroke Management support this and suggest that CAS is not routinely recommended for patients with asymptomatic carotid stenosis. It should be considered in the context of randomized clinical trials only [19].
The results of this trial are expected to be the base for defining a proven standard for the treatment of asymptomatic carotid artery stenosis and would have wide impact on managing this disease.

1.3 Benefit / risk assessment

The benefit from every treatment modality is the proposed reduction of future cerebro- and also cardiovascular events. However, each treatment arm carries specific risks. Risks from the conservative treatment are mainly due to possible side effects of the used medication. Most feared risk of both CAS and CEA is the risk of periprocedural stroke. Differences between the risk of CAS and CEA are based on technical details. CEA is usually performed under general anesthesia, which might contribute to the procedure related complication rate, up to now only a few centers offer local anesthesia as an alternative. In contrast CAS is generally performed under local anesthesia, general anesthesia is only required in patients with poor cooperation. CAS always needs interventional angiography, which increases the risk of stroke by 0.1–0.3% [7]. Current experience suggests that CAS without embolic protection devices causes more microembolic events than does CEA and these events seem to be associated with an increased risk of postinterventional DWI lesions, however the clinical impact of these lesions is still under discussion [13]. Although CAS causes fewer cranial nerve lesions, it might be associated with more-frequent restenoses than CEA.
To minimize these risks every individual in the trial will be treated by named experts and a close monitoring for such events will be done. In addition both endarterectomy and

stenting will be done only be certified physicians with a high level expertise and continuous quality control. For any treatment modality quality committees are defined. These committees define the rules for the treatment and the quality control criteria (see Appendix).

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 General aim / primary objective

The objective of this study is to compare up-to-date medical (conservative) treatment including life-style modification with carotid artery stenting and carotid endarterectomy in addition to those conservative treatments in treatment of individuals with asymptomatic atherosclerotic carotid artery stenoses.

OLD: Therefore on the first level, a superiority trial of intervention (CAS or CEA) versus state of the art conservative treatment is designed. In case of superiority of both interventions, a non-inferiority endpoint will be tested between CAS and CEA.

NEW: Therefore on the first level, a superiority trial of interventions versus best medical treatment (BMT) is designed. Both interventional treatment-groups (CEA and CAS) will be compared with the BMT patients of the specific substudy. In addition data from the CEA and CAS-groups will be compared in an explorative manner by an indirect treatment comparison. This data can also be used for a combined analysis with other international trials comparing these treatment modalities (e.g. ACST2).

2.2 Assessment of safety

Safety is assessed as the rate any stroke within 30 days of treatment, and death from any cause within 30 days. This endpoint has been used in many trials concerned with treatment of carotid stenoses [7-8, 10, 16].

2.3 Composite primary efficacy endpoint

The primary efficacy endpoint is the cumulative rate of any stroke or death from any cause within 30 days plus ipsilateral ischemic stroke within 5 years of follow up.

The primary effect expected from surgery or stenting is to reduce hemodynamic or thromboembolic ischemia of ipsilateral brain tissue. The clinically relevant figure is the sum of periprocedural complications and ipsilateral ischemia during a longer period. Conservative treatment is expected to go along with low 30-day complication rates but higher long-term ipsilateral ischemia rates. The reverse is to be expected with surgery

and stenting. The efficacy endpoint takes into account both components. This endpoint has been used in many previous carotid stenosis trials [7-8, 16].

2.4 Secondary and tertiary outcomes

Secondary and tertiary efficacy endpoints are single components of the primary endpoint, cardiac events, technical failures and observations at different time points. These are described in detail in chapter 6.3.

3 TRIAL DESIGN

OLD: SPACE-2 is a randomized, controlled, open, multi-center study with three parallel groups:

Best medical treatment (BMT)

Carotid endarterectomy (CEA) + BMT

Carotid artery stenting (CAS) + BMT

A hierarchical study protocol has been developed with a superiority design of intervention vs. conservative treatment. In case superiority for CAS and CEA is established, a non-inferiority comparison between the two interventions will be performed.

NEW: SPACE-2 is a randomized, controlled, open, multi-center study with two parallel substudies:

- SPACE2a: CEA vs. BMT
- SPACE2b: CAS vs. BMT

Primary aim of the study is to compare BMT with any type of intervention (CEA or CAS). In addition, data from the CEA and CAS-groups will be compared in an explorative manner. In order to analyze the effect between the two interventional methods, an indirect treatment comparison will be applied [17].

All patients are treated with a best medical treatment regimen tailored to their individual risk factor profile consisting in treatment of risk factors, lipid-lowering and anti-platelet medication. Rules for the BMT will be formulated by the BMT-subcommittee and are an appendix to this protocol.

The overall duration of the trial is expected to be approximately 9 years. Recruitment of subjects will start in October 2008. The actual overall duration of recruitment may vary.

4 SELECTION OF SUBJECTS

4.1 Number of subjects

OLD: As calculated in section 9.1 'Sample Size Calculation', 3,640 subjects should be enrolled in the clinical trial, 540 to the BMT-Arm, 1,550 to the surgical and 1,550 to the stenting-group.

NEW: As calculated in section 9.1 'Sample Size Calculation', 1636 subjects should be enrolled in the group sequential clinical trial with one interim analysis, 818 patients per arm. This is the case for SPACE2a comparing CEA with BMT and for SPACE2b comparing CAS with BMT. Both trials would require a total of 3,272 patients.

Recruitment and treatment of subjects should be performed in around 100 trial centers. The minimum / maximum number of subjects per trial centre should be 10/200.

4.2 General criteria for subjects' selection

In daily clinical practice most asymptomatic carotid stenoses are discovered by extracranial ultrasound techniques performed for screening purposes in patients with vascular disease in other vascular territories. Only some stenoses are diagnosed by extracranial MRA or due to cervical bruits. Due to the ultrasound-based screening procedure used in SPACE-2, the study population should closely resemble the population with asymptomatic carotid stenoses in general.

4.3 Inclusion criteria

Subjects meeting all of the following criteria will be considered for admission to the trial:

Males or females aged >/=50 and </=85 years

Carotid artery stenosis of >/=70% following ultrasound criteria

No stroke or stroke-like symptoms due to the stenosis within the last 180 days

Stenosis treatable with CEA **or** CAS

Ability of the patient for follow-up examinations

Personally written informed consent from the patient

For women with childbearing potential, adequate contraception

4.4 Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the trial:

Non-atherosclerotic stenosis (e.g. dissection, floating thrombus, fibromuscular dysplasia)

Stenosis following radiotherapy

Previous CEA or CAS in the artery to be randomized

Additional higher grade intracranial or intrathoracic stenosis (tandem stenosis)

Intracranial bleeding within the last 90 days

Known intracranial angioma or aneurysms

Severe pre-existing disability (modified Rankin scale more than one)

Contraindications for heparin, aspirin, clopidogrel or contrast media

OLD: Indication for anticoagulation with Phenprocoumon (Marcumar®) or Warfarin

NEW: Deleted

Life expectancy of less than 5 years

Recent history of malignoma

Major surgery (with exception of trial related procedures) planned within 8 weeks after randomization

No subject will be allowed to enroll in this trial more than once.

4.5 Criteria for withdrawal

4.5.1 Withdrawal of subjects

A subject may be withdrawn from all trial related procedures (including follow-up visits) for the following reasons:

at his/her own request or at request of his legal representative

non-adherence to the trial-related requirements, which may (have) influence(d) the validity of the trial data

If, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being, e.g. if a patient was randomized into the BMT arm and suffers ipsilateral neurological symptoms, patient treatment based on actual guidelines either with CEA or CAS

Occurrence of exclusion criteria

If, in the investigator's opinion, protocol violations caused by the subject would lead to invalid data (e.g. non-compliance with planned study procedures).

The Executive Committee (see chapter 10.2) decides about withdrawal of subjects from trial treatment in case of occurrence of criteria mentioned above. A withdrawn patient will be treated as censored at time of leaving the study.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. In case of withdrawal of a subject at his/ her own request, the reason should be asked for as extensively as possible and documented. All efforts will be made to follow up the subject and, all examinations scheduled for the final trial day will be performed as far as possible on all subjects and documented. All ongoing Adverse Events (AEs) / Serious Adverse Events (SAEs) of withdrawn subjects have to be followed up until no more signs and symptoms are verifiable or the subject is on stable condition.

4.5.2 Replacement of Subjects

Subjects will not be replaced.

4.5.3 Premature Closure of the Clinical Trial

If the 30-day complication rate (any stroke or death) of one or both treatment modalities exceeds 3% (with an 80% confidence interval), the Data Safety and Monitoring Board (DSMB, see chapter 0) can give a recommendation to the steering committee to stop the trial. If the complication rate exceeds 5%, the DSMB will recommend stopping the trial.

The trial can be prematurely closed or suspended by the Excecutive Committee in case of new data about the risk-benefit of one of the treatment regimes becomes available or if the DSMB recommends study closure. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material must be returned to the Coordinating Clinical Centre (Department of Neurology, University of Heidelberg)

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centers and investigators.

4.6 Prior and concomitant illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the case report form (CRF). Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Patients with related stroke symptoms within the territory of the treated vessel within the last 180 days are not allowed to include into the trial.
Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

4.7 Prior and concomitant treatments

Relevant additional treatments administered to the subjects on entry to the trial or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF. There are medical or surgical treatments prohibited during the trial. If a major surgery is planned during the first 8 weeks after randomization patients should no be included prior this operation.

5 TRIAL PROCEDURES

5.1 Description of trial days

Study visits are scheduled as follows:
Screening
Randomization (Screening and randomization can be done on the same day, must be done within 14 days after screening)
Therapy [=day 0] (if randomized to CAS or CEA, must be within 28 days after randomization)
Day 1 ± 0 after therapy (if randomized to CAS or CEA)
30 ± 3 days after randomization (if randomized to BMT) resp. after therapy (if randomized to CAS or CEA)
6 months ± 7 days after randomization
1 year ± 14 days after randomization
2 years ± 14 days after randomization
3 years ± 28 days after randomization
4 years ± 28 days after randomization
5 years ± 28 days after randomization
An overview about the procedures to be done at specific visits can be found on page 9.

5.2 Screening and randomization

To qualify for this trial, patients must have met all above described inclusion and none of the exclusion criteria. Screening and randomization can be done at the same day, and randomization must be done within 14 days after screening, otherwise screening-examinations have do be repeated. The interventional therapy that will be tested vs. BMT has to be chosen by the treating physician and the patient prior to randomization. Following this decision patients will be assigned to SPACE2a or SPACE2b. Randomization between BMT and intervention is performed after the eligibility of a patient has been accepted by the involved discipline and after the patient has been examined from the study neurologist. Randomization will be done with an internet-based system provided by the data-center in Munich. Randomization will be stratified by an age-limit of 75years, providing the same numbers of instances per group in both age-cohorts. If the patient has been randomized to the interventional arm, treatment must be done within 4 weeks after randomization. Events occurring between randomization and treatment are counted within the allocated treatment group. Events between screening and randomization are not counted, but have to be noticed in preexisting condition in the CRF.

Before randomization following procedures has to be done:

5.2.1 Informed consent

The patient must be able to understand the nature of the trial and the related procedures and sign the informed consent form in person. Informed consent must be available before any study related procedures.

5.2.2 Risk factor screening

Blood pressure: Measured at both arms after 5 minutes rest

Diabetes: Measurement of fasting blood glucose and of the HbA1c

Lipids: Fasting Cholesterol including LDL and HDL, and triglycerides. The necessary blood samples will be taken as clinical routine and are not study specific.

Peripheral pulse status

Smoking history

Bodyweight, height, hip-waist-ratio

Assessment of physical activity measured as numbers of time-intervals of above 30minutes activity.

5.2.3 Neurological examination

Modified Rankin Score (mRS) and NIH-Stroke Scale (NIHSS) are determined at screening as the basis for the follow-up-examinations. A mRS > 1 at baseline is an exclusion criterion. All neurologists must have a NIHSS certificate (http://asa.trainingcampus.net/uas/modules/trees/windex.aspx).

5.2.4 Drug history

Relevant medication (e.g. antiplatelets, antihypertensives, lipid-lowering-drugs) will be documented with name and dosage and way of application at every visit. In case of an outcome event any medication will be documented.

5.2.5 Ultrasound examination

The ultrasound examination including color-coded extracranial Duplex and examination of the intracranial circulation must be done by a certified examiner (see Appendix). Documentation contains at least grading of the stenosis, Plaque morphology and a measurement of the Intima-Media-Thickness in the common carotid arteries.

Stenosis severity as measured with ultrasound is usually expressed following the method of the ECST. If a conversion from a NASCET measurement is necessary following equation will be used: $\%^{NASCET} = (\%^{ECST} - 43) \times (100 / 57)$ [11].

5.3 Treatment

5.3.1 Allocation to treatment

Eligibility of a patient will be determined by a Neurologist.

Old: Both surgeons and interventionalists need to confirm that treatment is feasible.

New: Surgeon or interventionalist need to confirm that treatment is feasible

BMT should start immediately after randomization; CEA or CAS must be performed within 4 weeks after randomization. In the case of a bilateral stenosis, randomization is performed for one side only, usually the side with the more severe stenosis.

Keeping a screening log is mandatory. The screening log should list all patients which are suitable for the trial but were not randomized and includes the reason (e.g. on of the Exclusion criteria) why the patients were not randomized and the method of treatment. The Steering Committee will look into this screening log and compare it to the sites surgical and interventional program. All centers are encouraged to include the majority of potential patients into the study.

5.3.2 Best medical treatment

All patients, also those individuals randomized for treatment with CEA or CAS, will be treated with up-to-date medication following national and international guidelines. Recommendations for this treatment will be given by the 'best medical treatment' subcommittee (see Appendix).

5.3.3 Carotid endarterectomy

Standards for surgical treatment are formulated by the 'vascular surgery' subcommittee (see Appendix)

5.3.4 Carotid artery stenting

Standards for endovascular treatment are formulated by the 'endovascular treatment' subcommittee (see Appendix)

5.4 Blinding

Due to the nature of the treatments involved, blinded treatment is not possible; with ultrasound it is clear to see how the patient is treated. Therefore the study has to follow an open design. However, to minimize a potential bias due to the open design, a physician, not directly involved in the CAS or CEA-procedure, is responsible for the follow-up examinations and end-point evaluation.

5.5 Follow-up examinations

The duration of the trial for each subject is 5 years. After the periprocedural phase yearly examinations are scheduled. Each visit consists of an event-screening, a risk-factor screening, and an ultrasound-examination.

The 30day visit for patients randomized into the BMT-arm is primarily used to evaluate if the recommendations for risk-factor-modification have been fulfilled.

Events are screened using a standardized questionnaire. An event has occurred if one of the following questions has been answered positively:

"Ist (seit der letzten Untersuchung) eine vorübergehende Sehstörung auf einem Auge aufgetreten?"

„Ist (seit der letzten Untersuchung) eine Schwäche oder Sensibilitätsstörung auf einer Körperseite aufgetreten?"

„Ist (seit der letzten Untersuchung) eine Sprachstörung aufgetreten?"

„Haben sich (seit der letzten Untersuchung) neue Beschwerden entwickelt?"

If a cerebrovascular outcome-event occurred an appropriate neuroimaging should be performed to distinct between possible types of stroke. In addition the mRS and NIHSS have to be assessed and documented. 30 days after symptom onset the patient has to be contacted to assess the mRS at this time point. In case of an ipsilateral cerebrovascular event in a subject randomized into the BMT-arm, patient should be considered for CEA or CAS following actual guidelines for treatment of symptomatic stenosis.

Risk-factor screening, assessment of medication, and ultrasound-examinations has to be done at any follow-up visit like described above (section 5.2)

5.6 Plan for treatment or care after the trial

Medical treatment with risk-factor modification will be continued after the end of the follow-up period (5 years in each individual). Responsible for control of these procedures will be the general practitioner of the patient.

6 ASSESMENTS

6.1 Definitions

Ischemic Stroke: New focal neurological deficit of vascular origin lasting more than 24 hours, absence of intracranial hemorrhage upon brain imaging.
Hemorrhagic Stroke: New focal neurological deficit of vascular origin lasting more than 24 hours, proof of intracranial hemorrhage upon brain imaging.
Ipsilateral stroke: Stroke within the territory of the treated carotid artery.
Disabling stroke: Stroke leading to a disability of at least 3 on the modified Rankin scale at day 30±3 after symptom onset.
Myocardial infarction: Detection of rise and/or fall of cardiac biomarkers (preferable troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following [21]

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB)
- New onset of pathological Q waves in ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Vascular death: Deaths due to stroke, myocardial infarction, or hemorrhage as well as any deaths those were not clearly non-vascular.

Technical failure: Inability to treat the stenosis with the allocated method or remaining stenoses of at least 70% following ultrasound-criteria at day 1.

Restenosis: Recurrent stenosis of at least 70% following ultrasound-criteria, which will be defined in the 'Neurology quality appendix'.

Observation period: 30 day endpoints for patients randomized into the BMT-group are evaluated after 30±3 days after randomization. 30 days risks for patients randomized into the CAS or CEA-arm are evaluated between randomization and 30±3 days after the procedure. Medium-term (up to 2 years) observational period's starts at the time of randomization, assessment can be done in a time period ±14 days around the calculated date. Long-term (up to 5 years) observational period's starts at the time of randomization, assessment can be done in a time period ±28 days around the calculated date.

6.2 Evaluation of Safety

Safety is assessed as the rate of any stroke and death from any cause within 30 days of treatment. This safety endpoint will only evaluate in patients randomized to CEA or CAS.

6.3 Evaluation of efficacy

6.3.1 Primary endpoint

The primary efficacy endpoint is the cumulative rate of any stroke (ischemic or haemorrhagic) or death from any cause within 30 days plus ipsilateral ischemic stroke within 5 years of follow up.

6.3.2 Secondary endpoints

All single components of the primary endpoint clusters

Any stroke, death or myocardial infarction within 30 days

Any disabling stroke and death within 30 days

Any stroke up to 5 years since randomization

Any disabling stroke up to 5 years since randomization

Any stroke or vascular death up to 5 years since randomization

Ipsilateral ischemic stroke within 30 days and after 5 years since randomization

Ipsilateral disabling stroke within 30 days and after 5 years since randomization

Technical failure of intervention

Rate of re-stenosis (>/=70%^{ECST}) up to 5 years since randomization

Rate of myocardial infarction at 30 days after the procedure in patients randomized to CAS or CEA

6.3.3 Tertiary endpoints

All primary and secondary endpoints will also be assessed after 1 and 3 years since randomization.

6.4 Endpoint evaluation

All suspected strokes, as well as all myocardial infarctions, and all deaths will be evaluated by a committee of experts blinded to treatment, who will determine the final classification of these events. This committee, named ‘endpoint evaluation committee’ is described in section 10.3 at page 40.

7 ADVERSE EVENT REPORTING

7.1 Definitions

7.1.1 Adverse event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

New symptoms/ medical conditions

New diagnosis

Changes of laboratory parameters

Intercurrent diseases and accidents

Worsening of medical conditions/ diseases existing before clinical trial start

Recurrence of disease

Increase of frequency or intensity of episodically diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

7.1.2 Serious adverse event

A serious adverse event (SAE) is one that at any dose:

Results in death

Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have cause death if it was more severe)

Requires subject hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability/ incapacity or

Is a congenital anomaly/ birth defect.

7.1.3 Expectedness

An ‘unexpected’ adverse event is one the nature or severity of which is not consistent with the trial procedures. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute ‘unexpected’ events.

7.1.4 Outcome event

Outcome events are the components of the endpoints (see chapter 6.3). Most of these will also be SAEs.

7.2 Period of observation and documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject’s medical records.

In this trial, all AEs that occur after the subject has signed the informed consent document will be documented on the pages provided in the CRF. All subjects who have AEs, whether considered associated with the use of the trial medication or not, must be

monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

The intensity of an AE should be assessed by the investigator as follows:

Mild: temporary event which is tolerated well by the subject.

Moderate: event which results in discomfort for the subject and impairs his/ her normal activity.

Severe: event which results in substantial impairment of normal activities of subject.

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale defined in the CTCAE v3.0:

Grade 1: mild AE

Grade 2: moderate AE

Grade 3: severe AE

Grade 4: life-threatening AE or AE causing disablement

Grade 5: Death related to AE

The grading of all AEs listed in the CTCAE v3.0 will be based on the information contained therein. The grading of all other AEs, i.e. those which are not listed in the CTCAE v3.0 will be performed by a responsible investigator, based on definitions given above.

The investigator will evaluate each AE that occurred after administration of investigational medicinal product regarding the coherency with the administration of the investigational medicinal product possibly:

Related: There is a reasonable possibility that the event may have been caused by IMP. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.

probable: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.

possible: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.

unlikely: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

not related: An AE that does not follow a reasonable temporal sequence related to IMP and is likely to have been produced by the subject's clinical

state, other modes of therapy or other known etiology.

not assessable: The relationship between an AE and the IMP that does not follow a reasonable temporal sequence from trial participation and that is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.

The outcome of an AE at the time of the last observation will be classified as:

recovered/ resolved: all signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation

recovering/ resolving: the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution

not recovered/ not resolved: signs and symptoms of an AE are mostly unchanged at the time of the last interrogation

recovered/ resolved with sequel: actual sings and symptoms of an AE disappeared but there are sequels related to the AE.

fatal: resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal'

unknown: the outcome is unknown or implausible and the information cannot be supplemented or verified

7.3 Reporting of SAEs by investigator

All SAEs must be reported by the investigator within 24 hours after the SAE becomes known using the 'Serious Adverse Event' form to the Data Management. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial procedures.

7.4 Reporting of OEs by the investigator

All Outcome-events must be reported by the investigator within 24 hours after the OE becomes known using the 'Outcome Event' form to the Data Management. The initial report must be as complete as possible including details of type of stroke (ischemic vs. hemorrhagic, territory of stroke, and severity of stroke). 30 days after symptom onset the modified Rankin Score patient has to be assessed and to be transferred to the Data management using the 'Outcome Event' form. All OEs are also evaluated by the EEC.

7.5 Expedited reporting

SAEs, and OEs resulting in death or being life-threatening will be reported to the ethics committee (EC) according to EC standing rules and to all participating investigators.

8 DATA MANAGEMENT

8.1 Data collection

All findings including clinical and laboratory data will be documented in the subject's medical record and in the electronic CRF. The electronic CRF has a series of inbuilt validation routines and plausibility checks. The investigator will be immediately informed if the data entered does not comply with the data validation rules. The fully entered parts of the CRF will be mailed as encoded PDF-Files to the main investigator of the specific site. The PDF can be printed and support monitoring activities at the study site. A second check will be performed by the data management which triggers the query process. Queries will be sent directly to the investigator and a copy to the monitor. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data.

8.2 Data handling

Data handling is described in detail in the Data Management Plan and the Data Validation Plan.

Each study site will have secured internet access to the electronic study data base. The data will be entered directly to the database. During entering a series of data check will be run automatically and the person entering the data will be reminded immediately if there are specific errors or inconsistencies. These data checks will be formulated in the data validation plan. After finishing specific parts of the eCRF the study site will get a PDF with the patient data via an encoded email.

A more thorough data check will be performed by the data management. This second view generates the queries which are sent to the study site as well as to the monitor.

A responsible investigator will be obliged either to correct the implausible data or to confirm its authenticity and to give appropriate explanation. If not corrected, the data will be flagged, rendering a check of all questionable entries conveniently possible. A responsible monitor will check all flagged data and will generate questions, which will be

sent back to the responsible investigator. The investigator will have to resolve all 'discrepancies'.

Further checks for plausibility, consistency, and completeness of the data will be performed after completion of the study. Queries will be generated on the basis of these checks combined with a visual control by a responsible monitor/data manager.]

All missing data or inconsistencies will be reported back to the center(s) and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

All data management activities will be done according to the current Standard Operating Procedures (SOPs) of the IBE.

8.3 Storage and archiving of data

All important trial documents (e.g. Investigator Site File, subject identification log, CRF) will be archived for at least 10 years after the end of the trial.

9 DATA ANALYSIS / STATISTICAL METHODS

9.1 Sample size calculation

Sample size calculations were performed for the efficacy endpoints.

OLD: Since a hierarchical testing procedure is used, a 5% significance level for each step of the procedure can be chosen. The first level consists of two simultaneously performed tests. In order to assure an overall level of 5% for this step, the closed testing procedure is used and the two comparisons CAS versus BMT and CEA versus BMT are performed as two-sided tests with α=2.5%. The event rate of CAS (as well as CEA) is assumed to be 6.4% (combining short-term and 5-year event rates). The BMT event rate is set to 11.8%. The sample size in the CAS (CEA) arm is twice the number of patients in the BMT arm. The power of each comparison is set to 90%. We need a high chance to show simultaneously superiority for CEA as well as CAS in comparison with BMT in order to clinically interpret the non-inferiority aimed at the second step of the procedure. The comparison needs 1,080 patients in the CAS and the CEA and 540 patients in the BMT arm when a two group continuity corrected chi-square test is used. For this scenario (1,080/1,080), a two-sided significance level of α=5%, and a non-inferiority margin of 2.5% implies for the non-inferiority assessment between CAS and CEA a power of 66%. A power of 80% for the non-inferiority test is reached with a sample size of 1,505 patients in each group (CAS/CEA).

The CAS/BMT as well as the CEA/BMT comparison (SPACE-2a) will be performed on an ITT population. In contrast the CAS/CEA non-inferiority assessment (SPACE-2b) will be based on an ITT as well as on a PP population [11]. The PP analysis for non-inferiority needs a group size of 1,505 patients. In SPACE 3% of the patients switched between treatment modalities or were not treated. A recruitment of 1,550 patients into the CEA and CAS groups is needed to correct for such a deviation from the allocated treatment and to allow a sufficient PP-analysis. This increases the power of the comparisons CAS/BMT and CEA/BMT to 93%.

Therefore, the total size of the trial is chosen as (1,550+1,550+540=) **3,640** patients.

NEW: The event rate in the BMT-group is expected as 0.01 per year, a hazard ratio with any type of intervention is set as 0.50 leading to an average risk of 0.005 per year including the periprocedural risk for both types of intervention. In case of a design without interim analysis 1,624 patients in total are needed to show the assumed difference on a two- sided significance level of 5% and with a power of 80% assuming an accrual time of 3 years and a follow-up time of 5 years.

Planning one interim analysis in a group sequential design after five years, a total of 1,636 patients is needed to show the assumed difference on a two- sided significance level of 5% and with a power of 80% assuming an accrual time of 5 years and a follow-up time of 3 years. 1,624The critical values and the test characteristics of the group sequential test design were calculated for the O'Brien and Fleming design.

9.2 Analysis variables

Safety is assessed as the rate any stroke within 30 days of treatment, and death from any cause within 30 days. The primary efficacy endpoint is the cumulative rate of any stroke or death from any cause within 30 days plus ipsilateral ischemic stroke within 5 years of follow up. Both safety and efficacy are also evaluated by analyzing secondary and tertiary endpoints as described in section 2 and 6.

9.3 Definition of trial population to be analyzed

The primary analysis will be intention-to-treat (ITT). In addition, due to the nature of a non-inferiority study, a per-protocol (PP) analysis will also be performed. The PP includes all patients without major protocol deviations. The following are considered major protocol deviations:

- Not meeting one or more of the Inclusion Criteria and/or falling into one or more of the Exclusion Criteria
- Not finishing the allocated therapy (change of treatment group)
- Operation or Stenting done by an non-certified interventionalist or using non-certified material
- Endpoint event between randomization and treatment (if allocated to CEA or CAS)

In case of problems with the decision if a protocol violation is major, the Endpoint Evaluation Committee (see page 40) is responsible for the allocation; this will be done prior the unblinding of the data.

9.4 Statistical methods

Biometric analysis will be defined in the statistical analysis plan which has to be authorized before closing the database by the biometrician, the sponsor, and the LKP.

OLD: Safety: The one-sided 97.5% confidence interval under H_0 for the difference of the event rates (rate in the CAS group – the rate in the CEA group) will be calculated. Non-inferiority is proven if the upper margin of this interval is less than 1.5%. This test has power of 90% if CAS shows a slight safety advantage compared to CEA (2.5% CAS versus 3% CEA). The power of the non-inferiority test is 80% in case of a slightly reduced risk in both procedures (CAS and CEA 2%).

Efficacy: In order to control the overall Type I error on the 5% level, a hierarchical testing procedure will be used. The first step of the procedure consists in a closed testing procedure for the difference between the three treatments. The tests are performed on a 5% level. If there are simultaneously significant differences between the pairs BMT and CEA as well as BMT and CAS on a 5% level, the hierarchical testing procedure enters step 2, otherwise there is no further statistical testing. Since superiority for CEA and CAS over BMT is not yet established in the studied population both tests need to be significant to allow the interpretation of step 2 in a clinically sensible way. Step 2 of the procedure consists in a non-inferiority test: The one-sided 97.5% confidence interval for the difference of the event rates (rate in the CAS group – the rate in the CEA group) will be calculated. Non-inferiority is proven if the upper margin of this interval is less than 2.5%.

In case of losses to follow up, the event rates and their standard errors will be calculated by Kaplan-Meier-techniques.

NEW:

Safety: If in the interim analysis the absolute rate of safety events (any stroke or death within 30 days after intervention) in the CEA-arm (for SPACE2a) or in the CAS-arm (for SPACE2b) with a confidence interval of 80% is higher than 3%, the DSMB can recommend stopping the trial. If the lower 80%-confidence-interval of the safety-event-rate is higher than 5%, the DSMB will recommend stopping the trial.

Efficacy: The primary analysis consists in testing the difference between BMT and intervention (CEA or CAS) with respect to the composite primary end point (Section 2.3) for each of the individuals substudies. The comparison will use the Cox-PH model. An explorative comparison of the event rates in the CEA and the CAS groups will be done (Calculating a 95% confidence interval of the hazard rate for the primary endpoint between both treatments). In order to analyze the effect between the two interventional methods, an indirect treatment comparison will be performed [17].

9.5 Interim analyses

OLD: No interim analysis is planned with respect to the primary endpoint. An interim analysis of the safety data is planned after three years. This will not influence the sample size calculation because this is based on the efficacy endpoint. In addition the safety committee will check the safety regularly.

NEW: One interim analysis is planned with respect to the primary endpoint after five years. An interim analysis of the safety data is planned after three years. This will not influence the sample size calculation, because this is based on the efficacy endpoint. In addition the safety committee will check the safety regularly.

10 STUDY ADMINISTRATION

In order to monitor specific aspects of the current trial the following Reference Committees will be established: Data Safety and Monitoring Board (DSMB), Steering Committee (SC), Executive Committee (ExC) as a subgroup of SC-members, and an Endpoint Evaluation Committee (EEC). The work of these committees will be based on the 'Guideline on Data Monitoring Committees' EMEA/CHMP/EWP/5872/03

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10.1 Data Safety and Monitoring Board (DSMB)

An independent Data Safety and Monitoring Board (DSMB) will be assembled. The DSMB will be composed of independent experts in the field of Neurology, Neuroradiology, Vascular Surgery assessing the progress, safety data and, critical efficacy endpoints. The mission of the DSMB will be to ensure the ethical conduct of the trial and to protect the safety interests of patients in this trial. In the context of overall patient safety the DSMB will receive periodic reports (also including center specific informations) as well as any special reports as requested by the DSMB and to be prepared by the trial data center. The DSMB will have access to all trial data. The need and frequency of face-to-face meetings will be determined by the DSMB and the SC, taking into account the possibility of teleconferencing and other electronic conference options.

The DSMB will define details of their working procedures in an extra protocol to keep the independence from the study. This DSMB protocol will be an appendix of this protocol.

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10.2 Steering Committee (SC) and Executive Committee (ExC)

The SC consists of 19 members of all involved disciplines and from different countries. Because of the amount of medical disciplines involved in the trial and the size of the steering committee, six members of the Steering committee build an Executive Committee (ExC); the members of the ExC are marked with a star (*) in the following list. Further (e.g. international) members might be nominated during the course of the trial.

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10.3 Endpoint Evaluation committee (EEC)

An Endpoint evaluation committee will confirm all outcome event notices, as it will make the final decision on whether the patient had one outcome event. All patients thought to have an outcome event will have their CRF and if necessary additional information's examined by the members of this committee. The committee can also request additional

ancillary information from an individual study investigator to assist their review. The EEC will also confirm the type (e.g. ischemic, hemorrhagic) and localization of each stroke.

Members of the EEC:

Name	Prof. Dr. M. Böhm
Affiliation	Department of Internal Medicine, University of Homburg/Saar
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Name	Prof. Dr. H.H. Eckstein
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Name	Prof. Dr. R. Stingele
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10.4 Quality Subcommittees

For each discipline involved, a subcommittee with experts in this field will formulate rules and recommendation for diagnosis and treatment. There will be recommendations for best medical treatment, neurology, vascular surgery and endovascular treatment. These recommendations will be appendixes of this protocol. The subcommittees will also define details of the quality criteria (see section 10.5.2) for participation of an investigator and will be responsible for the control of these criteria and the certification process. The head of each sub-committee is also a member of the SC.

Members of the Subcommittees:

Best medical treatment

Name	Prof. Dr. M. Böhm (head)
Affiliation	Medizinische Universitätsklinik III
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Name	Prof. Dr. G. Ertl
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Name	Prof. Dr. M. Hennerici
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Vascular Surgery

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Name	Prof. Dr. M. Jacobs
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Name Prof. Dr. Peter A. Ringleb
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eMail Peter.Ringleb@med.uni-heidelberg.de

10.5 Control of treatment quality

10.5.1 Centers

Each study center must consist of at least one neurologist, one vascular surgeon and one endovascular therapist. Clinics which lack of one of these components may join other centers. Certification of a participating center will follow upon compliance to all quality criteria. The steering committee or the executive committee can withdraw the certification to participate in the trial on recommendation of the DSMB and or the monitoring agency.

10.5.2 Investigators

For all involved disciplines quality criteria are defined by the appropriate quality committee (see Appendix). Every neurologist has to demonstrate his/her ultrasound-expertise and must have a NIHSS-certificate. Vascular surgeons and interventionalists must demonstrate at least 30 consecutive procedures with mortality and morbidity rates of these procedures. The local principal investigator has to confirm this documentation. Together with the DSMB the quality committees will monitor local complication rates and can recommend the steering-committee or the executive committee to withdraw a certificate.

10.6 Participating sites

The appendix will contain an extra document listing all participating sites.

11 ETHICAL AND LEGAL ASPECTS

11.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

11.2 Subject information and informed consent

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The subject must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

11.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law (Bundesdatenschutzgesetz, BDSG).

During the clinical trial, subjects will be identified solely by means of their initials, date of birth, and an individual identification code (subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized

persons (clinical monitors, auditors, inspectors) may inspect the subject-related data collected during the trial ensuring the data protection law.
The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.
Subjects who did not consent to circulate their pseudonymized data will not be included into the trial.

11.4 Responsibilities of investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.
The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

11.5 Approval of trial protocol and amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC). A written favorable vote of the EC is a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting.
Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) will be submitted to EC in writing as protocol amendments. They have to be approved by the EC.
The investigator will keep a record of all communication with the EC and the regulatory authorities.

11.6 Continuous information to independent ethics committee

The EC will be informed in case the risk/ benefit assessment had changed or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Annual Safety Report. The EC and the regulatory authorities will be informed of the end

of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LSO).

11.7 Registraton of the trial

Application has been filed to http://www.controlled-trials.com, the study code is ISRCTN 78592017. In addition the protocol of the study will be published in a peer-reviewed journal.

12 QUALITY ASSURANCE

12.1 Monitoring

The Monitoring will be performed by the Coordination Center for Clinical Trials (KKS) Heidelberg according to ICH-GCP (E6) and approved standard operating procedures of the KKS to ensure patients safety and integrity of the clinical data in adherence to study protocol. Prior to study start all participating centers will be trained and introduced into all study specific procedures by central initiations. Regular on-site monitoring visits are planned at all sites (approximately 9-10 on-site visits per center depending on the recruitment rate and quality of the data). Source data verification of predefined core and safety data will be done for all included subjects. For at least 10% of all subjects a 100% source data verification (SDV) for all items is planned. The extend of 100% SDV or the frequency of monitoring-visits will be increased for individual centers in case bad quality of data or common protocol violations are observed. In return frequency of monitoring visits can be reduced for reliable and compliant centers with high data quality. Queries of the data management (e.g. in case of missing values, implausibility etc.) have to be answered by the investigators contemporary to avoid that errors in data capture or entry will be carried forward. In addition to the SOPs all procedures are described in a study-specific monitoring-manual.

12.2 Inspections / Audits

Regulatory authorities and an auditor authorized by the sponsor may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

13 AGREEMENTS

13.1 Financing of the trial

The trial will be financed using funds of the BMBF and DFG (HA 1394/5-1). Co-financing by pharmaceutical industry and stent manufactures will be arranged.

13.2 Publication

All information concerning the trial is confidential before publication. The safety (30-day) results will be published first. Final results will be published after end of the trial. Publications will be prepared from a writing committee in the name of all SPACE-2 investigators.

14 SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned.

Date: _____ Signature: _____

Name (block letters): Prof. Dr. Dr. h.c. W. Hacke

Function: Principal Coordinating Investigator (LKP)

Date: _____ Signature: _____

Name (block letters): Prof. Dr. H.H. Eckstein

Function: Principal Co-Investigator

Date: _____ Signature: _____

Name (block letters): Prof. Dr. O. Jansen

Function: Principal Co-Investigator

Date: _____ Signature: _____

Name (block letters): Prof. Dr. U. Mansmann

Function: Biometrician

15 DECLARATION OF INVESTIGATOR

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.
I will enroll the first subject only after all ethical and regulatory requirements are fulfilled.
I pledge to obtain written consent for trial participation from all subjects.
I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.
I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible regulatory authorities.

Trial Center (address): _____

_____

_____

Date: _____ Signature: _____

Name (block letters): _____

Function: Investigator

Date: _____ Signature: _____

Name (block letters): _____

Function: Investigator

Date: _____ Signature: _____

Name (block letters): _____

Function: Investigator

16 REFERENCES

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17 APPENDICES

Declaration of Helsinki (applicable Version)

List of participating centres

Standard procedures of the ‘Best Medical Treatment’ subgroup

Standard procedures of the ‘Neurology’ subgroup

Standard procedures of the ‘Vascular surgery’ subgroup

Standard procedures of the ‘Endovascular Treatment’ subgroup