Protokollanhang zur SPACE-2-Studie
Neurology Quality Standards

1. General remarks

In contrast to SPACE-1, the neurological center participating in the SPACE-2 trial will also be involved in the treatment of patients by providing the “best medical treatment” as defined by the “best medical treatment” standards. Therefore, expertise is needed for patient recruitment, screening and treatment of risk factors, ability to perform follow-up exams, and in ultrasound techniques both for screening and follow-up.

2. Recruitment of patients

The neurologist decides on the necessity for treatment of an asymptomatic carotid stenosis based on the inclusion and exclusion criteria of the SPACE-2 study protocol. This requires thorough history taking, clinical exam and an ultrasound exam performed by a certified sonographer. In taking the patients history it is of particular importance to collect information on previous TIAs and attacks of retinal ischemia to avoid inclusion of symptomatic stenoses (A symptomatic stenosis is defined as a stenosis with symptoms within the past 180 days). Furthermore, a thorough history of vascular disease in other vascular territories (peripheral and coronary artery disease and strokes in non-target vascular territories) and of stroke and vascular risk factors must be taken, along with the corresponding treatments.

When all inclusion criteria are fulfilled and none of the exclusion criteria are met, it is the responsibility of the neurologist to provide the patient with detailed information on the SPACE-2 study and to obtain written inform consent.

After informed consent has been obtained, the neurologist needs to inquire with the associated vascular surgery and endovascular therapy partners on the theoretical feasibility of therapy with the respective methods. If either vascular surgery or endovascular therapy is not feasible, the patient is entered in a screening log and therapy outside the trial is considered. If both vascular surgery and endovascular therapy are feasible, the date of consent (first day at which both surgery and endovascular therapy agree to treat patient) is documented in the CRF and the patient is randomized immediately. It is the responsibility of the neurologist to

immediately inform both vascular surgery and endovascular therapy of the result of randomization in order to allow for a timely scheduling of therapy.

3. Post-procedural follow-up

The neurologist is responsible for the clinical follow-up of all patients, not only the patients randomized to “best medical treatment”. This requires that the neurological center is able to perform the clinical und ultrasound follow-up at the dates specified in the protocol, even if the patient is hospitalized in the respective treating department. It is the responsibility of the neurologist to document the results of the follow-up exams in the CRF. The required ultrasound follow-up exams must be performed or validated by a certified sonographer.

In addition, the neurologist is required to assess the adherence to the “best medical therapy” defined after inclusion in the study. She must record endpoints, adverse events and side effects of the medication taken.

4. Clinical expertise in stroke medicine

Experience in dealing with stroke patients is essential for sensitive detection of the stroke endpoints after randomization and for the definition and maintenance of the best medical therapy as defined in the protocol. Although the SPACE-2 study deals with asymptomatic stroke patients, knowledge of stroke medicine is important for the correct attribution of occurring symptoms to one of the endpoints.

4.1 Number of stroke patients

Experience with stoke patients is difficult to measure, therefore we choose to define cut-off values for the number of stroke patients per year for certification of centers.

In order to be certified as a neurology center, al least 200 stroke patients per year must have been treated in the department (A stroke patient is defined as a patients coded with one of the following diagnoses: ICD I63.X, ICD I64.X, ICD 65.X or I67).

4.2 Ability to screen for and treat risk factors

The neurology department is responsible for screening of risk factors including the appropriate laboratory exams and for treatment as defined in the “best medical therapy” section of the protocol.

5. Sonographic quantification of carotid artery stenoses

All degrees of stenoses in the SPACE-2 trial must be provided according to ECST criteria (local degree of stenosis) based on color-coded duplex sonography of the carotid arteries. Different ultrasound labs use different techniques to arrive at a figure for the ECST-degree of stenosis. The techniques used include geometrical measurement of vessel diameters, some use duplex sonography together with ancillary findings such as flow direction of ophthalmic collaterals, retrograde ipsilateral anterior cerebral artery or low flow velocities in the ipsilateral middle cerebral artery. Other labs rely on calculation of indices, such as the ICA/CCA-Index or the mean-velocity ratio ($ICA_{stenosis}/ICA_{after\ stenosis}$). It is left to the discretion of the ultrasound laboratory which method is used to arrive at the ECST-degree of stenosis, but the ultrasound laboratory must document a number of parameters related to the degree of the target stenosis in order to allow comparison between the laboratories (see section 5.5). The ultrasound exam must be based on color-coded duplex sonography. Grading criteria for the different methods mentioned are provided as a guideline in section 5.4. These guidelines are meant as an orientation for grading. It is left to the discretion of the certified examiner which criteria to use for grading the stenosis.

5.1 Ultrasound equipment

Modern color-coded equipment allowing a reliable detection of stenoses of the extracranial carotid arteries must be available. Each ultrasound laboratory must provide the make of the Duplex-equipment including a list of the available ultrasound probes with frequencies. The availability of CW- and PW-sonography equipment is not mandatory. The system of documentation must allow post-hoc validation of the findings by third parties. The ultrasound laboratory must provide typical examples of a documentation of a carotid ultrasound exam for certification in order to judge the quality of the B-Mode/color coding and documentation.

5.2 Frequency of ultrasound exams of extracranial arteries

In order to ensure a high level of experience, the ultrasound lab must have performed exams of extracranial arteries of the neck in excess of 1200 patients during the year 2007.

5.3 Expertise of the examiner

All ultrasound exams required in the protocol of SPACE-2 must be either done personally or validated by a certified sonographer. The certification of the examiner is ad personam, i.e. is not transferable to other sonographers of the department. More than on sonographer can be certified in each center.

For certification, each sonographer has to provide 25 well documented, non-selected ultrasound exams of patients with carotid stenoses ≥ 70 % (ECST), including printouts of screenshots of the exam. Each of the 25 exams should contain a grading of the stenosis according to ECST-criteria. An ultrasound – certificate (DEGUM/ÖGUM/SGUM) is not mandatory, but will be asked for during the certification process. Each examiner is asked to provide an estimate of the number of patients examined personally per year.

5.4 Guidelines grading criteria for carotid artery stenoses

The degree of carotid stenosis required for inclusion in the SPACE-2 study is ≥ 70% according to ECST criteria. Guidelines for the different grading methods are provided for this cut-off only:

- Systolic flow velocity (V_{max}) (corrected for angle of insonation): >200 cm/sec
- Enddiastolic flow velocity (corrected for angle of insonation): >120 cm/sec
- Poststenotic turbulences: Moderate, detectable up to the distal region of insonation.
- Carotid index (defined as V_{max} ICA / V_{max} CCA): ≥ 2
- Mean velocity ratio (defined as V_{mean} $ICA_{stenosis}$ / V_{mean} $ICA_{after\ stenosis}$): >3
- Flow direction of ipsilateral ophthalmic collateral: Orthograde
- Flow direction in ipsilateral anterior cerebral artery: Orthograde
- Flow velocities in ipsilateral middle cerebral artery: Normal

5.5 Documentation of ultrasound findings

According to the principles of good clinical practice (GCP) the results of the ultrasound exams are documented twice, in the CRF and in the routine documentation of the ultrasound laboratory. All results documented in the CRF must also be documented in the laboratory database.

The ultrasound exam must include the following documented findings:

- CCA (both sides): Longitudinal B-Mode, with and without color coded picture, Longitudinal B-mode with PW-Doppler (gate at center of vessel, angle of insonation corrected, Doppler-shift given as cm/sec).
- Bifurcation (both sides): Longitudinal B-Mode, with and without color coded picture, Longitudinal B-mode with PW-Doppler (gate at center of ICA, angle of insonation corrected, Doppler-shift given as cm/sec). Transversal B-Mode with and without color-coded information.
- ACE (both sides): Longitudinal B-Mode, with and without color coded picture, Longitudinal B-mode with PW-Doppler with visible artifacts of undulation from compression of superficial temporal artery.
- ACI (both sides): Longitudinal B-Mode, with and without color-coded picture at systole. Longitudinal B-mode with PW-Doppler (gate at center of vessel, angle of insonation corrected, Doppler-shift given as cm/sec). Transversal B-Mode with and without color-coded information.
- Vertebral arteries (both sides): longitudinal B-Mode with color coded picture and measurement of the vessel diameter in V2-segment.
- Additional documentation for target stenosis: Longitudinal and transversal B-mode at maximum of stenosis for assessment of plaque morphology. Longitudinal B-mode with angle corrected PW-Doppler spectra at maximum of stenosis and proximal and distal of the stenosis. The Doppler spectra should be given in cm/sec. It must be possible to discern systolic and enddiastolic flow velocities.

Ancillary findings (should be documented if examined, but not mandatory for study documentation):

- CW-findings of extracranial arteries
- Direction of ophthalmic collateral (both sides)
- Results of transcranial Doppler- or Duplex-sonography (retrograde ACA?, low flow velocity in MCA?, Evidence for second stenosis in distal ICA?)

6. Certification criteria and pathways

Certification by the Neurology Standards Committee covers three aspects:

- Certification of stroke medicine expertise

- Certification of the ultrasound laboratory
- Certification of one or more sonographic examiners ad personam

The three components are checked in one certification process and is based on the criteria defined above (see also certification check list in section 7.).

An alternative pathway to obtain certification is possible for those centers recruiting better than average during the SPACE-1 trial (>35 patients included in SPACE-1). Those centers already have demonstrated their expertise in stroke medicine and ultrasound techniques and thus have the possibility to undergo a simplified certification process (see check list). In these cases, certification of stroke medicine expertise and of the ultrasound laboratory are not necessary. Certification of sonographic expertise must be obtained, if the person certified during SPACE-1 is not longer available at the center.

7. Certification check list

Department: _____

Address: _____

Direktor: _____

Kontakt (Tel.; email): _____

_____

Has your center recruited ≥ 35 in the SPACE-study? If yes, you may skip to section C, unless significant structural changes in your department or in the ultrasound laboratory have occurred since your participation in the SPACE-1 study.

Yes / No

A. Stoke medicine expertise

Is outpatient follow-up of included patients possible in your department?

Yes / No

Does your department cooperate with vascular surgeons on a regular basis?

Yes / No

If yes, which surgeon/department?

_____

Does your department cooperate with an endovascular therapist?

Yes / No

If yes, which department?

_____

Is it possible that neurologists from your department perform follow-up exams of treated patients hospitalized in other departments?

Yes / No

Please, provide the number of patients coded with the following ICD diagnoses during the year 2007:

ICD I63 (Cerebral infarction) _____
ICD I64 (Stroke, not specified if hemorrhage or ischemia) _____
ICD I65 (Occlusion or stenosis of extracranial arteries without stroke) _____
ICD I67 (Other cerebrovascular disorders) _____

Is it possible in your department to provide “best medical therapy” including the necessary laboratory screening test for risk factors, blood pressure management, ECG?

Yes / No

B: Ultrasound laboratory

Please provide al list of the ultrasound equipment that will be available to you for the management of SPACE-2 patients. Include the make of the Duplex machine and a list of the available ultrasound probes. Please also list CW- and PW- sonography equipment if available.

Done? Yes / No

Please provide a representative example of a color-coded duplex sonography exam that allows to judge the B-mode quality, the quality of color-coded exams and the

quality of documentation done with the equipment that you intend to use for the examination of SPACE-2 patients.

Done Yes / No

How many patients has the ultrasound laboratory of your department examined during the year 2007?

_____

How many technicians work in your ultrasound lab?

_____

Is your ultrasound lab able to provide the necessary documentation listed in section 5.5?

Yes / No

C: Ultrasound examiner (please provide one form per examiner to be certified)

Last name: _____

First Name: _____

Titel: _____

Position: _____

Have you been a certified sonographer in the SPACE-1 trial?

Yes / No

If yes, has your department recuited ≥ 35 patients?

Yes / No

If you have responded “yes” to the last two questions, you may skip the rest of the certification check list.

Do you hold a DEGUM/SGUM/ÖGUM – ultrasound certificate?

Yes / No

Please provide 25 well documented, non-selected ultrasound exams of patients with carotid stenoses ≥ 70 % (ECST), including printouts of screenshots of the exam.

Each of the 25 exams should contain a grading of the stenosis according to ECST-criteria.

Done? Yes / No

Give an estimate of the number of patients that you personally examined (Duplex-ultrasound of extracranial arteries) in the past three years.

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