RESEARCH PROTOCOL

Carotid Artery Stenting during Endovascular treatment of acute ischemic Stroke (CASES) versus deferred treatment of carotid artery stenosis

A randomized multicenter clinical trial in patients with acute ischemic stroke and carotid artery stenosis undergoing endovascular treatment

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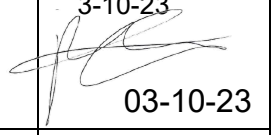
[Coordinating Investigator/Project leader/Principal Investigator]: ***<please include name and function>***	dr. M. Uyttenboogaart, interventional neurologist UMC Groningen, the Netherlands dr. P.J. Nederkoorn, stroke neurologist Amsterdam UMC, location AMC, the Netherlands prof. dr. R. Lemmens, stroke neurologist, UZ Leuven, Belgium	29-09-2023  P.J. Nederkoorn 3-10-23  03-10-23
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Version	Changes
2.2 21-04-2023	Accepted by METC (Netherlands) 6.1: Removal of Carotid Artery Stent Cristallo Ideale, Medtronic → out of stock 6.5: moved to 7.5 6.6 moved to 7.6 8.2: removal of “and administration of prior IVT” 10.2: addition of “estimated with proportional odds regression 10:2: removal of “Predefined subgroup analyses will be performed to test for interaction between specific variable and the treatment.” 10.4: Addition of “For the subgroup analyses, the point estimates with confidence intervals per subgroup will be presented with the p value for interaction, obtained from the difference in model fit of a model with and without interaction term (treatment * concerning subgroup, where applicable as a continuous variable) tested with a likelihood ratio test. “
2.3 08-05-2023	Accepted by CEC (Belgium) 17.7: Addition of “Uw gegevens worden gepseudonimiseerd. Dit betekent dat ze gecodeerd worden (uw identiteit zal vervangen worden foor een identificatiecode in de studie, die apart wordt bewaard.” 17.7: Removal of “De onderzoekers schrijven uw naam nergens op. En zij vertellen aan niemand dat u aan het onderzoek heeft meegewerkt.” 17.8: Addition of “Your data will be pseudonymised. This means they will be encrypted (your identity will be replaced by an identification code in the study, which will be stored separately).” 17.8: Removal of: “This means that they are not traceable to you. The researchers do not tell anyone that you participated in the study” 17.8: Addition of: “Vos données seront pseudonymisées. Cela signifie qu'elles seront cryptées (votre identité sera remplacée par un code d'identification dans l'étude, qui sera conservé séparément). » 17.8 Removal of : Autrement dit, celles-ci ne permettront pas de vous identifier. Les chercheurs ne dévoilent à personne que vous avez participé à l’étude. »
2.4 25-07-2023	5.3: Addition of “or eptifibatide IV (bolus of 180 microgram/kg followed by 2.0 microgram/kg/min)” 7.1: Addition of Aspiration catheter React by Medtronic. 8.1.3: Addition of “Subarachnoid hemorrhage within 90 days” 8.1.4: Study parameters: added such as but not limited to for all parameters and examples 8.3: Removal of “For all included patient, the stroke severity at baseline, at 24 hours and at day 5-7 (or at discharge) is evaluated with the NIHSS score.” 8.4: anonymised → anonymized 8.6: communicate to the patients or legal representatives who do not consent, that we will anonymously register at least SAE’s 9.2.2: is a congenital anomaly or birth defect (not applicable for CASES) 12.1: Removal of “digitally” 12.1: Addition of “Pseudonymized imaging data should be sent as DICOM files to the imaging core lab. 17: Questionnaires: changed French Euro-Qol 5D-5L from Paper Interviewer Administration to Paper Self-Complete version so that it matches English and Dutch versions 17: Questionnaires: IMTA-MCQ and IMTA-PCQadded version numbers and changed so that the English, Dutch and French versions so that they match.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

A1	A1 segment of the anterior cerebral artery
ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
ADL	Activities of Daily Living
AE	Adverse Event
AR	Adverse Reaction
ASPECTS	Alberta Stroke Program Early CT Score
BMT	Best Medical Treatment
CA	Competent Authority
CAS	Carotid Artery Stenting
CASES	Carotid Artery Stenting during Endovascular treatment for acute Stroke
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CEA	Carotid endarterectomy
CI	Confidence Interval
CONTRAST	COllaborations for New TReatments of Acute Stroke
CT	Computed Tomography
CTA	Computed Tomography Angiography
CV	Curriculum Vitae
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
EQ5D	Euro-QoL 5 dimensions
EU	European Union
EVT	Endovascular Thrombectomy
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator's Brochure
IC	Informed Consent
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Kg	Kilogram
M1	M1 segment of the middle cerebral artery
M2	M2 segment of the middle cerebral artery

METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
Mg	Milligram
mRS	Modified Rankin Scale
NASCET	American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institute of Health Stroke Scale
cOR	common odds ratio
PI	Principal Investigator
PROBE	Prospective, Randomized, Open, Blinded End-Point
PTA	Percutaneous transluminal angioplasty
RCT	Randomized Clinical Trial
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischemic Attack
TICI	Thrombolysis In Cerebral Infarction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Approximately 20% of the patients with acute ischemic stroke due to an intracranial large vessel occlusion (LVO) has a high-grade stenosis in the ipsilateral cervical carotid artery. It is uncertain whether immediate carotid artery stenting (CAS) of a cervical carotid artery stenosis during endovascular thrombectomy (EVT) is beneficial. Immediate CAS could improve cerebral perfusion and prevent recurrent ischemic stroke but could also increase the chance of intracranial hemorrhagic complications due to hyperperfusion syndrome or to the required antiplatelet treatment to prevent stent occlusion. Moreover, some patients end up with a severe disabling stroke after EVT. In these patients carotid revascularization by carotid endarterectomy (CEA) or CAS would usually not be performed but these patients would be treated by medical management only.
Objective: to assess the safety and efficacy of immediate cervical CAS during EVT in patients with acute ischemic stroke due to LVO with a high-grade stenosis >50% or occlusion of the ipsilateral cervical carotid artery.
Study design: prospective randomized open label controlled trial comparing immediate CAS during EVT versus EVT with deferred treatment of the cervical carotid artery lesion (deferred CAS/CEA or medical management alone). Outcome assessment will be blinded for treatment allocation.
Study population: patients with acute ischemic stroke with a CT-angiography proven intracranial LVO in the anterior circulation (ICA, A1, M1 or M2) as well as an ipsilateral cervical carotid artery tandem lesion of presumed atherosclerotic origin with a stenosis >50% or an ipsilateral acute proximal internal carotid artery occlusion who are treated with EVT according to the guidelines.
Intervention (if applicable): in the intervention group, the cervical carotid artery lesion will be treated with a stent during the EVT (just before or directly after intracranial thrombus removal), the control group will be treated according to the national guidelines with carotid endarterectomy of carotid artery stenting (for patients with non-disabling stroke) or medical management alone (for patients with severe disabling stroke).
Main study parameters/endpoints: the primary endpoint is the modified Rankin Scale (mRS) score at 3 months after stroke onset. Ordinal logistic regression analyses will be done with adjustment for prognostic variables: age, sex, baseline NIHSS, prestroke mRS score, collateral score on baseline CTA and onset to reperfusion time.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: All patients are being treated with EVT according to the local guidelines. The patients allocated to the intervention group will undergo CAS during EVT, which carries a risk of cerebral hyperperfusion syndrome and subsequent intracerebral hemorrhage. The potential benefits of immediate CAS during thrombectomy include: an improvement of cerebral blood flow during and after EVT. A second benefit is a lower risk of recurrent stroke in the first 14 days compared to the deferred treatment strategy. A third benefit of immediate CAS is that the patient does not need a second invasive treatment (carotid revascularization surgery (CEA or CAS) during the rehabilitation period which again carries some risk of complications. At last, the immediate CAS approach is likely to reduce health care costs.

1. INTRODUCTION AND RATIONALE

Acute ischemic stroke is an important cause of death and disability. After introduction of IV thrombolysis, the management of acute ischemic stroke treatment has been further improved by mechanical thrombectomy for proximal intracranial occlusions.[1]

Around 20% of the patients with proximal intracranial occlusion have a tandem lesion in the cervical ICA that may necessitate a different treatment approach during the EVT.[2,3] Huge variation in clinical practice exists with regards to the management of these tandem lesions. While some interventionalists advocate immediate stenting of the cervical carotid artery lesion (CAS), others argue that the treatment of the tandem lesion should be deferred after the very acute phase of ischemic stroke.[4]

The advantage of immediate CAS is improvement of cerebral blood flow, and prevention of early recurrent stroke or TIA. Some interventionalist do even feel that stenting is necessary to perform a successful intracranial thrombectomy.[4] Further, in immediate CAS, patients do not have to undergo a second invasive treatment (CEA or CAS) for secondary prevention. However, a direct stenting approach may also carry some disadvantages. To prevent in-stent thrombosis dual platelet therapy is often prescribed for patients who are electively treated with CAS. However in the acute phase during EVT, administration of dual antiplatelet therapy could increase the risk intracerebral hemorrhage (ICH).[5] Second, carotid revascularization could lead to a cerebral hyperperfusion syndrome especially in case of a chronic high grade proximal ICA stenosis. Cerebral hyperperfusion can lead to severe complications, such as ICH. In stent thrombosis may occur, especially in the hyperacute phase, if antiplatelet therapy is not administered and in stent thrombosis may lead to recurrent stroke.[6]
A post-hoc analysis of the MR CLEAN trial has shown that the clinical outcome in the group of patients with cervical carotid artery stenosis was worse compared to patients without tandem lesions.[2] In two large patient registries, it has been shown that among patients with tandem lesions treated with EVT, the immediate CAS group had better outcomes compared to the deferred treatment group.[7,8] Others have found that immediate CAS was associated with an increased risk of intracranial hemorrhage, probably due to aggressive double antiplatelet therapy.[5] Three systematic reviews and meta-analyses have been performed that included mostly retrospective and uncontrolled cohort studies.[9–11] Two of these reports did not reveal major differences between an immediate CAS and a deferred strategy, while one meta-analysis suggested that the patients with immediate CAS had a greater likelihood of favorable outcome compared to deferred treatment strategy. Firm conclusions could not be drawn because of the study design and the high likelihood for both selection and publication bias of the included studies.

In carotid revascularization secondary prevention trials, CEA has shown to be slightly superior to CAS regarding the composite endpoint of recurrent stroke, myocardial infarction and/or death.[12,13] Both CEA and CAS have been tested in patients with TIA or minor non-disabling stroke. It is uncertain which of the two strategies (acute stenting versus delayed CEA or CAS) is the most effective and safe approach during EVT in patients with acute stroke and a proximal ICA stenosis/occlusion.

This RCT will compare the efficacy and safety of two different strategies in patients undergoing EVT with an ipsilateral tandem lesion (proximal atherosclerotic ICA stenosis > 50% or occlusion and an ipsilateral proximal intracranial occlusion):

- immediate CAS during EVT (before or after the intracranial thrombectomy)
- EVT without immediate CAS during EVT (PTA of the proximal ICA stenosis/occlusion is allowed in order to perform the intracranial thrombectomy), but deferred treatment by carotid revascularization (CEA or CAS) according to the current guidelines (preferably within 2 weeks after stroke onset in patients who have recovered to a non-disabling stroke, or best medical management in case of a persistent disabling stroke.

2. OBJECTIVES

The primary objective of this trial is to assess the efficacy of immediate CAS among patients with acute ischemic stroke treated with EVT and a severe ipsilateral proximal carotid artery stenosis (>50%) or occlusion and compare this with the strategy of deferred treatment (including best medical treatment without CEA/CAS) of the proximal carotid artery stenosis according to the guidelines.

The secondary objective is to compare the safety of the two strategies (immediate CAS versus deferred treatment) regarding the incidence of symptomatic intracerebral hemorrhage, recurrent stroke and early proximal carotid artery re-occlusion.

The tertiary objective is to compare the quality of life and cost-effectiveness of both strategies.

3. STUDY DESIGN

This study is a phase 3 international multicenter randomized clinical trial with open label treatment and blinded outcome assessment (PROBE design). The study will be performed among thrombectomy capable stroke centers in the Netherlands and Belgium.

4. STUDY POPULATION

4.1 Population (base)

The study will be performed in patients with acute ischemic stroke due to proximal intracranial arterial occlusions and a severe ipsilateral proximal carotid artery stenosis (>50%) or occlusion, the so-called atherosclerotic tandem lesion. Approximately 2000 patients in the Netherlands and 1000 patients in Belgium are treated with EVT every year.[14] Around 80% (n=2400) of these EVTs are performed in the anterior circulation (supplied by the carotid artery) and 20% in the posterior circulation (supplied by the vertebrobasilar arteries). This means that yearly around 360-480 (15-20%[2,3,15] of 2400) patients with an ipsilateral cervical atherosclerotic carotid artery stenosis undergo EVT for acute ischemic stroke in the Netherlands and Belgium.

4.2 Participating centers

Each participating center should meet the following criteria in order to participate in the trial

- the center should be a stroke center with sufficient experience in EVT (>50 EVT's per year, >20 EVT's per interventionist per year)

- the center should have experience in conducting acute stroke trials

- the intervention team should have experience with CAS (at least 5 CAS procedures per interventionist performed)

- the EVT should be performed with devices approved by the steering committee

- the CAS should be performed with a CE marked stent approved to be used in the carotid artery and approved by the steering committee.

- all participating centers should offer deferred revascularization treatment (CEA of CAS) within 2 weeks after initial stroke onset.

4.3 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Acute ischemic stroke due to proximal intracranial occlusion in the anterior circulation (intracranial ICA, M1, proximal M2) on the CT angiography
- Stenosis >50% according to the NASCET criteria[16] or initial occlusion of the ipsilateral cervical carotid artery of presumed atherosclerotic origin on baseline CT angiography
- Eligible for EVT according to the guidelines: EVT within 6 hours of onset or EVT between 6-24 hours after onset based on perfusion CT imaging selection (conform current guidelines)
- Baseline National Institute of Health Stroke Scale (NIHSS) score ≥ 2
- Age >18 years
- Written informed consent (deferred consent)

4.4 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Any intracranial hemorrhage
- Cervical carotid artery stenosis or occlusion with other causes than presumed atherosclerosis (e.g. carotid artery dissection, floating thrombus, carotid web)
- Any exclusion criterion for EVT according to the guidelines
- Pre stroke disability (defined as a modified Rankin Scale score >2)
- Recent gastro-intestinal or urinary tract hemorrhage (<6 weeks)
- Recent severe head trauma (<6 weeks)
- Recent infarction on baseline brain CT in the same vascular territory (< 6 weeks)
- Known allergy to aspirin and/or clopidogrel
- Pregnancy

4.5 Sample size calculation

A non-inferiority design will be used. If immediate carotid artery stenting is not less effective compared to deferred treatment, immediate carotid artery stenting will be the new standard of care in this group of stroke patients. The justification for a non-inferiority design is as follows: when immediate CAS is not worse compared to the deferred treatment strategy, it will be implemented as standard practice because: 1) it will be highly cost-effective, as no second hospitalization is needed for a carotid revascularization procedure, and 2) the immediate CAS approach is a more patient friendly approach.

For the sample size calculation, we used data from the Dutch MR CLEAN registry, a nationwide cohort of EVT treated patients between 2014-2018.[17] Based on the mRS distributions in the immediate CAS group (mRS 0: 17.9%, mRS 1: 22.3%, mRS 2: 16.7%, mRS 3: 14.4%, mRS 4: 12.3%, mRS 5: 5.0%, mRS 6: 11.4%) and in the deferred treatment group (mRS 0: 6.9%, mRS 1: 20.2%, mRS 2: 17.9%, mRS 3: 16.4%, mRS 4: 17.2%, mRS 5: 8.0%, mRS 6: 13.4%), we calculated the assumed effect size to be a common odds ratio (cOR) of 1.15 for a shift in favorable direction on the full mRS. The non-inferiority margin was set to a cOR of 0.8, corresponding to an absolute difference of approximately 5% in favorable outcome (mRS 0-2). This is a generally accepted margin in the stroke research community and has been recently used in comparable EVT trials.[18,19] We used Monte Carlo simulations with 5000 runs to calculate the required sample size based on the assumptions above showing that a sample size of 610 patients, would provide 80% power (at a two-sided alpha level of 0.05) to determine that the lower bound of the cOR 95% confidence interval (CI) does not cross the non-inferiority margin of 0.8. Covariate adjustment for major prognostic variables that included age, pre-stroke mRS score, stroke severity, collateral score and time from symptom onset to randomization results in a reduction of at least 15% in the required sample size (n=520).[20,21] Assuming a crossover rate of 3% in each arm (6% for both groups), necessitates an increase in sample size by factor $1/(1- \%\ \text{crossover})^2 = 1/(1 - 0.06)^2 = 1.13$.[22] So taking crossovers into account, the sample size increases to 588 (520*1.13). Based on the experience of the MR CLEAN NO-IV trial and MR CLEAN-MED trial,[23,24] the number of patients lost to follow up is expected to be low

(0 in both recently completed trials). Assuming a combined percentage of 2% due to loss to follow up and to erroneous inclusions (for example inclusion of patients who appear to have carotid dissection or carotid pseudo-occlusion) the sample size will need to be increased to a total sample size of 600 patients (n= 300 per group).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

In patients allocated to the intervention group, the carotid artery stenosis will be stented during the EVT. The CAS may be done just before the intracranial thrombus removal or directly after (at the discretion of the interventionist). In case of unsuccessful intracranial reperfusion (TICI score < 2b), it is still recommended to perform CAS. In addition, if the first DSA run demonstrates intracranial recanalization but confirms a high-grade carotid artery stenosis, it is still recommended to perform CAS. Crossover to deferred treatment is strongly discouraged and will be considered a protocol violation unless a valid reason has been reported by the local PIs.

The patients allocated to the control group are being treated with EVT, without stenting of the carotid artery stenosis. Percutaneous transluminal angioplasty (PTA) of the carotid artery stenosis is allowed to gain access in order to remove the intracranial occlusion. Crossover to stenting during EVT is strongly discouraged. Crossovers without a valid reason according to the executive committee will be considered a protocol violation. If the patient recovers to a non-disabling stroke after EVT, CEA or CAS is offered according to the guidelines (usually CEA or CAS within 2 weeks after stroke onset). In case of a persistent disabling stroke, patients receive best medical treatment, without intervention of carotid artery stenosis.

5.2 Use of co-intervention (if applicable)

It is highly recommended to give patients allocated to the stenting group a loading dose of 500 mg intravenous aspirin (Aspegic®), just prior to or shortly after stenting (within 1 hour after groin closure), followed by an oral dose of 1x100 mg aspirin and 1x75 mg clopidogrel after 24 hours after the loading dose, and after ruling out intracranial hemorrhage on follow-up brain CT at 24 hours after EVT. Dual antiplatelet treatment is recommended for at least 3 months. If the patient is known to be a poor or intermediate CYP2C19 metabolizer, an oral dose of ticagrelor 2x 90 mg or prasugrel 1x10 mg is allowed. Patients using factor Xa inhibitors, thrombin inhibitors (direct oral anticoagulants (DOACs)) or vitamin K antagonists will not be treated with clopidogrel, but only in combination with aspirin, because the increased risk of hemorrhagic complication with “triple therapy”.[25] The use of periprocedural heparin is not recommended as the both intravenous aspirin and heparin increase the risk of intracranial hemorrhage.[24] Prior administration of intravenous thrombolysis should not be of influence for the prescribed antiplatelet regimen. The use of distal protection devices during CAS is discouraged, however, proximal flow arrest with balloon guiding catheter is allowed during CAS. In case of bradycardia that occurs during PTA and/or CAS, it is allowed to administer intravenous atropine. Blood pressure lowering therapy is advised when the systolic blood pressure is above 180 mm Hg, in order to prevent cerebral hyperperfusion. Patients allocated to the control group (no CAS during EVT) are being treated with antiplatelet or antithrombotic therapy according to national or European guidelines.

5.3 Escape medication (if applicable)

In case of periprocedural stent occlusion, the use of tirofiban IV (bolus of 25 microgram/kg followed by 0.15 microgram/kg/min) or eptifibatide IV (bolus of 180 microgram/kg followed by 2.0 microgram/kg/min) is allowed.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The invention in this trial is carotid artery stenting during EVT. The comparator is no stenting of carotid artery stenosis during EVT but a deferred treatment of the carotid artery stenose (BMT or CEA/CAS). The approved carotid artery stents are listed below:

Device name	Manufacturer	Description
Roadsaver	Terumo	Carotid artery stent
Casper	Microvention	Carotid artery stent
CGuard	Inspire MD	Carotid artery stent
Wallstent	Boston Scientific	Carotid artery stent
Xact	Abbott	Carotid artery stent
Acculink	Abbott	Carotid artery stent
NexStent	EndoTex	Carotid artery stent
Protégé RX	Medtronic	Carotid artery stent
Precise Pro Rx	Cordis	Carotid artery stent

6.2 Summary of findings from non-clinical studies

Not applicable: carotid artery stents are currently being used as a regular treatment of carotid artery stenosis.

6.3 Summary of findings from clinical studies

CAS has been shown effective to prevent recurrent ischemic stroke in patients with TIA or non-disabling stroke, although trials that compared CEA with CAS showed a slight superiority of CEA.[12,13] No randomized controlled trials on CAS have been performed in EVT treated patients. Several retrospective studies have assessed the safety and outcomes of carotid artery stenting during EVT.[3,5,7,8] A summary of these studies, revealed no increased risk of hemorrhagic complications and no worse outcome but even a tendency towards better functional outcome in patients who were stented during EVT. However, several of these studies were prone to selection and publication bias as the number and characteristics of patients having a tandem lesion, not treated with carotid stenting were usually not reported.[9–11]

6.4 Summary of known and potential risks and benefits

The potential risks of stenting the ICA during EVT is an increased risk of:

- Periprocedural emboli in new vascular territories
- Intracerebral hemorrhage due to administration of antiplatelet therapy during EVT necessary to prevent stent thrombosis
- Cerebral hyperperfusion syndrome
- Temporary bradycardia and/or hypotension (due to activation of the carotid baroreceptors)

The potential benefits of stenting the ICA during EVT are:

- Immediate risk reduction of recurrent ischemic stroke
- Improvement of cerebral perfusion
- Avoidance of a second surgical treatment (usually CEA) when the patient recovers after stroke (reduction of health care costs, higher patient satisfaction)

6.5 Description and justification of route of administration and dosage

In the immediate CAS group, 500 mg of aspirin (Aspegic ®) will be given intravenously because this will ensure an immediate effect on platelet aggregation (much faster than oral administration). 500 mg is commonly used dose for carotid artery stenting.[26] Clopidogrel will be administered orally in a dose of 75 mg and not with a loading dose, because a loading dose for aspirin was already administered. If the patient is known to be a poor or intermediate CYP2C19 metabolizer, an oral dose of ticagrelor 2x 90 mg or prasugrel 1x10 mg are allowed to be used. Routine platelet function testing during EVT is not recommended.

When there is a strong indication for anti-thrombotic treatment, for instance in case of concomitant atrial fibrillation, it will be advised to start with a direct oral anticoagulant drug (DOAC) or vitamin K antagonist in combination with aspirin (and instead of clopidogrel). The combination of aspirin, clopidogrel and DOACs/vitamin K antagonists, is strongly discouraged, due to the increased hemorrhage risks.[25]

6.6 Dosages, dosage modifications and method of administration

In the intervention group, the following medication protocol is recommended:

- Aspirin dose: Aspegic ® 500 mg intravenously during or shortly after carotid artery stenting (within 1 hour after groin closure), followed the next day by oral dose of 100 mg daily
- Clopidogrel dose 24 hours after EVT, after ruling out intracranial hemorrhage on follow-up brain CT at 24 hours after EVT: oral dose of 75 mg daily

Dual antiplatelet therapy is recommended for a period of 3 months (standard of care after CAS), thereafter the treatment will be as recommended by the guidelines (usually monotherapy clopidogrel 75 mg daily, alternative aspirin 100 mg daily in combination with dipyridamole 2 time 200 mg.

6.7 Preparation and labelling of Investigational Medicinal Product

N/A

6.8 Drug accountability

The used mediation is a standard treatment for this specific population. Additional drug accountability is not necessary

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

EVT will be performed with either stent retriever or thrombus aspiration catheters at the discretion of the interventionist. Devices approved for this study are listed in the table below. If necessary the use PTA of the carotid artery stenosis is allowed in the control group.

Device name	Manufacturer	Description
Embotrap	Cerenovus	Stent retriever
Eric	Microvention	Stent retriever
Solitaire	Medtronic	Stent retriever
Catch	Balt	Stent retriever
Preset	Phenox	Stent retriever
Trevo	Stryker	Stent retriever
Tigertriever	RapidMedical	Stent retriever
Nimbus	Cerenovus	Stent retriever
NeVa	Vesalio	Stent retriever
ACE64/68/Red	Penumbra	Aspiration catheter
4Max	Penumbra	Aspiration catheter
3Max	Penumbra	Aspiration catheter
Sofia 5F or Sofia Plus	Microvention	Aspiration catheter
Embovac	Cerenovus	Aspiration catheter
Catalyst	Stryker	Aspiration catheter
AXS Vecta	Stryker	Aspiration catheter
React	Medtronic	Aspiration catheter
Merci	Stryker	Balloon guiding catheter
Flowgate2	Stryker	Balloon guiding catheter
Cello	Medtronic	Balloon guiding catheter

7.2 Summary of findings from non-clinical studies

Not relevant, as all devices are CE marked and approved for clinical use as intended.

7.3 Summary of findings from clinical studies

Several randomized controlled trials have demonstrated the efficacy of EVT by the use of stent retrievers, aspiration catheters or a combination of both. The number needed to treat to prevent one patient from becoming disabled varies between 3-7.[27] EVT is currently standard of care for stroke patients with large vessel occlusion. The treatment of carotid

artery tandem lesions during EVT is a matter of debate and there is a lot of practice variation among interventionist. In retrospective cohort studies, there were no major differences observed in clinical outcome or the safety endpoints between the immediate CAS group and deferred treatment group.[7,9–11]

7.4 Summary of known and potential risks and benefits

The risks and benefits of immediate stenting the carotid artery have been described in 6.4. Without immediate stenting there is an increased risk of recurrent ischemic stroke or early carotid artery (re-)occlusion. The other major disadvantage is that in case of recovery to a non-disabling stroke, the patient will have to undergo surgery later, extending hospital stay and exposing the patient to a second procedure with associated risks.

7.5 Description and justification of route of administration and dosage

See also 6.5

7.6 Dosages, dosage modifications and method of administration

See also 6.6

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable, see 6.7

7.8 Drug accountability

Not applicable, see 6.8

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome is the modified Rankin Scale Score at 90 days after stroke onset. The mRS is a disability scale ranging from 0 (no symptoms at all) to 6 (death).[28] The mRS score will be assessed by a stroke research personnel by telephone interview, blinded for the treatment allocation.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary endpoints are:

- mRS score of 0-1 at 90 days
- mRS score of 0-2 at 90 days
- mRS score of 0-3 at 90 days
- NIHSS score at 24 hours and day 5-7, or at discharge
- adequate recanalization after EVT (TICI 2b or higher)
- final infarct volume on brain CT at 24 hours
- arterial occlusive lesion (AOL) score on CTA at 24 hours
- any stroke within 90 days
- recurrent ipsilateral TIA/ischemic stroke within 90 days
- Carotid artery re-occlusion at 24 hours and 90 days.
- Mortality at 90 days
- Quality of life (EQ5D-5L) questionnaire at 90 days

For the purpose of health economic evaluation, additional questionnaires will be sent to the study participants at 90 days for measuring loss of productivity (IMTA productivity cost questionnaire (iPCQ)) and medical consumption (IMTA medical consumption questionnaire (iMCQ)).

8.1.3 Safety outcomes

- Incidence of symptomatic intracerebral hemorrhage (Heidelberg criteria)
- Asymptomatic intracerebral hemorrhage on brain CT at day 1
- Subarachnoid hemorrhage on brain CT at day 1
- Any extracranial hemorrhage within 90 days
- Embolization in new vascular territories during EVT
- Incidence of complications at the vascular access site (aneurysm, bleeding, vascular occlusion) within 72 hours after the intervention
- Incidence of bradycardia and/or hypotension during CAS
- Serious adverse events (renal function disorder, myocardial infarction, gastro-intestinal bleeding)

8.1.4 Other study parameters

Event characteristics such as prehospital and intra-hospital time intervals will be documented (such as but not limited to: stroke onset, arrival time primary and comprehensive stroke centers, prior IVT, arrival time angiosuite, time of groin puncture, time of recanalization, time of stent placement and end of procedure,). Baseline demographics, medical history, comorbidities and vascular risk factors will be recorded (such as but not limited to: age, sex, prestroke mRS, previous stroke, previous myocardial infarction, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, peripheral vascular disease, smoking status).Medication at baseline and during follow-up will be assessed (such as but not limited to: antiplatelet therapy, anticoagulant therapy, antihypertensive treatment, lipid lowering drugs). Other variables that will be recorded are: NIHSS score, GCS score, vital parameters, laboratory results (such as but not limited to: renal and liver function, glucose, thrombocytes, CRP), and multiple imaging characteristics (such as but not limited to ASPECTS score on non-contrast CT, infarct core volume, penumbra volume, location of intracranial occlusion on CTA and DSA). Various details regarding the endovascular treatment, study treatment and deferred treatment will be recorded (such as but not limited to: periprocedural general/local anesthesia or conscious sedation, stent type, administration of medication during and after EVT).

8.2 Randomization, blinding and treatment allocation

The randomization will be performed aby a computer and web-based procedure, using permuted blocks. Back-up by telephone will be provided. Randomization is allowed when the CTA at baseline demonstrates an ipsilateral high-grade stenosis (>50%) or occlusion of the proximal ICA of presumed atherosclerotic origin. Although DSA is more reliable to distinguish carotid pseudo-occlusions from cervical atherosclerotic lesions in the ICA, randomization during the EVT can be very challenging and might lead to lower inclusion rates. And CTA has been shown to have acceptable diagnostic accuracy for true cervical ICA lesions.[29] Only in case of significant doubt by the interventionist if there is a true cervical atherosclerotic lesion in the carotid artery, randomization is also allowed after the first angiographic run of the carotid artery that confirms the cervical atherosclerotic lesion. Randomization will be stratified for center. Both the patient and treating physicians are aware of the treatment assignment. The 90 days follow up will be performed by certified research personnel blinded for the treatment allocation. The assessment of secondary endpoints will not be blinded as for several secondary endpoints it will be obvious whether the patient was treated with CAS or not. Information on treatment allocation will be kept separate from the main study database. An independent trial statistician will combine the data on treatment allocation with the clinical data in order to report to the data safety monitoring board (DSMB). The trial steering committee will be kept unaware of the exact results of the interim analyses on efficacy and safety. Only the recommendation to continue, modify or stop the trial will be communicated.

8.3 Study procedures

All patients receive a non-contrast brain CT, perfusion CT and CT-angiography at baseline (as part of usual patient care) and at 24 hours a non-contrast brain CT and CT-angiography (for research purpose).. At 90 days a duplex ultrasound of the ICA is performed.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Data from patients who waive consent will not be used for the primary endpoint of the study, but their data will be used in a strictly anonymized form to obtain data for the purpose of safety analysis to accurately describe the group without consent.

8.4.1 Specific criteria for withdrawal (if applicable)

n/a

8.5 Replacement of individual subjects after withdrawal

For every patient without consent, an additional patient will be included.

8.6 Follow-up of subjects withdrawn from treatment

Due to the deferred consent procedure, the patients are already allocated to the intervention or control group, before informed consent from the patient or their legal representative has been obtained. In order to monitor the safety of the intervention and control group, we will explicitly communicate to the patients or legal representatives who do not consent, that we will anonymously register at least SAE’s, (symptomatic) intracerebral hemorrhage and mortality.

8.7 Premature termination of the study

The study will be terminated prematurely in case the DSMB advises to stop patient recruitment. The database will be closed after 90 days assessment and the trial results will be reported.

9 SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, and applicable local regulations of the participating countries, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; (not relevant for CASES) or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.
The investigator will report all SAEs to the sponsor without undue delay (< 24 hours) after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

N/A

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

The trial will be monitored by a DSMB, that will include a vascular neurologist, neuro-interventionist and an independent methodologist/statistician. The role of the DSMB is to monitor the safety of the trial and to provide the steering committee with recommendations on the continuation or termination of the trial.
The objectives of the DSMB are:

- To monitor the safety data of the included patients
- To analyze efficacy data in both arms of the trial
- To evaluate the overall conduct of the trial, protocol violations, compliance to previous DSMB recommendations, recruitment rates, losses to follow up, and trial monitoring

The DSMB will meet once before the first inclusion and thereafter twice a year during the patient recruitment phase. An efficacy interim analysis will be performed after 300 included patients have reached their 90 day follow-up. For the efficacy interim analysis, the DSMB will analyze the distribution of mRS scores at 90 days in both arms. The Haybittle-Peto boundary rule for premature termination of the trial will be applied.[30]

For the safety interim analyses, the DSMB will evaluate the mortality, the incidence of symptomatic intracranial hemorrhage and other endpoints concerning SAE’s. Safety assessments are required after every 5 symptomatic intracranial hemorrhages and after every 10 deaths. In the light of these analyses, the DSMB will advise the chairman of the Steering committee if, in their view, the randomized comparisons in the trial have provided both (i) "proof beyond reasonable doubt" that for all, or for some specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net

difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a safety endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

The advice(s) of the DSMB will only be sent to the sponsor of the study by the chair of the trial steering committee. Should the steering committee decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

The statistical analysis and reporting of the trial will be in accordance with the CONSORT guidelines. Baseline data will be reported by treatment allocation as categorical or continuous variables, where appropriate. Missing baseline data will be imputed using regression imputation. For the primary endpoint, statistical analyses will be performed according to the per-protocol (PP) principle as well as the intention to treat (ITT) principle. Both PP and ITT analyses must demonstrate non-inferiority in order to conclude that immediate CAS during EVT is non-inferior to a deferred treatment strategy.

10.1 Analysis populations

Three analysis sets will be defined:
1) A Full Analysis Set (FAS) which will include all randomized patients who provided informed consent or died during the index procedure. Patients will be analyzed according to the intention-to-treat (ITT) principle, that is, in the group to which they were randomized.
2) A Per Protocol set (PPS) which will all patients who were randomized, provided informed consent or died during the index procedure and had no major protocol violations. Patients will be analyzed according to the intention-to-treat (ITT) principle, that is, in the group to which they were randomized.
In a blinded to outcome review meeting just before the interim analysis for efficacy and the final data base lock, it will be determined which patients will be excluded from the PP set. All major protocol deviations that lead to exclusion from the PP set will be fully documented in the Analysis Sets Specification Document that will be dated and signed prior to database lock.
3) A safety set (SS) which will include all randomized patients. Patients will be analyzed in the group based on which treatment they actually received. In case a patient did not receive a stent, the patient will be analyzed in the group to which the patient was randomized.

The primary and secondary endpoints will be analysed for the FAS and PPS. Safety endpoints will be analysed for the 3 populations.

10.2 Primary study parameter(s)

The primary effect parameter will be expressed by a common odds ratio, estimated with ordinal logistic regression, evaluating a shift on the mRS score at 90 days after randomization. The common odds ratio will be estimated with proportional odds regression adjusted for age, baseline NIHSS score, pre-stroke mRS score, collateral score on baseline CTA and onset to reperfusion time. Both unadjusted and adjusted estimates will be reported with 95% confidence intervals.

10.3 Secondary study parameter(s)

Secondary effect parameters will be assessed with linear, logistic or ordinal regression, where appropriate, with the same adjustments as reported in 10.1.

10.4 Subgroup analyses

Predefined subgroup analyses will be performed to test for interaction between a specific variable and the treatment.

The following subgroups will be investigated:

- Intermediate grade stenosis (50-70%), high grade stenosis (>70%) versus occlusion of the ICA
- Occlusion location (ICA, M1, M2)
- Collateral score on baseline CTA (0,1,2 and 3)
- Performance of PTA during EVT(yes or no)
- NIHSS stroke scale severity (NIHSS >15 points versus NIHSS ≤15 points)
- Age (>80 years versus ≤ 80 years)
- Onset to groin puncture time (tertiles)
- ASPECT score (>6 versus ≤ 6)
- prior IVT (yes/no)

10.5 Other study parameters

The cost-effectiveness will be calculated by comparing the costs for patients with good functional outcome, costs per QALY and costs for the intervention and hospital admissions. Quality of life will be assessed with the EuroQol-5D-5L.[31] Costs for potential productivity loss will be assessed with a set of questions from the iMTA Productivity Cost Care (iPCQ) and costs for any other relevant healthcare resource use will be measured by a set of questions from the iMTA Medical Consumption Questionnaire (iMCQ).[32,33]

10.6 Interim analysis (if applicable)

See 9.5

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013)(33) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

This trial will include patients using a deferred written informed consent procedure.[34] This means that, after the treatment, written informed consent is obtained by asking the patient, or a legal representative of the patient. The justification for the deferred consent is as follows. Firstly, during acute ischemic stroke, the adagium “time is brain” holds. Reperfusion therapy should be initiated as soon as possible. For every hour delay, the chance of recovery to activities of daily living (ADL) independency decreases with 6%.[35] It has been observed in previous acute stroke trials, that obtaining informed consent before start of the treatment, led to an (unacceptable) delay in treatment onset.[1] Secondly, during the acute phase of acute ischemic stroke a patient is often unable to make a well thought out decision on whether to participate in a study, due to neurological deficits like language disturbances, unable to communicate or anosognosia (unaware of his or her medical condition). Obtaining consent from the patient’s proxy will also unacceptably delay the EVT itself. In summary due to the emergency situation as well as the lack of decision-making capacity, the trial cannot be performed without a deferred consent approach. This approach has been successfully used in recent acute stroke trials in the Netherlands.[34]

After treatment, informed consent will be obtained by asking the patient or a legal representative of the patient, preferably within 24 hours after EVT. The patient and/or representative will be provided with a verbal and written explanation of the study by the local investigator. They will be asked for consent to use their data, biomaterials for the purpose of the study and to perform follow up investigations. Participation in the study is voluntary and at any given time, informed consent can be withdrawn. If the patient has died before informed consent has been obtained, the patient’s proxy’s will be informed about the study, the treatment the patient has received and the use of the data that has been collected. Because mortality is an important safety endpoint, data of these patients will be (anonymously) stored, in order to provide these data to the DSMB.

11.3 Objection by minors or incapacitated subjects (if applicable)

Minors (patients of 18 years old and less) will not be included in the trial. About 99% of the patients eligible for the trial have acquired neurological deficits due to the stroke interfering with their decision-making capacity. We will follow the procedure as described in 11.2. In the situation that a legally incompetent patient shows behavior suggesting objection to participate in the trial, the patient will not be included in the study. The investigators will adhere to the following code of conduct: ‘Verzet bij wilsonbekwame (psycho) geriatrische patiënten in het kader van de Wet Medisch-Wetenschappelijk Onderzoek met Mensen’ (http://wetten.overheid.nl/BWBR0009408/2017-03-01

11.4 Benefits and risks assessment, group relatedness

Immediate stenting may be of benefit to the patient, because no second invasive treatment is needed anymore. Moreover, when the carotid artery stenosis has been treated during EVT, the risk of recurrent ischemic stroke is also reduced. Moreover, cohort studies and a systematic review have suggested a better clinical outcome after immediate stenting.[11]
Potential risks of immediate stenting, are the risks of ICH and cerebral hyperperfusion syndrome,[5,36] although this latter has not been reported in retrospective cohort studies. There is also the need for a longer period of dual antiplatelet therapy (3 months, instead of 3 weeks) in case of immediate stenting, that may increase the risk of hemorrhagic complications.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

For Belgian participating sites, Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies.
Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law, or delegate this responsibility to the national coordinator.

11.6 Incentives (if applicable)

The patients will not receive any incentives.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Study data will be entered into a web-based database by the local site investigators. The local investigators will keep a list of research numbers, codes and names. Documents with identifying data will be stored separately from the study and is only accessible to the study coordinator. Pseudonymized imaging data should be sent as DICOM files to the imaging core lab or to the sponsor.

12.2 Monitoring and Quality Assurance

Monitoring schedules will be planned as proposed in the NFU position paper “Kwaliteitsborging mensgebonden onderzoek 2.0. This study will be classified as a moderate risk study, as the risk of SAE’s, like symptomatic intracranial hemorrhage rate, was in previous cohort studies, similar between the immediate CAS and deferred treatment group, and the risk was around 5-10%. The frequency of monitoring will be twice a year in each participating center, performed by an independent study monitor. For the participating centers in Belgium, University Hospital Leuven will arrange the study monitoring (including the French speaking centers), in the Netherlands, the Erasmus MC will arrange the monitoring. The first 3 included patients in each center will be verified for the in- and exclusion criteria as well as informed consent and source data verification of the following variables: age, sex, time of onset, time of groin puncture, NIHSS at baseline, performance of baseline, follow up imaging, SAE’s, study log and documentation. Thereafter source data verification will be performed for 25% of the included patients for the same variables.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The study database will be closed within one month after the last patient's last visit. A manuscript will be submitted to a major clinical journal within 6 months from closure of the database. The manuscript will be shared with the financial sponsor(s) one month prior to submission, but the financial sponsor(s) will have no influence on its contents.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action
In the intervention group, the carotid artery stenosis is stented during the EVT. The carotid artery stent is placed deployed in the atherosclerotic lesion in the carotid artery by catheterization through the groin. Once the atherosclerotic lesion is being trapped between the stent and the vessel wall, the risk of thrombo-embolism from this lesion is immediately reduced. In the control group, the atherosclerotic lesion in the cervical carotid artery is not stented during EVT, but treated by carotid endarterectomy, CAS of medical management alone, according to the guidelines and dependent on the clinical condition of the patient. In the deferred treatment group, there remains a risk of recurrent stroke until the deferred treatment has been performed, usually within 1-2 weeks after stroke. CAS is a proven and effective technique to reduce the risk of recurrent ischemic stroke in patients with minor stroke or TIA. These RCT's compared CAS with CEA, performed within 1-3 weeks after stroke/TIA. No trials have been performed, assessing the efficacy of CAS in the hyperacute phase during EVT. Observational cohort studies have shown that CAS during EVT is feasible, but results regarding functional outcome and safety endpoints were heterogenous. Most previous studies revealed a better functional outcome in the immediate CAS group at 90 days and no increased risk of intracranial hemorrhage, while some did found a slight increased risk of hemorrhagic complications, associated with the use of dual antiplatelet therapy.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
see a

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
no

d. Selectivity of the mechanism to target tissue in animals and/or human beings
n/a

e. Analysis of potential effect
n/a

f. Pharmacokinetic considerations
we refer to chapter 5.2

g. Study population
we refer to chapter 4

h. Interaction with other products
n/a

i. Predictability of effect
see e.

j. Can effects be managed?
n/a

13.2 Synthesis

Based on previous observational studies, the risks of this RCT are acceptable. We expect a comparable to slightly higher risk of intracranial hemorrhage in the immediate CAS group, but an increased chance of favorable outcome in the immediate CAS group. If the effect of immediate CAS is not worse than the deferred treatment strategy, it will be of great benefit to the patients, by avoiding a second surgical treatment and it will also reduce health care costs. The burden of the study is low.

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15. TABLES

15.1 Modified Rankin Scale (mRS)

Modified Rankin Scale	
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	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

15.2 National Institute of Health Stroke Scale (NIHSS)

1a—Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b—Level of consciousness questions: What is your age? What is the month?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither questions correctly
1c—Level of consciousness commands: Open and close your eyes Grip and release your hand	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2—Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3—Visual	0 = No visual lost 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4—Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5—Motor arm Left arm Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
6—Motor leg Left leg Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7—Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8—Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe-to-total sensory loss
9—Best language	0 = No aphasia; normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute; global aphasia
10—Dysarthria	0 = Normal 1 = Mild-to-moderate dysarthria 2 = Severe dysarthria
11—Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Score = 0–42	

15.3 Extended thrombolysis in cerebral infarction (e-TICI) score

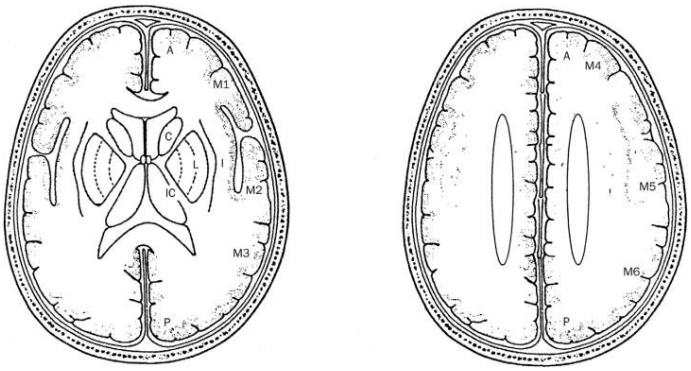
Score	Extended Thrombolysis in Cerebral Infarction Scale
0	No reperfusion or anterograde flow beyond site of occlusion
1	Penetration but no perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry of clearance from the bed is slower or incomplete when compared to non-involved territories
2a	Some perfusion with distal branches filling of < 50% of territory visualized
2b	Substantial perfusion with distal branches filling of ≥ 50% of territory visualized
2c	Near complete perfusion except for slow flow in a few distal cortical vessels, or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

15.4 Collateral score baseline CT angiography

Category	Score	Description
None	0	Absent collaterals
Poor	1	Collaterals filling ≤50% of the occluded territory
Intermediate	2	Collaterals filing >50%, but <100% of the occluded territory
Good	3	Collaterals filling 100% of the occluded territory

15.5 ASPECT score

Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point systematic quantitative topographic CT scan scoring system, to assess early ischemic changes on pretreatment NCCT in patients with acute ischemic stroke in the territory of the middle cerebral artery.[37] Segmental assessment of the MCA vascular territory is made, and for every defined region of ischemic change, such as focal swelling or parenchymal hypoattenuation, one point is subtracted from the initial score of 10. A score of 10 indicates a normal scan and a score of 0 diffuse ischemia throughout the territory of the MCA.



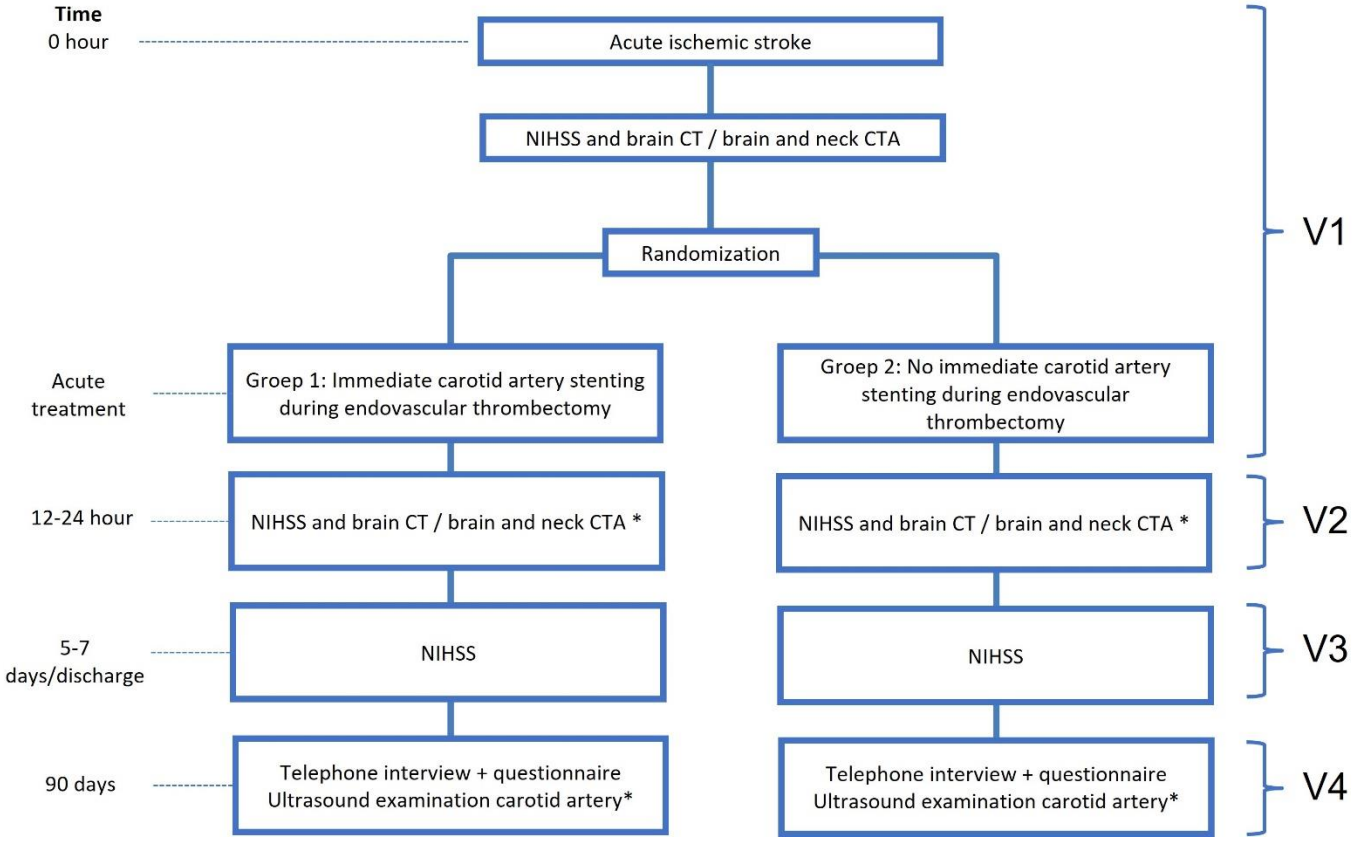
15.6 Arterial occlusive lesion (AoL) Score

Score	Description
0	No recanalization of the primary occlusive lesion
1	Incomplete or partial recanalization of the primary occlusive lesion with no distal flow
2	Incomplete or partial recanalization of the primary occlusive lesion with any distal flow
3	No recanalization of the primary occlusive lesion

16. FIGURES

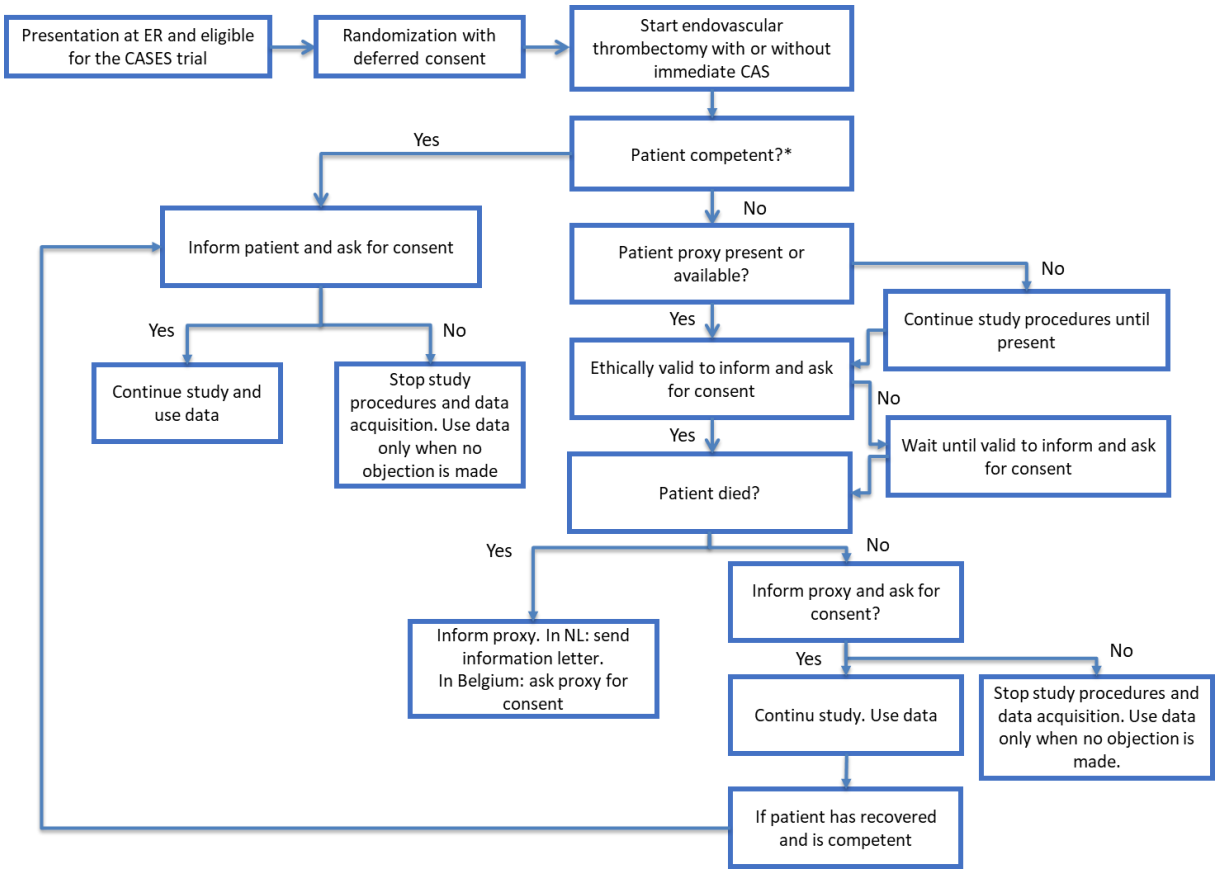
16.1 Figure 1: CASES trial logo

16.2 Figure 2: Patient flow in the trial



* not part of standard care

16.3 Figure 3: Flowchart of deferred consent procedure for the CASES trial



Based on the flowchart proxy-deferred consent in emergency critical care research.[34,38]

17. QUESTIONNAIRES

17.1 EuroQoL 5D-5L Dutch (versie 1.1, Paper Self-Complete)

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ☐
Ik heb een beetje problemen met lopen ☐
Ik heb matige problemen met lopen ☐
Ik heb ernstige problemen met lopen ☐
Ik ben niet in staat om te lopen ☐

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ☐
Ik heb een beetje problemen met mijzelf wassen of aankleden ☐
Ik heb matige problemen met mijzelf wassen of aankleden ☐
Ik heb ernstige problemen met mijzelf wassen of aankleden ☐
Ik ben niet in staat mijzelf te wassen of aan te kleden ☐

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ☐
Ik heb een beetje problemen met mijn dagelijkse activiteiten ☐
Ik heb matige problemen met mijn dagelijkse activiteiten ☐
Ik heb ernstige problemen met mijn dagelijkse activiteiten ☐
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ☐

PIJN / ONGEMAK

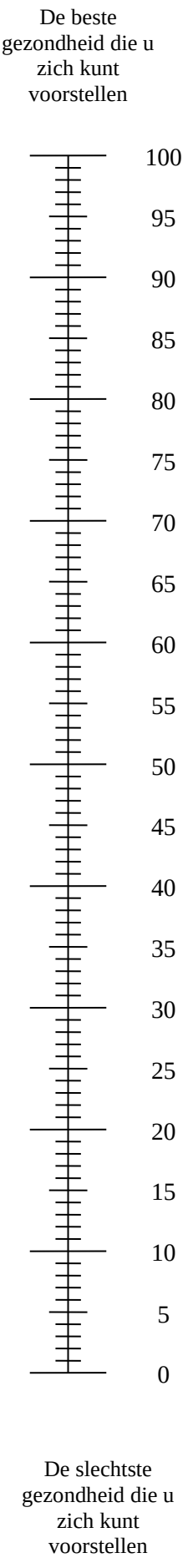
Ik heb geen pijn of ongemak ☐
Ik heb een beetje pijn of ongemak ☐
Ik heb matige pijn of ongemak ☐
Ik heb ernstige pijn of ongemak ☐
Ik heb extreme pijn of ongemak ☐

ANGST / SOMBERHEID

Ik ben niet angstig of somber ☐
Ik ben een beetje angstig of somber ☐
Ik ben matig angstig of somber ☐
Ik ben erg angstig of somber ☐
Ik ben extreem angstig of somber ☐

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de <u>beste</u> gezondheid die u zich kunt voorstellen.
  0 staat voor de <u>slechtste</u> gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐



17.2 EuroQoL 5D-5L English (version 1.2, Paper Self-Complete)

Under each heading, please tick the ONE box that best describes your health TODAY.

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

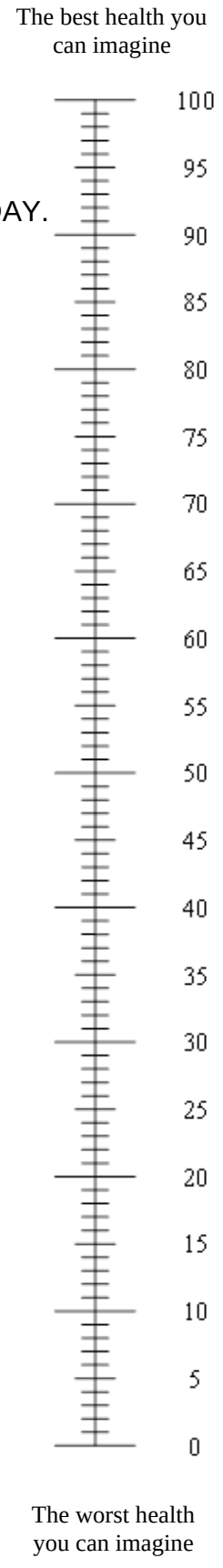
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



17.3 EuroQoL 5D-5L: French (Version 1.1, Paper Self-Complete)

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

Mobilité

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes légers pour me déplacer à pied ❑
J'ai des problèmes modérés pour me déplacer à pied ❑
J'ai des problèmes sévères pour me déplacer à pied ❑
Je suis incapable de me déplacer à pied ❑

Autonomie de la personne

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

Activités courantes *(EXEMPLES: TRAVAIL, ÉTUDES, TRAVAUX MÉNAGERS, ACTIVITÉS FAMILIALES OU LOISIRS)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes légers pour accomplir mes activités courantes ❑
J'ai des problèmes modérés pour accomplir mes activités courantes ❑
J'ai des problèmes sévères pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

Douleurs / gêne

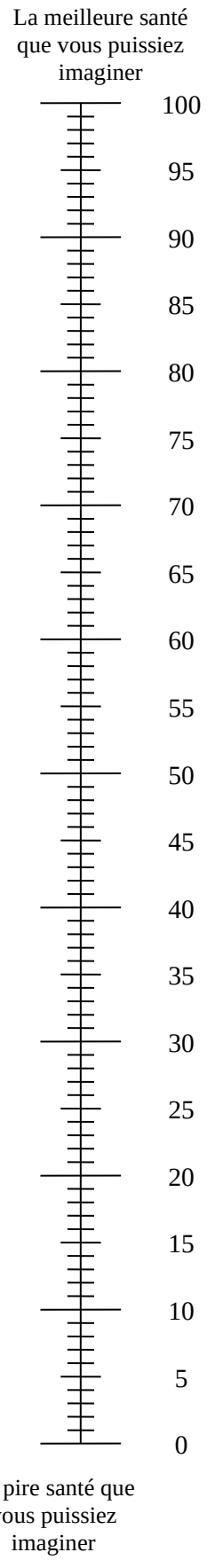
Je n'ai ni douleur ni gêne ❑
J'ai des douleurs ou une gêne légère(s) ❑
J'ai des douleurs ou une gêne modérée(s) ❑
J'ai des douleurs ou une gêne sévère(s) ❑
J'ai des douleurs ou une gêne extrême(s) ❑

Anxiété / Dépression

Je ne suis ni anxieux(se), ni déprimé(e) ❑
Je suis légèrement anxieux(se) ou déprimé(e) ❑
Je suis modérément anxieux(se) ou déprimé(e) ❑
Je suis sévèrement anxieux(se) ou déprimé(e) ❑
Je suis extrêmement anxieux(se) ou déprimé(e) ❑

- Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.
- Cette échelle est numérotée de 0 à 100.
- 100 correspond à la meilleure santé que vous puissiez imaginer. 0 correspond à la pire santé que vous puissiez imaginer.
- Veuillez faire une croix (X) sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.
- Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

VOTRE SANTÉ AUJOURD'HUI = ☐



17.4 Institute for Medical Technology Assessment Productivity Costs Questionnaire (iMTA PCQ) - Dutch (Version 2.0, 14/07/2023)

Vragenlijst over uw gezondheid en werk

Onderzoekers noemen deze vragenlijst de iMTA PCQ. (iPCQ)

Toelichting

Lees dit alstublieft eerst!

Kunt u de lijst niet zelf invullen?
Als u de lijst niet zelf kunt invullen, kan iemand u misschien helpen. Bijvoorbeeld een familielid.
Waar gaat de vragenlijst over?
De vragenlijst gaat over uw gezondheid en werk in de afgelopen 4 weken.
Hoe lang duurt het om de lijst in te vullen?
Het duurt ongeveer 10 minuten om de lijst in te vullen.
Hoe moet u de lijst invullen?

- Begin bij de eerste vraag en volg de nummering.
- Bij sommige vragen kunt u tekst of een getal invullen, bij andere vragen kunt u een hokje/optie aanklikken/aankruisen
- U kunt geen foute antwoorden geven.

Wat gebeurt er met uw antwoorden?
Uw antwoorden worden gebruikt voor onderzoek. Alleen de onderzoekers zien uw antwoorden. Dus niemand anders.
De onderzoekers schrijven uw naam nergens op. En zij vertellen aan niemand dat u aan het onderzoek heeft meegewerkt.

Fijn dat u de lijst voor ons wilt invullen!

Vraag 1. Wat doet u in het dagelijks leven? Kruis aan wat u de meeste tijd doet.

☐ Ik zit op school, ik studeer
☐ Ik werk in loondienst
☐ Ik ben zelfstandig ondernemer
☐ Ik ben huisvrouw, huisman
☐ Ik ben werkloos
☐ Ik ben arbeidsongeschikt, voor … %
☐ Ik ben met pensioen of prepensioen
☐ Ik doe iets anders, namelijk ……..

Vraag 2. Hebt u betaald werk?

☐ Nee
☐ Ja

De volgende vragen gaan over uw baan. Dus over werk waarvoor u betaald wordt. Hebt u geen betaalde baan? Ga dan verder met vraag 12. *Lees eerst de toelichting boven vraag 12.*

Vraag 3. Wat is uw beroep?

……

Vraag 4. Hoeveel uur per week werkt u? Tel alleen de uren waarvoor u betaald wordt.

…… uren

Vraag 5. Op hoeveel dagen in de week werkt u?

Op…… dagen

Vraag 6. Bent u in de afgelopen 4 weken afwezig geweest van uw werk omdat u ziek was?

☐ Nee
☐ Ja, ik ben ….. dagen afwezig geweest

(*Tel alleen de <u>werkdagen</u> in de afgelopen 4 weken)*

Heeft u “Ja” geantwoord? Beantwoord dan vraag 7.
Ga anders verder met vraag 9.

Vraag 7. Was u langer dan de gehele periode van 4 weken afwezig van uw werk doordat u ziek was? Het gaat om een aaneengesloten periode van werkverzuim.

☐ Nee
☐ Ja

Heeft u “Ja” geantwoord? Beantwoord dan vraag 8.
Ga anders verder met vraag 9.

Vraag 8. Wanneer heeft u zich ziek gemeld?

Dag/maand/jaar: …./…./…….

Ga verder met vraag 12. *Lees eerst de toelichting boven vraag 12*.

Vraag 9. Waren er in de afgelopen 4 weken dagen waarop u wel gewerkt heeft, maar tijdens uw werk last had van lichamelijke of psychische problemen?

☐ Nee
☐ Ja

Heeft u “Ja” geantwoord? Beantwoord dan vraag 10 en 11.
Ga anders verder met vraag 12. *Lees eerst de toelichting boven vraag 12.*

Vraag 10. Op hoeveel werkdagen had u tijdens uw werk last van uw lichamelijke of psychische problemen? Tel alleen de werkdagen in de afgelopen 4 weken.

…… werkdagen

Vraag 11. Op de dagen dat u last had, kon u misschien niet zoveel werk doen als normaal. Hoeveel werk kon u op deze dagen gemiddeld doen? Kijk naar de cijfers hieronder. Een 10 betekent dat u op deze dagen net zoveel kon doen als normaal. Een 0 betekent dat u op deze dagen niets kon doen. Zet een cirkel om het goede cijfer.

Ik kon op deze dagen niets doen					Ik kon onge-veer de helft doen				Ik kon net zoveel doen als normaal	
0	1	2	3	4	5	6	7	8	9	10

Toelichting bij vraag 12

Ook bij onbetaald werk, kunt u last hebben van uw lichamelijke of psychische problemen. Soms kunt u daardoor minder doen. U kunt bijvoorbeeld niet goed voor de kinderen zorgen of vrijwilligerswerk doen. Of geen boodschappen doen of in de tuin werken. Daarover gaan de volgende vragen.

Vraag 12. Waren er dagen waarop u minder onbetaald werk kon doen door uw lichamelijke of psychische problemen? Het gaat om dagen in de afgelopen 4 weken.

☐ Nee
☐ Ja

Heeft u “Ja” geantwoord? Beantwoord dan vraag 13 en 14.
Anders was dit de laatste vraag.

Vraag 13. Op hoeveel dagen was dit zo? Tel alleen de dagen in de afgelopen 4 weken. …. dagen

Vraag 14. Stel dat iemand, bijvoorbeeld uw partner, familielid of een bekende, u op deze dagen had geholpen. En al het onbetaalde werk wat u niet kon doen, voor u had gedaan. Hoeveel uur was die persoon hier op deze dagen dan gemiddeld mee bezig geweest?

Gemiddeld…… uur op deze dagen

Dit was de laatste vraag.

Heeft u vragen of opmerkingen?

Misschien heeft u nog vragen of opmerkingen? Schrijft u deze dan hieronder op.

…….

…….

Hartelijk dank!

17.5 Institute for Medical Technology Assessment Productivity Costs Questionnaire (iMTA PCQ) - English (Version 2.0, 14/07/2023)

UK version

Questions about your health and work

Researchers call this questionnaire the iMTA PCQ (iPCQ).

Explanatory notes

Please read this first!

Are you unable to complete the questionnaire yourself?

If you are unable to complete the questionnaire yourself, perhaps someone can help you. A member of your family, for example.

What is the questionnaire about?

The questionnaire is about your health and work in the past 4 weeks.

How long does it take to complete the questionnaire?

It takes roughly 10 minutes to complete the questionnaire.

How should you complete the questionnaire?

- Start with the first question and follow the numbering.
- .
- For some questions, you can enter a number or something else on the dotted line.
- There are no wrong answers.

What will happen with your answers?

Your answers will be used for research. Only the researchers will see your answers. So nobody else will.

The researchers will not write down your name anywhere. And they will not tell anyone that you have taken part in the trial.

It is great that you want to complete the questionnaire for us!

Question 1. What do you do in daily life? Check the box for what best describes your primary occupation.

☐ I am at school, I study
☐ I am in paid employment
☐ I am self-employed
☐ I am a housewife/husband
☐ I am unemployed
☐ I am disabled for working, for, … % (bodily percentage)
☐ I am retired or have taken early retirement
☐ I do something else, namely ……..
……

Question 2. Do you have paid work?

☐ No

☐ Yes

You will first have questions about your job. So, about work for which you are paid. *Do you <u>not have a paid job</u>?* Then continue with question 12. First, read the explanatory notes above question 12.

Question 3. What is your occupation?

..…….

Question 4. How many hours a week do you work? Add together all the hours for which you are paid.

…… hours

Question 5. How many days a week do you work?

…… days

Question 6. Have you been absent from your work in the past 4 weeks because you were ill?

☐ No

☐ Yes, I was absent for….. days

(*Only count the <u>working days</u> in the past 4 weeks)*

Have you checked the “Yes” box? Then answer question 7.

Otherwise continue with question 9.

Question 7. Have you been absent from your work because of being ill for longer than the entire period of 4 weeks? This refers to an uninterrupted period of absence from work.

☐ No

☐ Yes

Have you checked the "Yes" box? Then answer question 8. Otherwise continue from question 9.

Question 8. When did you report being ill?

Day/month/year: …../…../…… Continue with question 12. *First, read the explanatory notes above question 12*.

Question 9. Have there been days over the past 4 weeks when you worked but suffered from physical or psychological problems during your work?

☐ No

☐ Yes

Have you checked the "Yes" box? Then answer questions 10 and 11.

Otherwise continue with question 12. *First, read the explanatory notes above question 12.*

Question 10. On how many working days have you suffered from physical or psychological problems during your work? Just count the working days over the past 4 weeks.

…… working days

Question 11. On the days when you were suffering from problems, perhaps you were not able to do as much work as normal. On those days, how much work could you do on average? Look at the numbers below. A 10 means that you were able to do just as much as normal on those days. A 0 means that you were not able to do anything on those days. Circle the right number.

I was not able on those days	I could do around half	I was able to do anything	to do just as much as normal

0 1 2 3 4 5 6 7 8 9 10

Explanatory notes to question 12

You may also suffer from your physical or psychological problems during unpaid work. Sometimes you can do less as a result. For example, you cannot care properly for the children or do volunteer work. Or you may not be able to do the shopping or do gardening. That is what the next questions are about.

Question 12. Have there been any days on which you were able to do less unpaid work because of your physical or psychological problems? This relates to days over the past 4 weeks.

☐ No

☐ Yes

Have you checked the “Yes” box? Then answer questions 13 and 14.
Otherwise, this was the last question..

Question 13. On how many days was this the case? Only count the days in the past 4 weeks.

…. days

Question 14. Suppose that someone, for example your partner, a family member or an acquaintance, has helped you on these days. And did all that unpaid work for you, that you could not do. How many hours, on average, was that person busy with it on these days?

On average …… hours on these days

That was the last question.

Have you got any questions or comments?

Perhaps you have some more questions or comments? If so, please enter them below.

……

……

……

Thank you very much!

17.6 Institute for Medical Technology Assessment Productivity Costs Questionnaire (iMTA PCQ) – French (Version 2.0, 14/07/2023)

Questionnaire sur votre santé et votre travail

Les chercheurs appellent ce questionnaire l'iMTA PCQ (iPCQ).

Explication
Veuillez lire ceci avant de compléter le questionnaire.

Vous ne pouvez pas remplir le formulaire tout(e) seul(e) ?
Si vous n'êtes pas en mesure de compléter le formulaire tout(e) seul(e), quelqu'un peut peut-être vous aider, un membre de votre famille par exemple.

Sur quoi ce questionnaire porte-t-il ?
Ce questionnaire porte sur votre santé et votre travail au cours des quatre dernières semaines.

Combien de temps cela prend-il de remplir le formulaire ?
Compléter le formulaire prend environ 10 minutes.

Comment devez-vous remplir le formulaire ?
- Commencez par la première question puis suivez la numérotation.
-
- Pour certaines questions, vous pouvez écrire un nombre ou répondre sur les pointillés.
- Il n'y a pas de mauvaises réponses.

Qu'adviendra-t-il de vos réponses ?
Vos réponses serviront à la recherche. Seuls les chercheurs verront vos réponses. Cela veut donc dire que personne d'autre n'y aura accès.
Les chercheurs n'écriront votre nom nulle part. Et ils ne diront à personne que vous avez participé à ce projet de recherche.

Nous vous sommes très reconnaissants de bien vouloir compléter ce formulaire pour nous !

Question 1. Quelle est votre occupation ? Inscrivez une **x** dans la case correspondant à votre activité habituelle.

☐ Je vais à l'école, je suis étudiant(e)
☐ Je suis salarié(e)
☐ Je suis travailleur/se indépendant(e)
☐ Je suis femme/homme au foyer
☐ Je suis demandeur/se d'emploi
☐ Je suis en incapacité de travail à hauteur de .... %
☐ Je suis à la retraite ou bénéficie d'une retraite anticipée
☐ J'ai une autre occupation, à savoir……

Question 2. Avez-vous un emploi rémunéré ?

☐ Non
☐ Oui

Les questions suivantes portent sur votre travail. C'est-à-dire, un emploi pour lequel vous êtes rémunéré(e). Vous n'avez pas d'emploi rémunéré ? Passez à la question 12. *Veuillez d'abord lire l'explication précédant la question.*

Question 3. Quel est votre profession ?

……

Question 4. Combien d'heures par semaine travaillez-vous ? Comptez uniquement les heures rémunérées.

…….. heures

Question 5. Combien de jours par semaine travaillez-vous ?

……. jours

Question 6. Vous êtes-vous absenté(e) de votre travail au cours des 4 dernières semaines pour raison de santé ?

☐ Non
☐ Oui, je me suis absenté(e) …… jours.

(Comptez uniquement les jours d'arrêt de travail au cours des 4 dernières semaines.)

Vous avez répondu « Oui » ? Passez à la question 7.
Sinon, passez à la question 9.

Question 7. Vous êtes-vous absenté(e) de votre travail avant la période des 4 semaines pour raison de santé ? Cela concerne une période ininterrompue complète d'arrêt de travail à cause d'une maladie.

☐ Non
☐ Oui

Vous avez répondu « Oui » ? Passez à la question 8.
Sinon, passez à la question 9.

Question 8. Quand votre congé maladie a-t-il débuté ?

Jour/mois/année : …./…./…….

Passez à la question 12. *Veuillez d'abord lire l'explication précédant la question 12.*

Question 9. Au cours des 4 dernières semaines, y a-t-il eu des jours où vous avez été gêné(e) au travail par des problèmes physiques ou psychologiques ?

☐ Non
☐ Oui

Vous avez répondu « Oui » ? Passez aux questions 10 et 11.

Sinon, passez à la question 12. *Veuillez d'abord lire l'explication précédant la question 12*.

Question 10. Pendant combien de jours avez-vous été gêné(e) par des problèmes physiques ou psychologiques lorsque vous étiez au travail ? (Comptez uniquement les jours où vous avez travaillé au cours des 4 dernières semaines.)

..... jours de travail

Question 11. Les jours où vous avez été gêné(e) par ces problèmes, avez-vous eu des difficultés à accomplir la même charge de travail que d'habitude ? Ces jours-là, quelle charge de travail avez-vous pu réaliser en moyenne ? Observez les chiffres ci-dessous. Un 10 signifie que vous avez été capable d'accomplir la même charge de travail que d'habitude. Un 0 signifie que vous n'avez été capable de réaliser aucune tâche ces jours-là. Entourez le chiffre qui correspond le mieux à votre cas.

Ces jours-là, je n'ai rien pu faire du tout.			J'ai pu accomplir la même charge de travail que d'habitude					J'ai pu accomplir la moitié du travail habituel.		
0	1	2	3	4	5	6	7	8	9	10

Explication à la question 12

Même dans le cadre d'un travail non rémunéré, vous pouvez souffrir de problèmes physiques ou psychologiques. Parfois, vous pouvez avoir plus de difficultés à effectuer certaines activités quotidiennes. Vous avez par exemple du mal à vous occuper de vos enfants ou à faire du bénévolat. Ou bien vous n'êtes pas capable d'aller faire vos courses ou de jardiner. Les questions suivantes portent sur cela.

Question 12. Y a-t-il eu certains jours où vous avez été contraint(e) de réaliser moins de travail non rémunéré à cause de problèmes physiques ou psychologiques ? Cela concerne uniquement les quatre dernières semaines.

☐ Non
☐ Oui

Vous avez répondu « Oui » ? Passez aux questions 13 et 14.

Sinon, c'était la dernière question.

Question 13. Combien de jours cela vous est-il arrivé ? Comptez uniquement les jours inclus dans les 4 dernières semaines.

……. jours

Question 14. Imaginez que quelqu'un, votre compagne/compagnon, un membre de votre famille ou un ami par exemple, vous ait aidé ces jours-là et qu'il ou elle ait accompli pour vous tout le travail non rémunéré que vous n'avez pas été capable d'effectuer. Combien d'heures en moyenne cette personne a-t-elle passé à réaliser ces tâches ces jours-là ?

…….. heures en moyenne ces jours-là

C'était la dernière question de ce formulaire.

Avez-vous des questions ou des commentaires à formuler ?

Vous avez peut-être des questions ou des commentaires à formuler ?

Veuillez les écrire ci-dessous.

……

……

Merci!

17.7 Institute for Medical Technology Assessment Medical Consumption Questionnaire Vragenlijst Productivity & Health Research Group (iMTA MCQ) – Dutch (Version 3.0, 13/07/2023)

Vragenlijst over uw zorggebruik

Onderzoekers noemen deze vragenlijst de iMTA MCQ (iMCQ).

Toelichting

Lees dit alstublieft eerst!

Kunt u de lijst niet zelf invullen?
Als u de lijst niet zelf kunt invullen, kan iemand u misschien helpen. Bijvoorbeeld een familielid.

Waar gaat de vragenlijst over?
De vragenlijst gaat over uw zorggebruik in de afgelopen 3 maanden.

Hoe lang duurt het om de lijst in te vullen?
Het duurt ongeveer 20 minuten om de lijst in te vullen.

Hoe moet u de vragenlijst invullen?

Begin bij de eerste vraag en volg de nummering.

- Bij sommige vragen kunt u tekst of een getal invullen, bij andere vragen kunt u een hokje/optie aanklikken
- U kunt geen foute antwoorden geven.

Wat gebeurt er met uw antwoorden?
Uw antwoorden worden gebruikt voor onderzoek. Alleen de onderzoekers zien uw antwoorden. Dus niemand anders.
De onderzoekers schrijven uw naam nergens op. En zij vertellen aan niemand dat u aan het onderzoek heeft meegewerkt.

Fijn dat u de lijst voor ons wilt invullen!

Vragen over zorggebruik

Toelichting

Wij willen graag weten met welke dokters u in de afgelopen 3 maanden een afspraak had. Het gaat om afspraken voor uzelf. Ook andere zorgverleners tellen mee. Bijvoorbeeld de fysiotherapeut.
Welke afspraken tellen mee?
- Controles
- Afspraken omdat u een lichamelijke of psychische klacht had
- Afspraken waarbij de dokter bij u thuis kwam
- Telefonische afspraken
- Telefoontjes met de receptenlijn

Wat telt niet mee?
- Afspraken voor een ander, bijvoorbeeld voor uw kind
- Telefoontjes om een afspraak te maken

Weet u niet precies hoeveel afspraken het waren? Schrijf dan op hoeveel het er ongeveer waren.

Vraag 1a. Heeft u in de afgelopen 3 maanden afspraken gehad met uw huisarts?

☐ Nee
☐ Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 1b.
Ga anders verder met vraag 2.

Vraag 1b. Hoeveel afspraken had u in de afgelopen 3 maanden met uw huisarts?

☐ ..... afspraken met de huisarts

Vraag 2. Hoeveel afspraken had u in de afgelopen 3 maanden met een fysiotherapeut? Of met een caesartherapeut, therapeut mensendieck of een manueel therapeut? Tel alle afspraken met deze therapeuten bij elkaar op.

☐ Geen enkele afspraak
☐ …… afspraken

Vraag 3. Hoeveel afspraken had u in de afgelopen 3 maanden met een ergotherapeut?

☐ Geen enkele afspraak
☐ …… afspraken

Vraag 4. Hoeveel afspraken had u in de afgelopen 3 maanden met een logopedist?

☐ Geen enkele afspraak
☐ …… afspraken

Vraag 5. Hoeveel afspraken had u in de afgelopen 3 maanden met een psycholoog? Of met een psychotherapeut of psychiater? Tel alle afspraken met deze zorgverleners bij elkaar op.

☐ Geen enkele afspraak
☐ …… afspraken

Vraag 6a. Heeft u in de afgelopen 3 maanden hulp van de thuiszorg gehad?

☐ Nee
☐ Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 6b-6d.
Ga anders verder met vraag 7a.

Vraag 6b. Wat voor hulp van de thuiszorg heeft u gehad in de afgelopen 3 maanden?
U kunt meer dan 1 hokje aankruisen.

☐ Huishoudelijke hulp
voorbeeld: stofzuigen, bed opmaken, boodschappen doen

☐ Verzorging van uzelf
voorbeeld: hulp bij douchen of aankleden

☐ Verpleging
voorbeeld: verband omdoen, medicijnen geven, bloeddruk meten

Vraag 6c. Hoeveel weken heeft u deze thuiszorg gehad? Tel alle weken in de afgelopen 3 maanden bij elkaar op. *Let op: een periode van 3 maanden telt <u>13 weken</u>*.
Huishoudelijke hulp: …. weken in de afgelopen 3 maanden

Verzorging van uzelf: …. weken in de afgelopen 3 maanden

Verpleging: …. weken in de afgelopen 3 maanden

Vraag 6d. Hoeveel uur thuiszorg kreeg u in deze weken gemiddeld?

Huishoudelijke hulp: gemiddeld … uur in de week

Verzorging van uzelf: gemiddeld … uur in de week

Verpleging: gemiddeld … uur in de week

Vraag 7a. Heeft u in de afgelopen 3 maanden bloedverdunners*, gebruikt?

☐ Nee
☐ Ja

* carbasalaatcalcium (ascal, acetylsalicylzuur), clopidogrel (plavix, grepid, iscover), prasugrel (efient) , ticagrelor (brilique), dipyidamol (persantin), acenocoumarol (sintrom), fenprocoumon (marcoumar), dabigatran (pradaxa), rivaroxaban (xarelto), apixaban (eliquis), edoxaban (lixiana)

Heeft u “Ja” aangekruist? Vul dan bij vraag 7b in welke medicijnen en hoeveel.
Ga anders verder met vraag 8.

Vraag 7b. Welke bloedverdunners heeft u in de afgelopen 3 maanden gebruikt?.
Met bloedverdunners bedoelen we alle medicijnen die bij vraag 7a na het sterretje (*) worden genoemd. U ziet eerst twee voorbeelden.

Let op: pak de verpakking erbij! Daarop staat hoeveel u per keer moest nemen. En hoe vaak u dat moest doen. ***Heeft u meer of minder gebruikt? Vul dan in hoeveel u ook echt gebruikt heeft. Hoe heet het medicijn?***	***Hoeveel heeft u per keer genomen?*** *Kijk op de verpakking*	***Hoe vaak op een dag heeft u dit gedaan?*** *Kijk op de verpakking*	***Op hoeveel dagen in de afgelopen 3 maanden heeft u het medicijn gebruikt?***
Voorbeeld 1 *Carbasalaatcalcium*	*Voorbeeld* *100 mg*	*Voorbeeld* *1 keer*	*Voorbeeld* *14 dagen*
Voorbeeld 2 *Clopidogrel*	*Voorbeeld* *75 mg*	*Voorbeeld* *1 keer*	*Voorbeeld* *90 dagen*

Vraag 8a. Bent u in de afgelopen 3 maanden in het ziekenhuis geweest voor een bezoek aan een arts of spoedeisende hulp? Opnames in het ziekenhuis (dus met overnachting) tellen hier niet mee, het gaat alleen om bezoeken overdag

☐ Nee
☐ Ja

Heeft u “Ja” geantwoord? Beantwoord dan vraag 8b.
Ga anders verder met vraag 9.

Vraag 8b. Bij welke soorten dokters bent u in de afgelopen 3 maanden in het ziekenhuis geweest? En hoe vaak?

Bij welke soort dokter bent u in het ziekenhuis geweest?	***Hoe vaak bent u in de afgelopen 3 maanden bij deze dokter geweest?***
voorbeeld cardioloog	*voorbeeld* 2 keer
…… ….	… keer
…… ….	… keer
…… ….	… keer
…… ….	… keer
…… ….	… keer
…… ….	… keer
…… ….	… keer

Vraag 9a. Heeft u in de afgelopen 3 maanden opnieuw in het ziekenhuis gelegen?
U moest dus blijven slapen.

- ☐ Nee
- ☐ Ja

Heeft u “Ja” aangekruist? Beantwoord dan vraag 9b.
Ga anders verder met vraag 10.

Vraag 9b. Hoe lang heeft u in het ziekenhuis gelegen? Heeft u meer dan 1 keer in het ziekenhuis gelegen in de afgelopen 3 maanden? Tel dan alle dagen bij elkaar op.
…… dagen in totaal in de afgelopen 3 maanden

Vraag 10a. Bent u in de afgelopen 3 maanden ergens anders geweest dan in het ziekenhuis voor een behandeling? Bijvoorbeeld naar een woon-/zorgcentrum of een psychiatrische instelling. Of naar een revalidatiecentrum.

- ☐ Nee
- ☐ Ja, maar ik ging daar alleen overdag naartoe
- ☐ Ja, ik was daar opgenomen (ik bleef daar slapen)

Heeft u “Ja” aangekruist? Beantwoord dan vraag 10b en 10c.
Anders was dit de laatste vraag.

Vraag 10b. Wat voor instelling was dit? Kruis het goede antwoord aan. U kunt meer dan 1 hokje aankruisen.

- ☐ Woon-/zorgcentrum
- ☐ Revalidatiecentrum
- ☐ Psychiatrische instelling
- ☐ Een andere instelling, namelijk ……

Vraag 10c. Hoe lang bent u in deze instelling geweest? Heeft u bij vraag 11b meer dan 1 hokje aangekruist? Vul dan hieronder voor iedere instelling in hoe lang u er bent geweest. Bent u ergens meer dan 1 keer geweest in de afgelopen 3 maanden? Tel dan alle dagen en nachten bij elkaar op.
In het woon-/zorgcentrum: …… dagen en …… nachten in de afgelopen 3 maanden
In het revalidatiecentrum: …… dagen en …… nachten in de afgelopen 3 maanden
In de psychiatrische instelling: …… dagen en …… nachten in de afgelopen 3 maanden
In de andere instelling: …… dagen en …… nachten in de afgelopen 3 maanden

Dit was de laatste vraag.

Heeft u vragen of opmerkingen?

Misschien heeft u nog vragen of opmerkingen? Schrijft u deze dan hieronder op.

……

……

Hartelijk dank!

17.8 Institute for Medical Technology Assessment Medical Consumption Questionnaire Vragenlijst Productivity & Health Research Group (iMTA MCQ) – English (Version 3.0, 13/07/2023)

Researchers call this questionnaire the iMTA MCQ (iMCQ).

Comment

Please read this first!

Can you not fill in the list yourself?
If you cannot fil in the list yourself, someone might be able to help you. For example, a family member.

What is the questionnaire about?
The questionnaire is about your use of care in the past 3 months.

How long does it take to fill in the list?
It takes about 20 minutes to fill in the list.

How do you have to fill in the list?

- Start with the first question and follow the numbering.
- For each question, tick 1 box, except if the question states that you can tick more than 1 box.
- For some questions you can enter a number or something else on the dotted line.
- You cannot give wrong answers.

What happens to your answers?
Your answers are used for research. Only the researchers will see your answers. So no one else.
The researchers will not write down your name anywhere. And they will not tell anyone that you have taken part in the trial.

Thank you for filling in the list for us!

Questions about healthcare use

Comment
We would like to know which doctors you have consulted in the past 3 months. It is about consultations for yourself. Other healthcare providers also count. For example, the physiotherapist.

Which consultations count?

- Control visits
- Appointments because you had a physical or psychological complaint
- Appointments where the doctor came to your home
- Telephone appointments
- Phone calls with the recipe line

Which consultations do not count?

- Appointments for another person, for example for your child
- Telephone calls to make an appointment

Are you unsure about the exact number of consultations? Please fill in how many consultations you have had approximately.

Question 1a. Have you consulted a general practitioner in the past 3 months?

☐ No
☐ Yes

Have you ticked "Yes"? Then answer question 1b.
Otherwise, continue with question 2.

Question 1b. How many appointments did you have with your general practitioner in the past 3 months?

☐ ..... appointments with a doctor
☐ ..... appointments with a nurse practitioner

Question 2. How many appointments did you have with a physiotherapist in the past 3 months? Or with a Caesar therapist, therapist Mensendieck or a manual therapist? Add up all appointments with these therapists.

☐ No appointment
☐ …… appointments

Question 3. How many appointments did you have with an occupational therapist in the past 3 months?

☐ No appointment
☐ …… appointments

Question 4. How many appointments did you have with a speech therapist in the past 3 months?

☐ No appointment
☐ …… appointments

Question 5. How many appointments did you have with a psychologist in the past 3 months? Or with a psychotherapist or psychiatrist? Add up all appointments with these healthcare providers.

☐ No appointment
☐ …… appointments

Question 6a. Have you received home care in the past 3 months?

☐ No
☐ Yes

Have you ticked "Yes"? Then answer questions 6b through 6d. Otherwise, continue with question 7.

Question 6b. What kind home care have you had in the past 3 months? You can tick more than 1 box.

☐ Housekeeping and domestic help
example: vacuuming, making the bed, going for daily groceries
☐ Personal care
example: help with bathing or dressing
☐ Nursing
example: putting on a bandage, administering medication, measuring blood pressure

Question 6c. How many weeks did you have this home care? Count up all weeks in the past 3 months. *Note: a period of 3 months counts 13 weeks*.

Domestic help: ..... weeks in the past 3 months

Personal care: ..... weeks in the past 3 months

Nursing: ..... weeks in the past 3 months

Question 6d. How many hours of home care did you receive on average in these weeks?

Domestic help: on average ..... hours a week

Personal care: on average ..... hours a week

Nursing: on average ..... hours a week

Question 7a. Did you take any blood thinners* in the past 3 months?

☐ No
☐ Yes

* carbasalatecalcium (ascal, acetylsalicylic acid), clopidogrel (plavix, grepid, iscover), prasugrel (efient) , ticagrelor (brilique), dipyidamole (persantin), acenocoumarol (sintrom), fenprocoumon (marcoumar), dabigatran (pradaxa), rivaroxaban (xarelto), apixaban; (eliquis), edoxaban (lixiana)

Have you ticked "Yes"? Then fill in question 7b listing which medications you used and how much.
Otherwise, continue with question 8.

Question 7b. What blood thinners did you take in the past 3 months? By blood thinners we mean all drugs listed in Question 7a after the asterisk (*). There are twoexamples below.

Pay attention: look at the package! It shows how much you had to take at each time. And how often you had to do so per day. ***Have you used more or less? Then enter how much you have actually used.***

What is the name of the medicine?	***How much did you take at each time?*** *Look at the packaging*	***How many times did you take this per day?*** *Look at the packaging*	***On how many days in the past 3 months have you used the medication?***
example 1 Carbasalate calcium	*example* 100 mg	*example* 1 time	*example* 14 days
example 2 clopidogrel	*example* 75 mg	*example* 1 time	*example* 90 days
……	……	……	……
……	……	……	……
……	……	……	……
……	……	……	……
……	……	……	……
……	……	……	……
……	……	……	……
……	……	……	……

Question 8a. Did you have an appointment at the outpatient clinic of the hospital in the past 3 months? It is about appointments for yourself with a doctor. For example with the cardiologist, rheumatologist or neurologist. Hospital admissions (i.e. with an overnight stay) do not count here, it is only regarding daytime visits.

☐ No
☐ Yes

Have you ticked "Yes"? Then fill in question 8b the types of doctors you have visited. And how often. There is an example in the first row.
Otherwise, continue with question 9.

Question 8b. Which types of doctors have you been to in hospital for the past 3 months? And how often?

Which type of doctor did you visit in the hospital?	***How often have you been with this doctor in the past 3 months?***
example cardiologist	*example* 2times
……	……times
……	……times
……	……times
……	……times
……	……times
……	……times
……	……times

Question 9a. Have you been hospitalised again in the past 3 months? In other words, you hade to stay overnight.

☐ No
☐ Yes

Have you ticked "Yes"? Then answer questions 9b.
Otherwise, continue with question 10.

Question 9b. How long have you been in the hospital? Have you been in the hospital more than once in the past 3 months? Then add up all the days.

…… days in total in the past 3 months.

Question 10a. Did you go elsewhere in the past 3 months? For example, you went to a residential/care centre or a psychiatric institution. Or a rehabilitation centre.

☐ No
☐ Yes, but I only went during the day
☐ Yes, I was admitted there (I stayed there overnight)

Have you ticked "Yes"? Then answer questions 10b and 10c. Otherwise, continue with question 11.

Question 10b. What kind of institution was this? Tick the correct answer. You can tick more than 1 box.

☐ Residential care centre or nursing home
☐ Rehabilitation centre
☐ Mental health institution
☐ Another institution, namely .....

……

Question 10c. How many times did you have to go here in the past 3 months?
Have you ticked more than one box in question 10b? Then enter the number of days and nights you have been there for each institution below.

To a residential care or nursing home:	..... days and ….. nights in the past 3 months
To the rehabilitation centre:	..... days and ….. nights in the past 3 months
To the mental health institution:	..... days and ….. nights in the past 3 months
To the other institution:	..... days and ….. nights in the past 3 months

That was the last question.

Do you have questions or comments?
If you have any questions or comments, list them here.

……
……
……
……
……

Thank you!

17.8 Institute for Medical Technology Assessment Medical Consumption Questionnaire Vragenlijst Productivity & Health Research Group (iMTA MCQ) – Français (Version 3.0, 13/07/2023)

Questions sur votre consommation en soins de santé

Les chercheurs appellent ce questionnaire l'iMTA MCQ (iMCQ).

Instructions

Veuillez lire ceci avant de commencer !

Vous n'êtes pas en mesure de remplir le questionnaire vous-même ?
Si vous n'êtes pas en mesure de remplir le questionnaire vous-même, une autre personne peut vous y aider. Par exemple, un membre de la famille.

De quoi traite ce questionnaire ?
Le questionnaire étudie votre utilisation de soins au cours des trois derniers mois.

Combien faut-il de temps pour remplir le questionnaire ?
Compléter ce formulaire vous prendra environ 20 minutes.

Comment devez-vous remplir le questionnaire ?

- Commencez par la première question et suivez l'ordre des numéros.
- Pour chaque question, cochez une seule case, sauf si la question indique explicitement que vous pouvez cocher plusieurs cases.
- Pour certaines questions, vous pouvez écrire un nombre ou quelque chose d'autre sur la ligne en pointillés.
- Aucune réponse n'est mauvaise.

Comment vos réponses sont-elles utilisées ?
Vos réponses sont utilisées pour la recherche. Seuls les chercheurs verront vos réponses. Cela veut donc dire que personne d’autre n’y aura accès . Les chercheurs n’écriront votre nom nulle part. Et ils ne diront à personne que vous avez participé à ce projet de recherche.

Nous vous remercions pour votre collaboration avec ce questionnaire !

Questions sur votre consommation en soins de santé

Commentaire
Nous aimerions savoir quels médecins vous avez consultes au cours des trois derniers mois. Nous faisons référence aux consultations pour vous-même. Les autres prestataires de soins doivent aussi être comptabilises. Les physiothérapeutes, par exemple.

Quelles consultations doivent être prises en compte
- Visites de contrôle
- Consultations en raison d'un problème physique ou psychologique
- Consultations pour lesquelles votre médecin est venu chez vous
- Consultations par téléphone
- Appels téléphoniques avec la ligne des ordonnances

Quelles consultations ne doivent pas être prises en compte ?
- Consultations pour une autre personne, par exemple pour votre enfant
- Appels téléphoniques pour prendre un rendez-vous

Vous n'êtes pas certain(e) du nombre de consultations ? Veuillez indiquer approximativement combien de consultations vous avez effectuées.

Question 1a. Avez-vous consulté un médecin généraliste au cours des trois derniers mois ?

☐ Non
☐ Oui

Vous avez coché « Oui » ? Vous devez alors répondre à la question 1b.
Si vous avez coché « Non », vous pouvez passer à la question 2.

Question 1b. Combien de consultations avez-vous effectuées avec votre médecin traitant au cours des trois derniers mois ?

☐ ..... consultations avec le médecin traitant

Question 2. Combien de consultations avez-vous effectuées avec un physiothérapeute au cours des trois derniers mois ? Ou avec un thérapeute César, un thérapeute Mensendieck ou un thérapeute manuel ? Ajoutez toutes les consultations avec de tels thérapeutes.

☐ Aucune consultation
☐ …… consultations

Question 3. Combien de consultations avez-vous effectuées avec un ergothérapeute au cours des trois derniers mois ?

☐ Aucune consultation
☐ …… consultations

Question 4. Combien de consultations avez-vous effectuées avec un orthophoniste au cours des trois derniers mois ?

☐ Aucune consultation
☐ …… consultations

Question 5. Combien de consultations avez-vous effectuées avec un psychologue au cours des trois derniers mois ? Ou avec un psychothérapeute ou un psychiatre ? Ajoutez toutes les consultations avec ces prestataires de soins.

☐ Aucune consultation
☐ …… consultations

Question 6a. Avez-vous reçu des soins à domicile au cours des trois derniers mois ?

☐ Non
☐ Oui

Vous avez coché « Oui » ? Vous devez alors répondre aux questions 6b à 6d. Si vous avez coché « Non », vous pouvez passer à la question 7.

Question 6b. Quel type de soins à domicile avez-vous reçus au cours des trois derniers mois ? Vous pouvez cocher plusieurs réponses.

☐ Entretien de la maison et aide ménagère
exemples : passer l'aspirateur, faire le lit, aller faire des courses
☐ Soins personnels
exemples : aide pour prendre un bain ou s'habiller
☐ Soins infirmiers
exemples : faire un bandage, administrer des médicaments, mesurer la tension artérielle

Question 6c. Pendant combien de semaines avez-vous fait appel à ce type de soins à domicile ? Comptez toutes les semaines au cours des trois derniers mois. *Remarque : une période de trois mois comprend treize semaines*.

Aide ménagère : ..... semaines au cours des trois derniers mois

Soins personnels : ..... semaines au cours des trois derniers mois

Soins infirmiers : ..... semaines au cours des trois derniers mois

Question 6d. Combien d'heures de soins à domicile avez-vous reçues en moyenne au cours de ces semaines ?

Aide ménagère : en moyenne ..... heures par semaine

Soins personnels : en moyenne ..... heures par semaine

Soins infirmiers : en moyenne ..... heures par semaine

Question 7a. Avez-vous pris des médicaments anticoagulants* au cours des trois derniers mois ?

☐ Non
☐ Oui

* carbasalaatcalcium (ascal, acetylsalicylzuur), clopidogrel (plavix, grepid, iscover), prasugrel (efient) , ticagrelor (brilique), dipyidamol (persantin), acenocoumarol (sintrom), fenprocoumon (marcoumar), dabigatran (pradaxa), rivaroxaban (xarelto), apixaban; (eliquis), edoxaban (lixiana)

Vous avez coché « Oui » ? Vous devez alors répondre à la question 7b et dresser une liste des médicaments que vous avez utilisés avec la quantité administrée.
Si vous avez coché « Non », vous pouvez passer à la question 8.

Question 7b. Quels médicaments anticoagulants avez-vous pris au cours des trois derniers mois ? Les médicaments anticoagulants comprennent tous les types de médicaments énumérés à la question 7a après l'astérisque (*).. Vous pouvez retrouver deux exemples ci-dessous.

Attention : lisez attentivement la posologie ! Elle indique combien vous avez dû en prendre à chaque fois. Et la fréquence avec laquelle vous avez dû le faire chaque jour. ***Vous avez utilisé plus ou moins ? Veuillez alors indiquer la quantité réellement utilisée.***

Quel est le nom des médicaments ?	***Combien en avez-vous pris à chaque fois ?*** *Regardez la posologie*	***Combien de fois en avez-vous pris par jour ?*** *Regardez la posologie*	***Combien de jours au cours des trois derniers mois avez-vous utilisé le médicament ?***
exemple 1 carbasalaatcalcium	*exemple* 100 mg	*exemple* 1 fois	*exemple* 14 jours

exemple 2 Clopidogrel	*exemple* 75 mg	*exemple* 1 fois	*exemple* 90 jours
……	……	……	……
……	……	……	……
……	……	……	……
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……	……	……	……

Question 8a. Avez-vous eu une consultation à la policlinique de l'hôpital au cours des trois derniers mois ? Il s'agit de consultations pour vous-même avec un médecin. Par exemple avec un cardiologue, un rhumatologue ou un neurologue.
Autrement dit, sans passer de nuit à l'hôpital

☐ Non
☐ Oui

Vous avez coché « Oui » ? Vous devez alors répondre à la question 8b sur les types de médecins que vous avez consultés. Et à propos de la fréquence. Vous pouvez retrouver un exemple à la première ligne.
Si vous avez coché « Non », vous pouvez passer à la question 9.

Question 8b. Quels types de médecins avez-vous consultés à l'hôpital au cours des trois derniers mois ? Et à quelle fréquence ?

Quel type de médecin avez-vous consulté à l'hôpital ?	***À quelle fréquence avez-vous consulté ce médecin au cours des trois derniers mois ?***
exemple cardiologue	*exemple* 2 fois
……	……fois

……	……fois
……	……fois
……	……fois
……	……fois
……	……fois
……	……fois

Question 9a. Avez-vous été à nouveau hospitalisé au cours des trois derniers mois ? Vous avez donc dû passer la nuit à l'hôpital.

☐ Non
☐ Oui

Vous avez coché « Oui » ? Vous devez alors répondre aux questions 9b. Si vous avez coché « Non », vous pouvez passer à la question 10.

Question 9b. Pendant combien de temps êtes-vous hospitalisé(e) ? Avez-vous été hospitalisé plus d'une fois au cours des trois derniers mois ? Additionnez ensuite tous les jours.

..... jours au total au cours des 3 derniers mois

Question 10a. Avez-vous été autre part pour recevoir des soins au cours des trois derniers mois ? Vous avez, par exemple, été dans un centre de soins/résidentiel ou une institution psychiatrique. Ou dans un centre de réhabilitation.

☐ Non
☐ Oui, mais je n'y suis allé que pendant la journée.
☐ Oui, j'y été admis (j'y ai passé la nuit).

Vous avez coché « Oui » ? Vous devez alors répondre aux questions 10b et 10c. Si vous avez coché « Non », c'était la dernière question.

Question 10b. De quel type d'institution s'agissait-il ? Cochez la réponse adéquate. Vous pouvez cocher plusieurs réponses.

☐ Centre de soins résidentiels ou maison de retraite
☐ Centre de réhabilitation
☐ Institution de santé mentale
☐ Autre institution, à savoir .....

Question 10c. Combien de fois avez-vous rendu visite à cette/ces institution(s) au cours des trois derniers mois ? Vous avez coché plusieurs réponses à la question 10b ? Veuillez indiquer alors le nombre de jours et de nuits que vous avez visité ces institutions ci-dessous.

Centre de soins résidentiels ou maison de retraite:	..... jours et …… nuits au cours des trois derniers mois
Centre de réhabilitation:	..... jours et …… nuits au cours des trois derniers mois
Institution de santé mentale:	..... jours et …… nuits au cours des trois derniers mois
Autre institution:	..... jours et …… nuits au cours des trois derniers mois

C'était la dernière question.

Avez-vous des questions ou des commentaires ?
Si vous avez des questions ou des commentaires, n'hésitez pas à les indiquer ci-dessous.

……
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Merci !

18. IMAGING REQUIREMENTS

18.1 Baseline imaging

WHEN

1. Before randomization NCCT and CTA study should be performed to assess eligibility for the study.

HOW

1. Pre-randomization NCCT:

a. The NCCT study should contain both thick (5mm) and thin slices (maximum of 2.5mm).

b. The NCCT study should include the whole head.

2. Pre-randomization CTA:

a. The CTA study should cover the whole area from the aortic arch to the vertex

b. The CTA study should include thin slices (maximum of 1.0 mm)

c. The CTA study should include the following reconstructions:

-.Axial maximum intensity projection (MIP),

1. MIP slab thickness: 25 mm
2. Overlap: 5 mm

- Coronal MIP

1. MIP slab thickness: 25 mm
2. Overlap: 5 mm

3. After acquisition

a. All images (NCCT/CTA) should be saved to the DICOM format

b. All available series should be sent to the core lab for assessment, including thin slice series (for thrombus assessment).

18.2 Angiography during endovascular thrombectomy

WHEN

1. Before the intervention complete AP and lateral angiograms (of the carotid artery bifurcation and the whole head including venous phase) should be performed to evaluate the degree of carotid artery stenosis or occlusion, site of intracranial vessel occlusion, extent of thrombus, territories involved, concomitant pathologies and to assess collateral flow.
2. After each passage of a mechanical or aspirational device, a control angiogram should be performed.
3. After carotid artery stenting a control angiogram should be performed of the carotid artery bifurcation
3. After each bolus of (a rescue) thrombolytic agent a control angiogram should be performed.
4. At the end of the procedure complete AP and Lateral angiograms (of the carotid artery bifurcation and whole head and including venous phase) should be repeated. Without these complete runs optimal TICI scoring is not possible.

HOW

Pre-intervention and **end-of-procedure** angiogram:
1. Angiograms should be performed through the guiding catheter
2. Baseline and final AP views and lateral views of the intracranial arteries are mandatory. Both are required to assess reperfusion after the procedure.
3. Baseline and final angiograms should include both the arterial and venous phases of the injection to evaluate the collateral pathways and perfusion of the distal vascular bed.
4. Baseline and final angiograms should include the internal carotid artery feeding the target vessel as demonstrated on CTA.
5. Baseline and final angiograms of the common carotid artery should also be performed, visualizing the stent.
6. Angiograms should be performed via the guiding catheter with the same catheter position and same views before and after the procedures to adequately assess the results of therapy.
7. Documentation of percutaneous angioplasty, can be performed by single shot or store monitor.

After each device placement:
1. A non-contrast radiograph should be obtained
2. At least one view at the discretion of the interventionalist

After each passage of mechanical or aspirational device or bolus of (rescue) thrombolytic agent:
1. Angiograms should be performed through the guiding catheter
2. At least one view, at the discretion of the interventionalist.

After the procedure
1. Complete series of the angiograms, microcatheter injections (when performed), store monitors and single shots should be saved according to the DICOM standard.
2. All series, store monitors and single shots should be forwarded to the imaging assessment committee.

18.3 Imaging at 24 hours

WHEN

1. 24 hours after undergoing endovascular treatment a NCCT and CTA (24 hours +/- 12h) should be performed to assess treatment efficacy.
2. If clinically required (I.e. in cases of clinical deterioration of the patient) additional imaging as needed, at the discretion of the treating physician is acquired.

HOW

24 hours NCCT:
1. The NCCT study should contain both thick (5mm) and thin slices (maximum of 2.5mm).
2. The NCCT study should include the whole head.

24 hours CTA:
1. The CTA study should cover the whole area from the aortic arch to the vertex
2. The CTA study should include thin slices (maximum of 1.0 mm)
3. The CTA study should include the following reconstructions:

- Axial maximum intensity projection (MIP),
    - MIP slab thickness: 25 mm
    - Overlap: 5 mm
- Coronal MIP
    - MIP slab thickness: 25 mm
    - Overlap: 5 mm

After acquisition

- All images (NCCT, CTA and additional imaging) should be saved to the DICOM file format
- All available series should be sent to the core lab for assessment, including thin slice series (for thrombus assessment).

18.4 Duplex ultrasound examination carotid artery at 90 days

WHEN

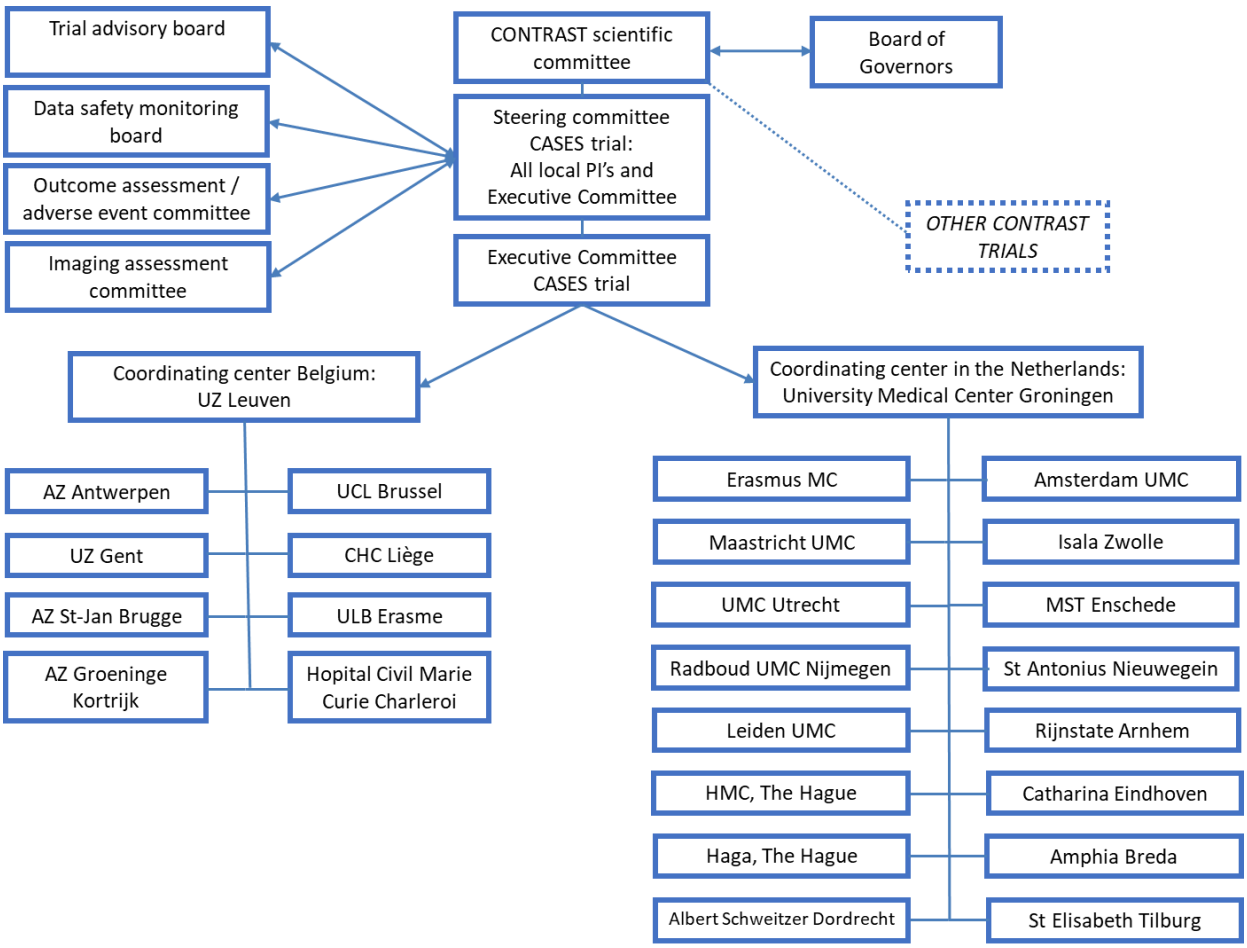
1. Duplex ultrasound of the ipsilateral carotid artery 90 days after randomization at the local site.
2. If clinically required (e.g. in case of deferred treatment and indication for CEA) earlier duplex ultrasound may be performed to assess eligibility for deferred surgical revascularization of the carotid artery stenosis

HOW

1. Duplex ultrasound examination is performed at the local site.
2. The measurements should be performed at least on the ipsilateral site (but additional measurements of the contralateral sides are recommended).
3. The measurements should include the peak systolic flow velocities in the common carotid artery and internal carotid artery as well as the end diastolic flow velocities in the internal carotid artery.
4. The recorded flow velocities should be reported in the eCRF by the local investigators
5. Duplex ultrasound images should be sent as DICOM images to the imaging core lab

19. GOVERNANCE OF THE CASES TRIAL

The steering committee of the trial will include 2 local principal investigators (one stroke neurologist and one neuro-interventionist) per participating center in Belgium and the Netherlands. The steering committee will meet twice a year and will discuss protocol changes, progress, publication and reporting of the trial. The steering committee is chaired by the prof.dr. Robin Lemmens, the national coordinator of Belgium and/or dr. M. Uyttenboogaart, national coordinator in the Netherlands. The executive committee consists of coordinating neurologists, radiologists and vascular surgeons (see project team) and the coordinating project managers. They will meet every two weeks during the recruitment phase of the trial to discuss the progress of the trial. The executive committee will prepare the main publication and distribute the trial results among the steering committee. A trial advisory board will be installed, with 4 independent neurologists/neuro-interventionists and 3 patient representatives (two from Belgium (Flemish and French speaking) and one from the Netherlands). For all the CONTRAST trials there is an independent outcome assessment committee, imaging assessment committee and adverse event committee. These committees will report to the executive committee of the CASES trial. Within the CONTRAST consortium, the progress of all trials is being monitored by the scientific committee of CONTRAST. The overall performance of the CONTRAST consortium is evaluated by a board of governors.



20. ACCESS TO THE STUDY DATA BY KCE

After the completion of the study the Sponsor will transfer the pseudonymised study data set to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g. IMA data by a trusted third party (TTP, eHealth platform) using the participant national number.

The participant information and consent includes wording that the national number will be recorded on site by the investigator for later data linkage, but will not be included in trial database available to the sponsor or any other third party. The participant information and consent will also include that in case the participant is randomized, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data. To this end, KCE will receive the link between the study number and the national number under pseudonymised form. KCE will never be able to use the link without authorisation of the ISC and the intervention of the TTP. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the participant that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by KCE. The processing of personal data for this analysis is necessary for the performance of a task carried out in the public interest, as specified in the law defining KCE's missions and tasks. To the extent the personal data is related to health, the processing is necessary for scientific or statistic purposes, as specified in the law defining KCE's missions and tasks. For all processing related to the analysis of effectiveness and cost-effectiveness of the intervention, KCE is the controller.

KCE and Sponsor have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.