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Clinical Endpoints in Peripheral Endovascular Revascularization Trials: a Case for Standardized Definitions

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Abstract *Background:* Endovascular therapy is a rapidly expanding option for the treatment of patients with peripheral arterial disease (PAD), leading to a myriad of published studies reporting on various revascularization strategies. However, these reports are often difficult to interpret and compare because they do not utilize uniform clinical endpoint definitions. Moreover, few of these studies describe clinical outcomes from a patients' perspective.

Methods and results: The DEFINE Group is a collaborative effort of an ad-hoc multidisciplinary team from various specialties involved in peripheral arterial disease therapy in Europe and the United States. DEFINE's goal was to arrive at a broad based consensus for baseline and endpoint definitions in peripheral endovascular revascularization trials for chronic lower limb ischemia. In this project, which started in 2006, the individual team members reviewed the

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existing pertinent literature. Following this, a series of telephone conferences and face-to-face meetings were held to agree upon definitions. Input was also obtained from regulatory (United States Food and Drug Administration) and industry (device manufacturers with an interest in peripheral endovascular revascularization) stakeholders, respectively. The efforts resulted in the current document containing proposed baseline and endpoint definitions in chronic lower limb PAD. Although the consensus has inevitably included certain arbitrary choices and compromises, adherence to these proposed standard definitions would provide consistency across future trials, thereby facilitating evaluation of clinical effectiveness and safety of various endovascular revascularization techniques.

Conclusion: This current document is based on a broad based consensus involving relevant stakeholders from the medical community, industry and regulatory bodies. It is proposed that the consensus document may have value for study design of future clinical trials in chronic lower limb ischemia as well as for regulatory purposes.

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Introduction

Endovascular therapy is a rapidly evolving option for the treatment of patients with peripheral arterial disease (PAD).¹ The excitement generated by the prospects of new technology has led endovascular therapists of various specialty backgrounds to pursue innovative approaches utilizing minimally invasive arterial revascularization.

Clinical trials are of utmost importance in the assessment of new technologies to ascertain clinical efficacy and safety, thereby prompting adoption for clinical use following regulatory approval. A number of clinical studies assessing technologies in endovascular lower limb arterial revascularization have recently been published. However, substantial variability in endpoint definitions has created a significant barrier for comparison of results across these trials.² Moreover, previous studies on lower limb peripheral arterial revascularization have rarely described clinical outcomes from a patients' perspective.²

The DEFINE Group was founded in 2006, consisting of a broad interdisciplinary team (interventional angiologists, cardiologists and radiologists as well as vascular surgeons, an endovascular neurosurgeon and non-invasive vascular medicine specialists) from Europe and the United States. The mission of this first DEFINE effort was to create a set of definitions which would increase consistency in future peripheral endovascular revascularization trials. The DEFINE Group reviewed the present literature and, after extensive correspondence and meetings, proposed the definitions outlined in the present manuscript. Two meetings including all authors of the manuscript, along with representatives of the United States Food and Drug Administration (FDA) and commercial device manufacturers were held in Washington, DC, in July 2007 and in New York, NY, in November 2007. Several teleconferences were also required to continue the process.

Key components of this effort included definitions for baseline clinical and anatomic characteristics, clinical outcomes relevant to the patients, morphologic outcomes, and complications. Existing standards for reporting lower extremity ischemia were modified and updated, if necessary, to apply specifically to peripheral endovascular procedures and to reflect new insights that have emerged over the last decade.²⁻⁵ Given the contribution by the multidisciplinary scientific members and the regulatory authorities, we

hope that the definitions described in the present manuscript will be applicable for future clinical investigations.

Proposed Baseline and Endpoint Definitions

Patient clinical and anatomical baseline characteristics

Baseline definitions include descriptions of clinical patient characteristics and of the characteristics of the vascular lesion(s) that are to be treated with the endovascular therapy under investigation.

Pre-treatment evaluation should include objective and quantitative measures of disease severity, measurement of functional status and a description of known atherosclerotic risk factors which may have an impact on procedural and clinical outcomes (Table 1).

Clinical evaluation

Patients with intermittent claudication (IC) and those with critical limb ischemia (CLI) should be evaluated separately in outcomes analyses. Baseline clinical evaluations should include anatomic descriptions and functional status, as well as quality of life.

Functional status at baseline

Disease severity in patients with chronic lower limb ischemia should be objectively described according to criteria proposed by Rutherford (Appendix).³

Functional status must be quantified by **standardized treadmill testing** using a graded exercise treadmill protocol (speed constant at 2 miles per hour [3.2 km/h], 2% increase in grade every 2 minutes) in all patients studied for IC.⁶ This treadmill test should be performed until claudication pain occurs or to a maximum of 5 minutes. Changes in claudication onset time (COT: time after initiation of exercise when the patient first experienced symptoms of claudication) and absolute claudication time (ACT: time after initiation of exercise until he/she can not walk further due to severe claudication pain) are to be reported in minutes and seconds. Patients who are not able or willing to undergo standardized treadmill testing should be excluded from IC trials.

Table 1 Patient clinical and anatomical baseline characteristics

- Separate outcome reporting for patients with claudication and critical limb ischemia.
- Rutherford stages at baseline.
- In claudicants: standardized treadmill testing (2 miles per hour [3.2 km/h] at a 12% grade or 2 miles per hour [3.2 km/h] with 2% increase in grade every 2 minutes); claudication onset time (COT) and absolute claudication time (ACT).
- Quality of life at baseline: EuroQOL 5 Dimension.
- Walking ability: walking impairment questionnaire.
- In claudicants: ankle-brachial index (ABI) at rest and after exercise.
- In patients with critical limb ischemia: systolic ankle pressure and ABI.
- Oscillographic reading or toe pressure measurement if ABI cannot be appropriately measured.
- Risk factors and comorbidities: Age, gender, race, hypertension, hyperlipidemia, diabetes mellitus, smoking, ischemic heart disease, congestive heart failure, renal insufficiency, cerebrovascular disease.
- Medication: Anticoagulants, antithrombotic agents, statins, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists.
- Anatomic levels, arterial segments, arterial in- and outflow, involvement of arterial origin/ostium, lesion length, degree of obstruction (as determined by intra-arterial pressure measurement, intravascular ultrasound, angiography, magnetic resonance or computed tomography angiography or by duplex ultrasound, calcification (none, moderate, heavy).

Quality of life at baseline

The EuroQol 5 Dimensions (EQ5D) is recommended to be used to measure quality of life,⁷ whereas the walking impairment questionnaire is recommended to assess walking distance and speed of patients with IC.^{7,8}

Hemodynamic evaluation at baseline

In patients with IC, ankle brachial index (ABI) measurements at rest and after treadmill exercise (after reaching the absolute claudication distance, ACD) should be performed according to the AHA recommendations.^{5,9} In patients with CLI, only systolic ankle pressure, ABI and digital pressures or photoplethysmographic waveforms at rest are required.

In scenarios in which the ABI cannot be measured, such as in case of medial arterial calcification (e.g. diabetes mellitus or renal insufficiency), photoplethysmographic or oscillometric reading or toe pressure measurement and determination of the toe brachial index should be used.^{3,5,10}

Risk factors and comorbidities

The following risk factors and comorbidities should be recorded:

- Age
- Gender
- Race

- Hypertension, as defined by the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure¹¹ or if the patient is on antihypertensive therapy for the indication of hypertension:
 - Normal blood pressure: systolic < 120 mmHg and diastolic < 80 mmHg
 - Prehypertension: systolic 120–139 mmHg or diastolic 80–89 mmHg
 - Stage 1 hypertension: systolic 140–159 mmHg or diastolic 90–99 mmHg
 - Stage 2 hypertension: systolic \geq 160 mmHg or diastolic \geq 100 mmHg
- Hyperlipidemia: Patients with hyperlipidemia as defined by the accepted standards or National Cholesterol Education Program Adult Treatment Panel III or if patient is taking blood lipid-lowering medication for the indication of hyperlipidemia¹²
- Diabetes mellitus: HbA1c > 7% or if or if patient consumes oral hypoglycaemic agents¹³
- Smoking: Current smoking status (active/previous/never), and if ever smoked, include number of pack years (i.e. number of packs smoked daily multiplied by the number of years smoked), as well as the number of years since the patient last smoked tobacco
- Ischemic heart disease¹⁴: History of myocardial infarction (Q or non-Q wave MI), angina pectoris, previous percutaneous or surgical coronary revascularization, positive exercise test, anti-anginal therapy
- Congestive heart failure (according to New York Heart Association Classification I to IV, ejection fraction < 40%)
- Renal insufficiency: glomerular filtration rate < 60 ml/min (calculated according to Cockcroft formula¹⁵)
- Cerebrovascular disease: known carotid artery disease and history of minor or major stroke or transient ischemic attack (TIA)

Medication usage

Pre-, peri-, and post-procedural medications should be specified as follows (including generic name, dose, frequency, and (if possible) duration of use):

- Anticoagulants (warfarin, unfractionated or low molecular weight heparins, etc)
- Antithrombotic agents (acetylic salicylic acid, clopidogrel, ticlopidine, glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, etc)
- Statins or other lipid lowering agents
- Beta-blockers
- Angiotensin converting enzyme inhibitors
- Angiotensin-II receptor antagonists
- Insulin and oral hypoglycaemic agents
- Medications for the treatment of IC (ie cilostazol, pentoxifylline, etc.)

Baseline anatomic characteristics

Baseline anatomic characteristics should be reported for all enrolled patients: anatomic levels, arterial segments, inflow, outflow, involvement of ostium, along with

specific location of lesion within the named vessel(s), lesion length, stenosis or occlusion; degree of thrombus and calcification. The TASC lesion classification,^{10,16} although commonly utilized, may not be the ideal schema,¹⁷ and we suggest a more complete description of the arterial lesion.

Anatomic levels

- aortoiliac level (distal limit: deep circumflex iliac artery, inguinal ligament)
- femoropopliteal level (distal limit: origin of anterior tibial artery)
- crural level (including foot arteries)

Multilevel disease is defined as presence of significant obstructive lesions at more than one level. The right and left leg are considered separately. Thus, the combination of a lesion in the left common iliac combined with a lesion in the left popliteal artery equals multilevel disease, whereas presence of a lesion in the left common iliac combined with a lesion in the right popliteal artery is considered bilateral single level disease.

Arterial segments

Segments refer to specific locations in which patient outcomes of endovascular therapy may differ. The following segments should be differentiated:

- Infra-renal abdominal aorta
- Common iliac artery
- Internal iliac artery
- External iliac artery
- Common femoral artery
- Deep femoral (profunda femoris) artery
- Superficial femoral artery (ends upon exiting adductor canal of Hunter angiographic approximation: crossing of artery over medial cortex of femur when viewed in an anterior-posterior projection).
- Popliteal artery, subdivided into:
 - P1 segment (above knee popliteal artery): from Hunter's canal to proximal edge of patella
 - P2 segment: from proximal part of patella to center of knee joint space
 - P3 segment (below knee popliteal artery): from center of knee joint space to origin of anterior tibial artery
- Tibioperoneal trunk (from the origin of the anterior tibial artery to the bifurcation of the posterior tibial and peroneal artery)
- Proximal anterior tibial artery (from origin to longitudinal midpoint of the tibial shaft)
- Proximal posterior tibial artery (from origin to longitudinal midpoint of the tibial shaft)
- Proximal peroneal artery (from origin to longitudinal midpoint of the tibial shaft)
- Distal anterior tibial artery (from the longitudinal midpoint of the tibial shaft to the level of the upper part of the tibio-talar joint space)
- Distal posterior tibial artery (from the longitudinal midpoint of the tibial shaft to the level of the distal tip of the medial malleolus)

- Distal peroneal artery to (from the longitudinal midpoint of the tibial shaft to its normal terminus above the ankle mortise).
- Dorsalis pedis artery (distal to the tibio-talar joint space)
- Posterior tibial artery at foot level (distal to the tibio-talar joint space)
- Plantar and pedal foot arcades
- Digital arteries

Arterial inflow and outflow

Arterial inflow is defined with regard to the above-defined anatomic levels (2.5.1). The inflow to a vascular lesion at a certain level refers to the combined levels proximal to the lesion. Thus, for a lesion in the superficial femoral artery (i.e. femoropopliteal level), arterial inflow refers to the common femoral artery and the aortoiliac level. For a lesion in the anterior tibial artery (i.e. crural level), inflow refers to both the aortoiliac and femoropopliteal levels. Good inflow implies straightline vessels proximal to a site that are free of hemodynamically significant obstruction (i.e. $\geq 50\%$ stenosis) of the inflow arteries.

Impaired inflow means that the vessels proximal to the site contain hemodynamically significant lesions (i.e. $\geq 50\%$), whereas impaired inflow represents the presence of such lesions. Arterial outflow is defined accordingly, with the outflow of a vascular lesion being defined as the combined levels distal to a lesion. The superficial and deep femoral arteries are the runoff vessels for iliac artery procedures, and the tibial arteries are the runoff vessels for femoropopliteal procedures.

For further definition of below-the-knee outflow, the number of patent arteries with patency directly to the foot arteries should be specified. Thus, for a lesion in the superficial femoral artery (i.e. femoropopliteal level) with an occlusion of the peroneal artery, arterial outflow should be "2-vessel outflow". Moreover, to define arterial outflow in the foot, the patency of both the dorsal and plantar pedal arch should be specified ("yes/no").

Involvement of arterial origin/ostium

It should be provided whether or not the lesion involves the origin/ostium of a specific artery.

Lesion length

We propose to define the following lesion lengths for use in all segments that apply to stenoses and occlusions alike:

- Focal lesions: ≤ 1 cm
- Short lesions: >1 and < 5 cm
- Intermediate lesions: ≥ 5 cm and < 15 cm
- Long lesions: ≥ 15 cm

In case of vessel occlusion within a stenosed segment, both the length of the stenosed segment and the length of the occluded segment should be reported.

Degree of obstruction

Hemodynamic significance of a lesion can be assessed utilizing the following measurement techniques (listed in a hierarchical order):

- 1.) Intra-arterial measurement of mean translesional pressure gradient >10 mmHg at rest or during pharmacological dilatation of the arterial bed (by papaverine, tolazolin, nitroglycerine, or a similar substance) as assessed by means of two simultaneous measurements using two pressure channels proximally and distally to the lesion.
- 2.) Intravascular ultrasound (IVUS) measurements indicating $\geq 50\%$ diameter stenosis or $\geq 75\%$ area stenosis.
- 3.) Intra-arterial digital subtraction angiography indicating $\geq 50\%$ diameter stenosis by visual estimation or by quantitative vessel analysis software assessing at least two different angiographic projections.
- 4.) Contrast-enhanced magnetic resonance or multi-slice computed tomography angiography using state-of-the-art imaging protocols indicating $\geq 50\%$ diameter stenosis or $\geq 75\%$ area stenosis.
- 5.) Duplex ultrasound indicating $\geq 50\%$ diameter stenosis as defined by a peak systolic velocity index (defined as the ratio of intra-stenotic peak systolic velocity to pre-stenotic peak systolic velocity) > 2.4 .¹⁸

Calcification

A semi quantitative distinction between no, moderate, and heavy calcification at the site of the lesion should be provided according to findings on the fluoroscopic image obtained prior to the intervention.

Endpoint Definitions: Clinical Outcomes and Complications

Endpoint definitions encompass immediate procedural success, complications, and clinical outcome during follow-up (Tables 2a–d). All failures occurring within 30 days of the procedure (i.e. absence of procedural success) are considered “acute procedural failures”, and are attributed to the procedure. To evaluate clinical outcomes we propose a **minimum follow-up** period of 12 months, which is considered short-term follow-up. **Mid-term follow-up** refers to follow-up periods of greater than 1 year to 3 years and **long-term follow-up** to be greater than 3 years of post-procedural follow-up. Special care was taken to grant applicability of clinical outcome definitions (chapters 3.2 and 3.3) also to trials assessing the efficacy of open surgical revascularization.

Table 2a Immediate outcome

- Procedural success: Combination of technical success, device success and absence of procedural complications.
- Technical success: successful vascular access and completion of the endovascular procedure and immediate morphological success with less than 30% residual diameter reduction of the treated lesion on completion angiography.
- Device success: exact deployment of the device according to the instructions for use as documented with suitable imaging modalities and in case of digital subtraction angiography, in at least two different imaging projections.

Table 2b Clinical outcome in patients treated for claudication

- Distribution of Rutherford stages during follow-up as compared to baseline.
- Changes in claudication onset time (COT) and absolute claudication time (ACT).
- Change in quality of life according to EuroQOL.
- Change in walking ability according to walking impairment questionnaire.
- Primary sustained clinical improvement (sustained upward shift of ≥ 1 category on Rutherford classification without the need for repeated target lesion revascularization (TLR) in surviving patients).
- Secondary sustained clinical improvement (sustained upward shift of ≥ 1 category on Rutherford classification including the need for repeated TLR in surviving patients).
- Primary sustained resolution of symptoms from PAD (sustained absence of claudication without the need for repeated TLR in surviving patients).
- Secondary sustained resolution of symptoms from PAD (sustained absence of claudication including the need for repeated TLR in surviving patients).
- Clinical deterioration (downgrade of ≥ 1 category on the Rutherford classification after endovascular treatment).
- Immediate hemodynamic improvement: increase in ABI of ≥ 0.10 or to an ABI ≥ 0.9 .
- Sustained hemodynamic improvement: persistent improvement of ABI-values with ≥ 0.10 as compared to baseline values or to ABI ≥ 0.9 throughout follow-up without need for repeated TLR in surviving patients.
- 30-day (procedure-related and all-cause) mortality and mortality during follow-up.
- Need for minor (below the ankle) and major (above the ankle) unplanned amputation. Major amputation specified as below-the-knee and above-the-knee amputations. Planned versus unplanned amputations.

Procedural success

Technical or device success is defined as achievement of a final residual diameter stenosis of $<30\%$ on the procedural completion angiogram, using the assigned device only, whereas lesion success is defined as achievement of $<30\%$ residual stenosis using any percutaneous method.

Procedural success is technical or device success without the occurrence of major adverse events during the hospital stay.

Clinical outcomes for treatment of IC

Change in functional status in patients treated for IC

Change in disease severity should be described according to the categories proposed by Rutherford (Appendix).³

Change in walking capacity should be assessed to measure the objective functional response to therapeutic interventions according to the above-mentioned standardized treadmill protocols.^{2,10,16} Changes in **claudication onset time** (COT, defined as the time after initiation of exercise when the patient first experienced symptoms of claudication) and **absolute claudication time** (ACT, defined as the time after initiation of exercise until he/she can not

Table 2c Clinical outcome in patients treated for critical limb ischemia

- Distribution of Rutherford stages during follow-up as compared to baseline.
- Change in quality of life according to EuroQOL.
- Primary sustained clinical improvement (upward shift on the Rutherford classification to a level of claudication without the need for repeated TLR in surviving patients without the need for unplanned amputation).
- Secondary sustained clinical improvement (upward shift on the Rutherford classification to a level of claudication, including the need for repeated TLR in surviving patients without the need for unplanned amputation).
- Clinical deterioration (downgrade of ≥ 1 category on the Rutherford classification after endovascular treatment).
- Immediate hemodynamic improvement: increase in ABI of ≥ 0.10 or to an ABI ≥ 0.9 .
- Sustained hemodynamic improvement: persistent improvement of ABI-values with ≥ 0.10 as compared to baseline values or to ABI ≥ 0.9 throughout follow-up without need for repeated TLR in surviving patients.
- 30-day (procedure-related and all-cause) mortality and mortality during follow-up.
- Need for minor (below the ankle) and major (above the ankle) unplanned amputation. Major amputation specified as below-the-knee and above-the-knee amputations. Planned versus unplanned amputations.

walk further due to severe claudication pain) must be reported in minutes and seconds.

Change in disease severity in patients treated for IC

Sustained clinical improvement has to be regarded a primary clinical endpoint in trials assessing outcomes of patients with IC.² **Primary sustained clinical improvement** is defined as sustained upward shift of at least one category on the Rutherford classification³ (Appendix) without the need for repeated target lesion revascularization (TLR) in surviving patients (i.e. dead patients will be censored at the time point when they were last examined). **Secondary sustained clinical improvement** is defined as sustained upward shift of at least one category on the Rutherford classification³ (Appendix) including the need for repeated TLR in surviving patients.

Moreover, **primary sustained resolution of symptoms from PAD** is defined as sustained absence of IC without the need for repeated TLR in surviving patients. In contrast, **secondary sustained resolution of symptoms from PAD** describes sustained absence of IC including the need for repeated TLR in surviving patients.

Clinical deterioration should be described as a downgrade of ≥ 1 category on the Rutherford classification (Appendix) as a result of endovascular treatment (improvements that occur after secondary procedures are not included, i.e. this endpoint does not include repeated TLR/TER). Furthermore, distribution of clinical stages according to Rutherford³ (Appendix) during all follow-up visits should be given as compared to baseline.²

No change in functional outcome will be captured as absence of primary or secondary sustained clinical improvement or absence of deterioration. Thus, in the cumulative

Table 2d Complications

- Adverse events (AE).
- Serious adverse events (SAE).
- Adverse device effect.
- (Serious) Adverse device effect (SADE).
- Unanticipated adverse device effect (UADE).
- Major Adverse Event (MAE).

Examples of complications according to different categories

- Access site complication:
 - Hematoma/bleeding; arterial/venous occlusion/thrombosis; severe vasospasm; intimal injury/dissection; pseudoaneurysm; AV fistula; vascular perforation or rupture; arterial embolizations at puncture site.
- Vessel specific complication:
 - Hematoma/bleeding; arterial/venous occlusion/thrombosis; severe vasospasm; intimal injury/dissection; pseudoaneurysm; AV fistula; vascular perforation or rupture; arterial embolizations remote from puncture site.
- Organ specific complication:
 - Neurological: TIA, Minor and major stroke, seizure.
 - Cardiovascular: Hypotension or hypertension requiring treatment, arrhythmia requiring treatment, myocardial ischemia/infarction, chronic heart failure.
 - Respiratory: Profound Hypoxia, pulmonary edema, respiratory arrest, pulmonary embolism, pneumothorax, local infection, septicemia/bacteremia.
 - Gastrointestinal: Gastric bleeding, pancreatitis, peritonitis, abscess, unintended perforation of hollow viscus.
- Systemic complication:
 - Allergic/anaphylactoid reaction, renal failure, tissue extravasation, idiosyncratic reaction to drug, fluid/electrolyte imbalance.

analysis for primary or secondary sustained clinical improvement patients not experiencing any change in the Rutherford classification (Appendix) will have to be *uncensored*, whereas they will have to be *censored* in the analysis for clinical deterioration.

Clinical outcomes for treatment of critical limb ischemia (CLI)

Change in functional status in patients treated for CLI

Change in disease severity should be described according to the categories of the criteria proposed by Rutherford (Appendix).³

Change in disease severity in patients treated for CLI

Sustained clinical improvement has to be regarded a primary clinical endpoint.² Treadmill testing is not required in patients treated for CLI. **Primary sustained clinical improvement** is defined as an upward shift on the Rutherford classification (Appendix) to a level of IC without the need for repeated TLR in surviving patients without the need for unplanned amputation. **Secondary sustained clinical improvement** is defined as an upward

shift on the Rutherford classification (Appendix) to a level of IC, including the need for repeated TLR in surviving patients without the need for unplanned amputation.

Clinical deterioration is defined as a downgrade of ≥ 1 category on the Rutherford classification (Appendix) as a result of endovascular treatment (improvements that occur after secondary procedures are not included, i.e. this endpoint does not include repeated TLR/TER). Furthermore, distribution of clinical stages according to Rutherford³ (Appendix) during all follow-up visits should be given as compared to baseline.²

No change in functional outcome will be captured as absence of primary or secondary sustained clinical improvement or absence of deterioration. Thus, in the cumulative analysis for primary or secondary sustained clinical improvement patients not experiencing any change in the Rutherford classification (Appendix) will have to be *uncensored*, whereas they will have to be *censored* in the analysis for clinical deterioration.

Hemodynamic outcome

Immediate hemodynamic improvement after endovascular revascularization is defined as ankle brachial index (ABI) improvement of ≥ 0.10 or to an ABI ≥ 0.9 .

Sustained hemodynamic improvement is defined as persistent improvement of ABI-values with ≥ 0.10 as compared to baseline values or to an ABI ≥ 0.9 throughout follow-up without the need for repeated target lesion revascularization (TLR) in surviving patients (i.e. patients that died have to be censored in this analysis).³

Desirable for review of data quality is the declaration of **mean and median ABI at all follow-up visits** as compared to baseline.

In case ABI cannot be appropriately measured such as in patients with medial arterial calcification (e.g. diabetes mellitus or renal insufficiency), photoplethysmographic or oscillometric determination of toe pressure with the calculation of the toe-brachial index should be used.^{3,5,10}

Mortality

Causes of death associated with the endovascular procedure (procedure related mortality, i.e. mortality within 30 days post-procedure or mortality during a hospitalization > 30 days due to the procedure) should be reported separately as well as overall mortality.²

Amputation

Need for **minor** (below the ankle) and **major** (above the ankle) **unplanned amputation** have to be regarded as major outcome criteria in trials, but should be reported separately for patients with IC and chronic CLI.² Major amputation rates should be reported and specified as below-the-knee and above-the-knee amputations. Furthermore, planned and unplanned amputations should be reported separately.

Complications

Complications should be reported according to the general clinical research guidelines and the applicable (local) laws. For this purpose, reference is made to the International Society for Standardization (ISO) 14155,¹⁹ the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines²⁰ and the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) chapter §812.3.²¹

The primary mode of action of the investigational product as well as the region where the trial is performed will determine which regulations must be used. Additionally, combined products or non-medical devices such as cell therapy may require using a combination of these guidelines.

Any untoward occurrence in a subject should be differentiated as follows:

- Adverse events (AE)
- Serious adverse events (SAE)
- Adverse device effect
- (Serious) Adverse device effect (SADE)
- Unanticipated adverse device effect (UADE)
- Major Adverse Event (MAE)

In case the investigational product is classified different than a medical device, other general definitions may be applicable (e.g. Suspected Unexpected Serious Adverse Reaction [SUSAR]).

Adverse events (AE) - ISO 14155-1 (3.2)

An AE is defined as any untoward medical occurrence in a subject.

This definition, however, does not imply that there is a relationship between the adverse event and the device under investigation.

Serious adverse event (SAE) - ISO 14155-1 (3.19)

A SAE is an AE that

- led to a death.
- led to a serious deterioration in the health of the subject that
 - resulted in a life-threatening illness or injury.
 - resulted in permanent impairment of a body structure or a body function.
 - required inpatient hospitalization or prolongation of existing hospitalization.
 - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or bodily function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect

All AEs whether or not serious must be rated "related or unrelated to the investigational product".

Adverse device effect - ISO 14155-1 (3.1)

An adverse device defect is defined as any untoward and unintended response to a medical device. This definition

includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device as well as any event that is a result of a user error.

Serious adverse device effect - ISO 14155-1 (3.19)

A serious adverse device effect is defined as adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated adverse device effect - FDA 21

CRF § 812.3 (s)

Any serious adverse effect on health or safety or any life-threatening problem or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects is defined as an unanticipated adverse device effect.

Major Adverse Event (MAE)

The MAE definition is different for each protocol and must be defined in the protocol.

It is recommended to use an independent committee (Clinical Event or Data Safety and Monitoring Committee) for the adjudication of the SAEs to determine if an event is a MAE or not. The CEC may define, prior to the start of the study, the type of events that will be reviewed and adjudicated.

All AEs and SAEs must appear in the final report. Information related to the adjudication of the events may be added. Reporting by the manufacturer/sponsor to the regulatory bodies must be performed according the specified national regulations.

The following **Major Adverse Event definition** is recommended for studies involving patients with peripheral vascular disease:

- All deaths.
- Major amputation, planned and unplanned.

Additionally, the following occurrences should appear in the related publication or at a minimum in the final trial report:

- Procedural related serious adverse events.
- Investigational product related serious adverse events.
- Device failure or malfunction.

Next to the MAE, the reported (serious) adverse events should be classified and reported according to the following four complication categories: access site complications, vessel specific complications (treatment site including distal to the site), organ-specific complications, systemic complications (Table 2d).

Morphologic Outcome

We suggest replacing the term “patency” with “**absence of binary restenosis**”, which equals $\geq 50\%$ re-obstruction of the target lesion (Table 3). Moreover, cumulative rates of **reocclusions** (defined as complete occlusion of the initially treated target lesion).

We suggest that independent **core laboratory analysis** of angiographic and duplex ultrasound images be mandatory for assessment of new devices.

Intra-arterial **angiography** remains the current gold standard for depiction of lesions in peripheral arteries.⁵ Precise quantitative angiographic assessment of the target lesion with objective measures such as the percent diameter stenosis relative to the adjacent arterial segments is warranted.

Especially in trials comparatively reporting on different peripheral endovascular revascularization strategies (i.e. using stents or other devices aiming at the prevention of restenosis) angiographic analysis using **quantitative vessel analysis software** derived from the methods established for coronary artery analysis is desirable.^{22–25} However, we acknowledge that continued expansion of self-expandable stents might hamper comparison of immediate post-procedural results with follow-up imaging.

Moreover, **intravascular ultrasound (IVUS)** measurements indicating $\geq 50\%$ diameter stenosis or $\geq 75\%$ area stenosis can be used to determine restenosis.

Due to the less invasive character of the examination along with ethical considerations regarding serial intra-arterial angiography for study purposes, we recognize **duplex ultrasonography** for detection of binary restenosis. Unfortunately, duplex ultrasonography can be associated with a considerable inter- and intraobserver variability, especially in vessels as heterogeneous as the iliac and below-the-knee arteries,^{26,27} and, as opposed to angiography, does not help in precisely quantifying the percentage of stenosis in lower limb arteries.²⁸ Therefore, inter- and intra-observer variability of the performing ultrasound

Table 3 Morphologic outcome

- Cumulative rates of absence of binary restenosis ($\geq 50\%$ re-obstruction of the target lesion) and rates of reocclusions as assessed by:
 - Intra-arterial angiography in at least two different projections (preferably with quantitative vessel analysis).
 - IVUS measurements indicating $\geq 50\%$ diameter stenosis or $\geq 75\%$ area stenosis can be used to determine restenosis.
 - Duplex ultrasound (peak systolic velocity index greater than 2.4 at the target lesion).
 - Magnetic resonance and computed tomography angiography (pending positive results from accuracy studies assessing their ability to quantify arterial obstructions as outlined above).
- Repeated target lesion revascularization (TLR) rate.
- Repeated target extremity revascularization (TER) rate.
- Reporting of device-specific problems such as stent fractures.
- Independent core laboratory analysis of arterial imaging is warranted.

laboratory and core laboratory assessment should be included in the report. For uniform reporting standards, we suggest to define binary restenosis on duplex ultrasonography by a peak systolic velocity ratio greater than 2.4 at the target lesion as initially proposed by Ranke.¹⁸ Moreover, we recommend the use of rulers to document the exact distance of the lesion from anatomical landmarks (such as the patella or the iliac or femoral bifurcation) at baseline and during follow-up visits. Formal instruction by the independent core lab to the sites on the annotation of duplex ultrasound images to insure accurate image location to target lesion must be routine and clearly described.

Magnetic resonance and computed tomography angiography might become valuable tools in morphological follow-up after endovascular interventions. However, dedicated studies assessing their accuracy are currently lacking.

If non-angiographic modalities are used for follow-up, they must be compared to the same modality over time.

Since the terms primary patency, primary assisted patency, and secondary patency are mainly used in surgical trials¹⁰ and their use may be confusing after endovascular therapy, we propose, in accordance with coronary trials, the following terminology to describe need for re-interventions: Rates of **repeated target lesion revascularization (TLR)** should be reported in surviving patients with preserved limb to express the frequency of the need for repeated procedures (endovascular or surgical) due to a problem arising from the lesion (+1 cm proximally and distally to include edge phenomena) initially treated. **Repeated target extremity revascularization (TER)** should be reported in surviving patients with preserved limb to express the frequency of the need for repeated procedures (endovascular or surgical) due to a problem arising remote from the lesion initially treated. A subtraction of TLR from TER rates yields the rate of revascularizations performed due to progression of atherosclerosis.

Device-specific problems such as stent fractures should be reported according to specific standards.²⁹

Statistical Analysis

Number of patients lost to follow-up should not exceed 5% at 12 months and reasons for loss of follow-up should be noted.

Procedural success should be reported both on an **intention-to-treat** and on **per-protocol** analysis.

A **prospective randomized controlled study design** should be preferred to reliably assess the efficacy of endovascular revascularization.

Treatment outcomes should be based on the intent to treat and must include all patients who consent to undergo the procedure.

Except for analysis of technical success, periprocedural complications, and quantitative angiographic outcomes, the above-mentioned endpoints should be calculated using cumulative analyses (i.e. according to the life-table method³⁰) or according to the method proposed by Kaplan-Meier.³¹ Thus, patients who have reached specific clinical endpoints (e.g. repeated TLR) should be uncensored within this cumulative analysis and also be excluded from further follow-up assessments such as ABI comparisons

or descriptions of clinical stage beyond the time of uncensoring. Dead patients should be censored on the day between the time point when they were last examined and the actual date of death.

Patients undergoing further revascularizations outside the initially treated target lesion (repeated TER) should not be uncensored since this represents a progression of atherosclerosis rather than a failure of the treatment of the initially treated lesion.

Conclusions

With the present consensus document the DEFINE group aimed to establish definitions as a point of reference for future clinical trials. Particular care was taken to define clinical outcomes from a patient's perspective. Importantly, clinical outcome definitions can be equally applied to future trials comparing endovascular and open surgical revascularization for chronic lower limb ischemia. These definitions represent mandatory requirements to obtain comparability of studies dealing with endovascular therapy of peripheral arteries to further elucidate and prove long-term credibility of this method. Adherence to these definitions is recommended for future publications.

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Appendix

Clinical categories of chronic limb ischemia according to Rutherford³

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic - no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise ^b ; AP after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise ^b and AP after exercise <50 mm Hg
II ^a	4	Ischemic rest pain	Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg

(continued)

Grade	Category	Clinical description	Objective criteria
III ^a	5	Minor tissue loss - nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg
	6	Major tissue loss - extending above TM level, functional foot no longer salvageable	Same as category 5

AP, Ankle pressure; PVR, pulse volume recording; TP, toe pressure; TM, transmetatarsal.

^a Grades II and III, categories 4, 5, and 6, are embraced by the term chronic critical ischemia.

^b Five minutes at 2 mph on a 12% incline.

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