

Acute Stroke Imaging Research Roadmap II

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Special Report

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From the Department of Radiology, Division of Neuroradiology (M.W.) and Department of Neurology (E.C.H.), University of Virginia, Charlottesville, VA; Department of Radiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (M.W.); Department of Neurology, Stanford University School of Medicine, Stanford, CA (G.W.A., R.B., S.C., M.G.L., G.Z.); Department of Neurology, University of Cincinnati Neuroscience Institute, Cincinnati, OH (J.P.B., P.K.); Departments of Clinical Neurosciences and Radiology (A.M.D.) and Calgary Stroke Program, Departments of Clinical Neurosciences and Radiology (B.K.M.), Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada; Department of Neurology, Academic Neuroradiology, Center for Stroke Research Berlin, Charité—Universitätsmedizin Berlin, Berlin, Germany (J.B.F.); Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (J.F., G.T.); Department of Neurology, University of Texas Health Science Center, Houston, TX (J.C.G.); The Stroke Group, Centennial, CO (G.H.); Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute, Pittsburgh, PA (T.G.J.); UPMC Center for Neuroendovascular Therapy, Pittsburgh, PA (T.G.J.); Department of Medicine & Therapeutics, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, United Kingdom (K.R.L.); Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA (M.H.L., O.W., A.J.Y., W.A.C., P.W.S.); Department of Neurology, UCLA Stroke Center, Los Angeles, CA (D.S.L., J.A., J.L.S.); Stroke Diagnostics and Therapeutics Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD (M.L., L.L.L.); National Institutes of Health, Bethesda, MD (M.L., L.L.L.); Department of Neurology, Institute of Neurosciences and Psychology, University of Glasgow, Southern General Hospital, Glasgow, Scotland, United Kingdom (K.W.M.); Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle, New South Wales, Australia (M.W.P.); Department of Neuroradiology, Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany (R.v.K.); Department of Clinical Neurosciences, Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom (J.M.W., T.C.C.); Department of Neurology, Comprehensive Stroke Center, University of Alabama Hospital, Birmingham, AL (A.V.A.); Department of Medical Imaging, University of Toronto and Sunnybrook Health Science Centre, Toronto, Canada (R.I.A.); INSERM U894, Sorbonne Paris Cité, Paris, France (J.-C.B.); and Department of Clinical Neurosciences, University of Cambridge, United Kingdom (J.-C.B.); Department of Medicine, The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia (F.C., G.A.D.); Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia (B.C.V.C., S.M.D.); Department of Radiology, Washington University School of Medicine, St. Louis, MO (C.P.D.); Department of Diagnostic Radiology, Hokkaido University Hospital, Sapporo, Japan (K.K.); Department of Medical Imaging, The University of Western Ontario, London, Ontario, Canada (T.-Y.L.); Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD (R.L.); Biomedical Research Imaging Center (W.L.), Departments of Radiology, Neurology, Biomedical Engineering (W.L.), and School of Pharmacy (W.L.), University of North Carolina at Chapel Hill, NC; Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA (P.L.); Department of Neuroradiology, Division of Neuroimaging Sciences, Western General Hospital, Edinburgh, United Kingdom (G.M.); Department of Neurology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland (P.M.); Department of Neurology, International Clinical Research Center, St. Anne's Hospital, Brno, Czech Republic (R.M.); Department of Neurology, Marcus Stroke & Neuroscience Center, Grady Memorial Hospital, Emory University School of Medicine, Atlanta, GA (R.G.N.); Department of Neurology, Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark (L.Ø.); Department of Radiology, IDI, IDIBGI, University Hospital Dr Josep Trueta, Girona, Spain (S.P.); Department of Neuroradiology, University of Kiel, Kiel, Germany (C.H.R.); Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI (H.A.R.); Department of Radiology, Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY (P.C.S.); Department of Radiology, Institute for Biomedical Sciences, Iwate Medical University, Yahaba, Japan (M.S.); Department of Neurology, Johannes Wesling Klinikum Minden, Minden, Germany (P.D.S.); Comprehensive Stroke Center, Department of Neurology, University of Alabama at Birmingham, AL (G.T.); Second Department of Neurology, School of Medicine, University of Athens, Athens, Greece (G.T.); Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA (L.R.W.); Department of Neuroradiology, Institute for Ageing and Health, Newcastle University, United Kingdom (P.M.W.); Departments of Neurology, Neurosurgery, and Radiology, Medical College of Wisconsin and Froedtert Hospital, Milwaukee, WI (O.O.Z.); Department of Neurology, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH (A.J.F.); Department of Neurology, University of Heidelberg, Heidelberg, Germany (W.H.); Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, (Stroke. 2013;44:00-00.)

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The Stroke Imaging Research (STIR) Group, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored a series of working group meetings >12 months, with the final meeting occurring during the Stroke Treatment Academy Industry Roundtable (STAIR) on March 9 to 10, 2013, in Washington, DC. This process brought together vascular neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke, industry representatives, and members of the US Food and Drug Administration to discuss stroke imaging research priorities, especially in the light of the recent negative results of acute stroke clinical trials that tested the concept of penumbral imaging selection. The goal of this process was to propose a research roadmap for the next 5 years. STIR recommendations include (1) the use of standard terminology, aligned with the National Institute of Neurological Disorders and Stroke Common Data Elements; (2) a standardized imaging assessment of revascularization in acute ischemic stroke trials, including a modified Treatment In Cerebral Ischemia (mTICI) score; (3) a standardized process to assess whether ischemic core and penumbral imaging methods meet the requirements to be considered as an acceptable selection tool in acute ischemic stroke trials; (4) the characteristics of a clinical and imaging data repository to facilitate the development and testing process described in recommendation no. 3; (5) the optimal study design for a clinical trial to evaluate whether advanced imaging adds value in selecting acute ischemic stroke patients for revascularization therapy; and (6) the structure of a stroke neuroimaging network to implement and coordinate the recommendations listed above. All of these recommendations pertain to research, not to clinical care.

Stroke Imaging Terminology

STIR recommends the use of a standard terminology in compliance with the Common Data Elements developed by National Institute of Neurological Disorders and Stroke (http://www.commondataelements.ninds.nih.gov/stroke.aspx#tab=Data_Standards).¹ In addition, the following refinements are proposed.

Perfusion imaging with computed tomography (CTP) or MRI (MRP) needs to be accompanied by an explicit definition of the perfusion parameters that are going to be derived and used, for example, cerebral blood flow, cerebral blood volume, mean transit time, etc, and an explicit definition of the modality-specific imaging acquisition parameters, for example, scan techniques, scanner hardware, postprocessing software and contrast agent characteristics.

Conceptually, ischemic core represents ischemic brain tissue that is irreversibly injured and cannot recover and will proceed to infarction even in the presence of immediate

reperfusion. Penumbra represents functionally impaired ischemic brain tissue that has the potential to recover with early reperfusion, but is at high risk for irreversible injury (infarction) without early reperfusion.²⁻⁴ The penumbra does not include benign oligemia (ie, tissue with mild hypoperfusion unlikely to infarct even in the absence of reperfusion).

It is important to distinguish pathophysiological concepts from operational definitions that use CT or MRI to assess these concepts as part of research studies or clinical trials. CT and MR definitions of ischemic core and ischemic penumbra are probabilistic. Therefore, when the terms of ischemic core and penumbra are used, there should be an explicit qualification in the publication as to the specific (1) imaging technique, (2) perfusion parameter(s), and (3) threshold(s) under discussion.

The term malignant should be reserved for malignant edema, indicating rapidly progressive edema, mass effect, midline shift, and finally herniation with midbrain or brain stem compression. Use of the term malignant to refer to imaging features predictive of poor outcome or low probability of favorable response to therapy is potentially confusing and should be avoided.

Revascularization includes 3 separate concepts: (1) recanalization, which refers to arterial patency; (2) reperfusion, which refers to antegrade microvascular perfusion; and (3) collateralization, which refer to microvascular perfusion via pial arteries or other anastomotic arterial channels that bypass the primary site of vessel occlusion.

Imaging in Acute Ischemic Stroke Clinical Trials

In stroke clinical trials, imaging can be used as an efficacy and/or safety biomarker for patient selection or outcome assessment. Imaging in stroke clinical trials should be targeted to the specific treatment, trial requirements, and goals. The understanding of appropriate imaging modalities, acquisition parameters, thresholds, and postprocessing approaches is evolving as experience accrues. No single imaging approach addresses all issues. Regardless of the imaging techniques used, some general recommendations should be incorporated in clinical trial design involving imaging (Table 1).

Treatment-Relevant Acute Imaging Targets

Different imaging modalities may be optimal for different methods of treatment (intravenous versus endovascular or intra-arterial) and in distinct time windows (early versus late). Moreover, diverse modalities, perfusion parameters, and thresholds may have varying roles for determining potential treatment risks (eg, hemorrhage) versus potential treatment benefits (eg, functional recovery of ischemic brain tissue). Treatment-Relevant Acute Imaging Targets (TRAIT) is meant

South Korea (D.-W.K.); Department of Neurology and the Stroke Center, Georgetown University, Washington, DC (C.K.); Laboratory of Neurobiology, Vesalius Research Center, VIB, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease, University of Leuven (KU Leuven), Leuven, Belgium (V.N.T.); Department of Neurology, University Hospital Leuven, Leuven, Belgium (V.N.T.); Seton/UT Southwestern Clinical Research Institute of Austin, Austin, TX (S.J.W.); and Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Austin, TX (S.J.W.).

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Correspondence to Max Wintermark, MD, UVA Department of Radiology, Neuroradiology Division, Box 800170, Charlottesville, VA 22908. E-mail Max.Wintermark@gmail.com

Table 1. General Requirements for Imaging in Stroke Clinical Trials

Speed: In therapeutic trials, the benefits of additional imaging should be balanced against potential treatment delay; workflow should be optimized on the basis of best practice
Standardization: Acquisition parameters and perfusion post processing should be standardized (by common software processing at centers or centralized processing) and should conform to minimum, protocol-defined, common standards
Quality control: A well-defined image quality control process should be implemented to ensure that the predefined study imaging protocol is respected and to minimize the number of protocol violations
Reproducibility: If imaging is used to define patient selection then either a system for standardized central image processing and automated analysis, or appropriate training for neuroimaging raters at participating centers, should be undertaken. Imaging methods should have demonstrated acceptable interobserver and across-center reliability
Centralization: Central analysis of imaging outcomes should be conducted as the reference standard in multicenter trials. A system for standardized central image processing and interpretation, blinded to clinical information and local investigator decision, should be implemented

to capture imaging elements needed for inclusion (or exclusion) into specific treatment protocols. TRAITs acts as a shorthand term to describe the collection of specific imaging metrics used in protocols and simultaneously reminds trial designers to ensure imaging is directed to the key anatomic or physiological targets of their specific intervention. For revascularization therapies, the TRAIT could be an arterial occlusion, a perfusion defect causing neurological deficits, a penumbral pattern, or some combination of these. In neuroprotective trials, the TRAIT might simply require CT or MRI to confirm the diagnosis of stroke. Research studies and clinical trials should ensure that the proposed imaging is aligned with the TRAITs and should be constant for both arms of the clinical trial.

Imaging for Patient Selection in Stroke Clinical Trials

Potential uses of imaging for patient selection in stroke clinical trials include the approaches listed in Table 2. These uses are not mutually exclusive.

Imaging Selection Biomarkers for Clinical Trials in the 0- to 4.5-Hour Time Window

The positive randomized placebo-controlled trials of intravenous alteplase have been based on risk-minimization using noncontrast CT (NCT) to exclude intracranial hemorrhage and excessive volume of established parenchymal hypoattenuation. There are many unresolved issues on the potential role of advanced imaging selection, particularly in the 0- to 4.5-hour time window (Table 3). When designing trials or studies to address the issues in this time window, the potential value of advanced imaging in this time window must be balanced against the detrimental impact of delaying treatment.

Imaging Selection Biomarkers in the >4.5-Hour Time Window

Reported and ongoing randomized acute stroke trials have been testing the benefit of reperfusion and revascularization in

the >4.5-hour time window. Differential treatment outcomes on different imaging-selected subgroups have been shown in analyses of DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) and DIAS/DEDAS (Desmoteplase in Acute Ischemic Stroke Trial/Dose Escalation of Desmoteplase for Acute Ischemic Stroke) samples. However, a differential treatment effect in imaging-selected subgroups compared with subgroups not undergoing imaging selection has not yet been demonstrated. Imaging paradigms have included MRI diffusion-perfusion mismatch (subgroups of MR RESCUE [Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy], DIAS 1&2, DEDAS, EPITHET [Echoplanar Imaging Thrombolytic Evaluation Trial], IST-3), CT angiography (CTA)-confirmed occlusion (subgroups of IMS-3 [Interventional Management of Stroke Trial-3], IST-3 [International Stroke Trial-3]), and CTP (subgroups of DIAS-2, IST-3).

Ongoing randomized controlled trials of late revascularization are using a range of imaging selection criteria. In addition to proof of large artery occlusion (by CTA, MR angiography [MRA], or thrombus detection on thin slice CT), these criteria are based either on ischemic core size assessment in the context of certain clinical deficits (clinical/ischemic core mismatch), on an estimated mismatch between ischemic core and ischemic penumbra, or on specific imaging findings that provide an estimate of the age of a given ischemic lesion (ie, diffusion weighted imaging [DWI]-fluid attenuated inversion recovery [FLAIR] mismatch).

Clinical Trial to Test the Added Value of Imaging in Selecting Patients for Acute Revascularization Therapy

Because there are several ongoing efforts to assess the optimal therapy for stroke in the different time windows, it is a complex matter to test the added value of advanced imaging in addition to testing different interventions. Currently, it is reasonable to obtain the same advanced imaging TRAIT in

Table 2. Uses of Imaging in Stroke Clinical Trials

Selection of patients with imaging-confirmed diagnosis of stroke
Selection of patients appropriate to a mechanistic hypothesis: Treatment-Relevant Acute Imaging Target (TRAIT)
Exclusion of patients on the basis of imaging-defined risk of therapeutic intervention (eg, hemorrhage if testing thrombolytic)
Exclusion of patients on the basis of imaging-defined futility of therapeutic intervention
Sample enrichment, selection of a sample likely to maximize a treatment effect
Assessment of therapeutic intervention on TRAIT (eg, recanalization, reperfusion, and infarct size/growth)

Table 3. Unresolved Issues With Imaging Selection Biomarkers for Clinical Trials

Added value of vascular imaging
Added value of perfusion (penumbral) imaging
Whether additional imaging selects patients currently excluded from treatment
Whether additional imaging excludes patients from treatment who may otherwise benefit
Whether the additional time related to additional imaging is justified
Whether the optimal additional imaging modality varies depending on the time window and the type of treatment
Clinical relevance of the signal intensity of the diffusion weighted imaging abnormality
MRI vs CT in patient selection
Use of extracellular contrast agents for CTP and MRP

CT indicates computed tomography; CTP, perfusion imaging with CT; and MRP, perfusion imaging with MRI.

all arms of therapeutic clinical trials, which will allow secondary analyses addressing the value of imaging, while the primary focus of the trial is on therapy evaluation. Eventually, a clinical trial should be conducted to assess the added value of advanced imaging compared with what could have been extracted just from clinical information alone.

Imaging Biomarkers for Patients With Transient Ischemic Attacks and Minor Stroke

Imaging markers (including DWI positivity, intracranial and extracranial vessel occlusion) identify a subgroup of patients with transient ischemic attack and minor stroke at higher risk of future stroke or recurrent stroke and may represent trial enrichment selection criteria.^{5,6} Transcranial Doppler (TCD) high-intensity transient signals count has been used as a biomarker for antithrombotic drugs in phase 2 trials.⁷

Imaging as a Biomarker for Efficacy Outcome in Stroke Clinical Trials

Proof-of-concept phase 2 trials are typically of small size and may use imaging to test a mechanistic hypothesis or provide proof of therapeutic principle. Complete imaging data capture needs to be strictly enforced, as missing imaging data may mask a hazard (eg, if a higher death or adverse event rate precluded follow-up scanning in this arm). The choice of imaging outcome biomarkers will influence clinical and imaging selection criteria. More restrictive selection criteria and greater complexity associated with pretreatment imaging may provide more specific pathophysiological information, reducing sample size requirements and heterogeneity of the study population, but may reduce recruitment rate and generalizability of the results. If additional imaging data that are hypothesized to be TRAITs are used in trials primarily designed to test the efficacy of a therapeutic intervention, then the TRAIT can be evaluated only if it is not used as a selection criterion. Phase 2 trials using advanced imaging are optimally performed by collaborations among research centers with expertise in specific types of acute stroke imaging.

Imaging biomarkers of potential value in phase 2 studies include imaging of macrovascular, microvascular, and tissue outcomes (eg, recanalization, reperfusion, ischemic core volume, and combinations of these). Imaging biomarker selection should take into account interobserver reliability and measurement error for the selected technique.⁸ Moreover, validation criteria for biomarker use in stroke trials should be established. Trials using novel imaging biomarkers should

include reporting to a reference standard method, such as the STIR calibration described below.

Pivotal phase 3 trials with imaging selection aim at demonstrating effectiveness on a primary clinical end point.^{9–11} As many of the treatments studied, as well as imaging assessments are associated with substantial cost, incorporating cost effectiveness analyses into the design of acute stroke trials should be encouraged. Phase 3 trials with clinical end points typically involve many centers that may have limited experience and resources for acute specialized stroke imaging. Therefore, phase 3 trials must ensure that imaging protocols are sufficiently simplified and standardized, so that image acquisition is efficient, image interpretation for eligibility assessment can be performed by local investigators, and imaging is not an obstacle to enrollment. More sophisticated imaging selection criteria could confer benefits that may be partly or wholly negated by the additional time for acquisition, processing, and interpretation. Local investigator certification should be required to ensure accurate determination of patient eligibility and outcome assessment. A central core laboratory adjudication for imaging end points should be used (local reading should also be incorporated for generalizability). Timing of central adjudication should be as close as possible to enrollment/imaging to allow for the timely detection of protocol violations.

Significant relationships between imaging biomarkers of infarct volume, lesion growth, and penumbral salvage to clinical end points have been reported.^{12–15} However, imaging biomarkers in stroke have not met criteria to be used as a surrogate of clinical outcome for phase III clinical trials according to the Food and Drug Administration recommendations.¹⁶

Imaging as a Biomarker for Safety Outcome in Stroke Clinical Trials

Intracranial hemorrhage on post-treatment CT is widely used as a safety outcome in trials of revascularization therapies (drug or mechanical). Definitions are well established for CT, and STIR will propose in a separate article an extension of the CT definitions to MRI that will accommodate differences between 1.5 T and 3 T MRI scanners, and between 2-dimensional gradient recalled echo and 3-dimensional susceptibility-weighted imaging. Also, the definitions will be extended to include the patterns that can be seen on post-treatment CT scans, obtained after contrast has been administered, either for acute CTA/CTP or for digital subtraction angiography (DSA). Hemorrhagic transformation should typically be assessed with imaging between 18

and 72 hours, or earlier if the patient demonstrates clinical deterioration. The timing of hemorrhagic transformation routine assessment should be consistent between all trial arms.

Infarct swelling or edema is another cause of early neurological deterioration. The infarct swelling generally peaks \approx 3 days after stroke onset, although it can produce symptoms much earlier in patients with malignant pattern.¹⁷ Edema is a major confounder for using early subacute infarct/lesion volume as a surrogate for final infarct volume as it distorts actual infarct size substantially. Edema increases with infarct size (larger infarcts have more edema).¹⁸ Visual scales that score the degree of infarct swelling separate from the infarct extent¹⁹ seem to have good interobserver reliability.^{20–22}

The role of blood–brain barrier (BBB) disruption as a risk factor for subsequent complications in patients undergoing acute stroke treatment has not been clearly established. Preliminary studies suggest that imaging markers of the BBB disruption are associated with risk of hemorrhagic transformation and adverse outcome.^{23,24} Methods for measuring BBB disruption include postcontrast parenchymal imaging, delayed gadolinium-enhanced FLAIR, CTP, dynamic contrast-enhanced-MRP, and dynamic susceptibility contrast-MRP imaging. The sensitivity of postcontrast imaging to BBB disruption can be enhanced using FLAIR instead of T1-weighted imaging. Postcontrast FLAIR imaging can depict the hyperintense acute reperfusion marker, because of enhancement in CSF (cerebro spinal fluid) spaces from contrast leak through the BBB associated with reperfusion.^{25–27} Dynamic contrast-enhanced-MRP is the established measure of BBB disruption; however, long acquisition times limit its use in acute stroke. Dynamic susceptibility contrast-MRP offers potential for identifying acute BBB disruption, as it uses a sequence that is already part of the recommended acute stroke imaging protocol. Future research should focus on establishing reliable BBB permeability maps and assessing the use of BBB markers for prevention of symptomatic ICH (intracranial hemorrhage). Pooling of existing data will likely accelerate the development of this potential clinical tool.

Imaging Assessment of Revascularization

Standardization of Vascular Assessment in Acute Stroke Research Imaging

In trials of acute revascularization strategies, pathophysiology of acute ischemic stroke should be routinely documented at baseline angiography using systematic description of arterial occlusions and, ideally, collateral perfusion. In general, non-invasive vascular imaging with sufficient sensitivity and specificity for cerebral artery pathology should be performed before any invasive vascular imaging to limit the number of unnecessary invasive procedures. The same angiographic or tissue perfusion imaging modality should be used throughout the study design (ie, baseline, posttreatment, and next day), although more flexible use of different modalities (eg, CT at baseline, MRI for follow-up) helps to limit radiation exposure.²⁸

Revascularization Imaging Modalities

In ischemic stroke, early revascularization (which again encompasses both recanalization and reperfusion) remains the most critical process to impact positively on clinical outcome

by restoring blood flow while salvageable brain still persists. A meta-analysis of 2066 subjects with either spontaneous or therapeutic recanalization within 6 hours of symptom onset was associated with a 4- to 5-fold increase in the odds of an independent functional outcome and up to a 4-fold reduction in mortality.²⁹ The magnitude of effect may directly relate to the speed with which revascularization is achieved.³⁰ Recent randomized data from trials of endovascular treatment for acute ischemic stroke have confirmed that 3-month clinical outcome, as well as attenuated infarct growth, was associated with greater reperfusion and early revascularization.^{31,32}

Arteriographic demonstration of revascularization has 3 important components (Table 4).³³ Distal reperfusion is the primary determinant of tissue fate and ultimately clinical outcome. Recanalization is necessary but not sufficient for tissue reperfusion (eg, cases with distal embolization or no-reflow, in which contrast does not enter the affected tissue bed, although the parent artery may have reopened). Grading recanalization of the primary occlusion may provide prognostic information distinct to or in addition to tissue reperfusion in the setting of partial recanalization, where there may be a higher chance for reocclusion or distal embolization. Several diagnostic tools are capable of evaluating these components of revascularization.³⁴

Conventional angiography with contrast injection in the extracranial arteries supplying the brain tissue is the reference standard for assessment of recanalization of the primary occlusion and restoration of blood flow into the distal arterial bed. It is available during and immediately after intra-arterial or endovascular treatment. Although catheter angiography has also been used to grade tissue reperfusion, there are significant limitations. Prior trials have not had a uniform approach to grading either the arterial or the tissue bed components, and there are inherent challenges to quantifying the volume of tissue reperfusion on conventional angiography.

Noninvasive approaches are ideal for assessing revascularization after intravenous thrombolysis. Noninvasive angiographic imaging using CTA- and MRA can assess recanalization but cannot accurately assess reperfusion which requires tissue imaging with CTP or MRP. CTA is generally more accurate than time of flight MRA for occlusion detection when compared with reference standard conventional angiography, particularly for second-order intracranial arteries.³⁵ However, the radiation exposure and contrast load associated with CTA and CTP should be considered in choosing imaging options. TCD evaluation is hampered by attenuation of energy through thick bone windows in the elderly and limited to the assessment of more proximal arteries because of difficulty in distinguishing vessels on the cortical surface. However, it has been used for early diagnosis of large intracranial artery occlusion and does offer the advantage of bedside real-time monitoring of recanalization of large arteries for exact timing. CTP and MRP can assess tissue reperfusion. Flat-panel detector

Table 4. Three Components of Revascularization

Recanalization or restoration of patency in the original or primary arterial occlusive lesion
Reperfusion past the primary occlusion into the distal arterial bed
Reperfusion of the affected tissue

angiographic systems and Xpert-CT or dyna-CT scans have emerged as potential diagnostic tool for acute stroke patients. These systems might avoid delay in imaging of candidates for intra-arterial or endovascular therapy but currently they do not have enough spatial resolution to allow for the identification of early ischemic changes.

In some circumstances nonangiographic thrombus imaging may be an alternative to angiographic imaging. CTA and MRA do not precisely define occluded segments. These are displayed as gaps between contrasted nonoccluded vessels and thus their shape is ambiguous. Furthermore, nonoccluded segments close to the thrombus often do not show contrast because of slow flow or insufficient collaterals.³⁶ The hyperdense middle cerebral artery (MCA) sign on CT when clearly visible is highly predictive of an MCA main stem occlusion.³⁷ Hyperdense artery signs on CT involving other arteries have also shown high specificity.³⁸

Until recently, clot imaging using the MCA sign on CT was considered impractical because of the sign's low sensitivity. This problem can be overcome by reconstructing additional thin NCT slices. These allow for visualizing clots in the MCA main stem.^{39,40} The length and location of the hyperdense artery sign may also predict response to intravenous tissue-type plasminogen activator.^{41,42} Length of hyperdense sign should be measured using a standardized thin section NCT. Similarly, an absent flow void or altered signal (susceptibility vessel sign on gradient recalled echo or susceptibility-weighted imaging) on MRI can signify an intracranial occlusion.⁴³⁻⁴⁵

Limited literature is available concerning the use of nonangiographic thrombus imaging to assess revascularization. The disappearance of the hyperdense sign with intravenous tissue-type plasminogen activator has been described and is associated with improved outcome (versus persistence of the sign),⁴⁶ although is not yet validated against angiographic imaging in a large population.

Timing of Vascular Assessments

Timing of assessments should be recorded and should be as closely matched in all arms of the trial to avoid disparities in revascularization assessment between treatment arms, which could bias the conclusions. The number of assessments should be relevant to the trial question to avoid unnecessary excess radiation/contrast load/disruption to patient care.

Timing should be relevant to assess reocclusion where appropriate. Baseline (vascular status) should be as close in time as possible to the administration of treatment. Post-treatment assessment of revascularization should be early when nutritional reperfusion can still lead to salvage of significant regions of brain. If a comparison with endovascular treatment for revascularization is performed, this should take place within 2 to 6 hours of the treatment initiation, as long as this can be achieved without disrupting or compromising patient care. The timing of revascularization imaging could be later, for systemic thrombolysis because of more gradual revascularization, seen with such therapy. A late revascularization end point (next day/24 hours) could also be considered as a secondary revascularization end point. The relationship of this late revascularization end point to tissue salvage is less clear.

Recanalization-Arterial Patency and Grading

The primary target lesion evaluated for recanalization should be the most proximal intracranial occlusive segment(s) that is likely to be the cause of recent stroke symptoms, and the target of the intervention. Occlusion should be defined to include both complete and partial arterial obstruction. The primary target lesion should be described in detail: terminal internal carotid artery (ICA) occlusions (T, L, or I types), proximal or distal M1 (first half and second half, respectively), and M2 configuration. Of note, the M1 segment should be defined as the horizontal segment before the MCA bifurcation, accessible to endovascular treatment. When a large anterior temporal branch supplies brain tissue beyond the temporal pole, it is to be considered as an M2 equivalent, and the MCA segment between the anterior temporal branch and the MCA bifurcation is still M1.

Secondary lesion(s) are occlusive segments involving (1) extracranial arteries proximal to the primary lesion; (2) arterial segments distal to the primary lesion (ie, M2/M3); or (3) adjacent arteries involving other vascular territories (ie, anterior cerebral artery [ACA]) with smaller thrombus burden than the primary lesion. Of note, downstream territory for terminal ICA occlusions should be taken as the ACA and MCA territory unless there is clear evidence of ACA filling from the contralateral side.

Pial collaterals with retrograde flow should be routinely evaluated and scored with the ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology) grading system.⁴⁷ Other scoring systems, such as the Capillary Index Score that focuses on capillary staining in the venous angiographic phase, show promise in predicting outcome before treatment but have not been validated against the ASITN/SIR grading system.⁴⁸

Patients with no angiographic evidence of intracranial occlusion should not be pooled with patients with angiographically documented intracranial occlusion.

Normal variants of vasculature, such as hypoplastic or absent A1 ipsilateral to the occlusion, should be documented.

One reference standard recanalization grading scale should be used for each imaging modality (TCD, CTA, MRA, and DSA) to assess patency of arteries. TCD recanalization grading is best assessed with the thrombolysis in brain ischemia flow grading system now used in several TCD-based clinical trials.^{49,50} The thrombolysis in brain ischemia score has also been slightly modified to assess recanalization using TCD technologies (Consensus On Grading Intracranial Flow obstruction score).⁵¹ No CTA or MRA-based grading systems have been developed that are considered standard, although thrombolysis in myocardial infarction/TICI/arterial occlusion lesion scores have been used. Arterial occlusion lesion score has been applied to recanalization of the target arterial occlusive lesion. Such grading systems are variably applied and may perform poorly when conflating the scoring of the primary occlusion point, the distal arterial bed, and the tissue level perfusion in 1 score. This is a source of confusion and should absolutely be avoided.⁵² A STIR-revised version of the TICI score is detailed below. Reperfusion grading could be performed by a visual scale or by quantifiable methods. Choice of method will depend on trial questions and trial phase.

Modified TIC1 Score

DEFUSE 2 and IMS 3 provided data to support a correlation between modified TIC1 grades and clinical outcome at 3 months.^{32,53} However, conventional TIC1 2a and 2b grades, which comprised the majority of recent trial results, span a wide spectrum from marginal antegrade flow to substantial angiographic reperfusion, and the definition of the distinction between the 2 may be unclear. Substantial variability in partial perfusion thresholds with TIC1 was documented leading to different grading in $\approx 20\%$ of cases.⁵⁴ A TIC1 2c grading has been proposed to further distinguish partial perfusion, but remains too new to recommend.

There are operational definitions for what constitutes effective revascularization. STIR recommends a modified TIC1 scale to measure the extent of capillary-level opacification (ie, parenchymal blush) in the downstream territory after successful intra-arterial treatment on conventional angiogram (Table 5). This modified scale applies exclusively for conventional angiography and for revascularization assessment. STIR recommends using the reperfusion scale without alteration for the location of the target arterial occlusive lesion. The consensus definition of successful reperfusion is a mTIC1 score of 2b or 3, whereas mTIC1 of 0, 1 and 2a indicates a lack of successful reperfusion.

Future Collaborative Research

Studies of mTIC1 scale performance (including intra- and interobserver reliability, and validity) should be conducted. The correlation between mTIC1 grades and clinical outcomes should be studied, including comparisons between mTIC1 2b versus mTIC1 3. Similarly, studies of the mTIC1 scale at distinct sites of target arterial occlusions (eg, ICA versus M1 versus M2) should be conducted. There should be correlation studies between the mTIC1 grades and perfusion CT and MRI measurements, studies to correlate clot length, infarct size, and collateral status, as well as studies to determine whether incorporating a time to reperfusion metric into the mTIC1 scale would further improve outcome prediction.

STIR Calibration of Software Packages for Ischemic Core and Penumbra Imaging

STIR recognizes that imaging techniques continuously evolve, and that there will always be a newer, better ischemic core or penumbra imaging technique or processing software. Therefore, it is desirable to find a balance between continued attempts to improve on existing methods versus determining whether existing methods are good enough to be used in current clinical trials. For this discussion, software package refers to the combination of imaging acquisition and postprocessing algorithm.

STIR, therefore, has created a repository of shared stroke clinical and source imaging data available to the field of stroke researchers.^{55,56} The STIR repository pools CT and MRI data from large datasets and stroke clinical trials that can be used to compare head to head different acquisition techniques and software packages in their attempts to define ischemic core and penumbra, and determine acceptability criteria.

This STIR calibration process described below does not assess or recommend how to use ischemic core and penumbra information for prognosis, prediction of response to treatment, and selection of patients for reperfusion therapy. These are better answered in well-designed clinical trials or prospective validation studies. However, the data repository and analyses may be used to generate hypotheses and ischemic core/penumbra predictive/prognostic algorithms to be used in such clinical trials.

The clinical and imaging data to be included into the repository need to meet specific criteria to allow rigorous analyses of the validity of software performance in defining ischemic core and penumbra. The selected data need to match the analyses proposed as part of the calibration process. If the required data for the analyses cannot be collected by compiling existing datasets (because of the strict criteria that the data need to satisfy), then the repository will need to be populated from prospective data collection.

The first recommended analysis is to use existing digital phantoms to produce goodness-of-fit metrics for perfusion maps created by CTP or MRP software.⁵⁷⁻⁶⁰ The goodness-of-fit metrics will be evaluated against the digital reference object phantoms in terms of bias and variance as a function of signal-to-noise and simulation conditions. For each software package tested, the results of this analysis should be reported so that software users have objective information to select a software package for their research.

The second recommended analysis is a calibration/comparison of acute CTP and DWI to determine the optimal CTP parameter(s) or threshold(s) that produce a CTP abnormality that best matches the DWI abnormality (Table 6). It is assumed that most or all patients will have the CTP study done first, except perhaps in patients not eligible for reperfusion therapy. This will lead to some bias in the comparisons between the 2 imaging methods (CTP and DWI), such that CTP abnormality should, in general, underestimate the DWI abnormality. Postreperfusion DWI reversal is not relevant to this dataset as patients with revascularization between the CTP and the MRI study will be excluded. Derivation and validation datasets should be established to prevent overfitting of the perfusion data.

The third recommended analysis is another calibration effort between software packages. The goal of this calibration effort is that all acceptable software packages provide similar

Table 5. Modified Treatment in Cerebral Ischemia Scale

0	No reperfusion
1	Flow beyond occlusion without distal branch reperfusion
2a	Reperfusion of less than half of the downstream target arterial territory
2b	Reperfusion of more than half, yet incomplete, in the downstream target arterial territory
3	Complete reperfusion of the downstream target arterial territory, including distal branches with slow flow

This relates to capillary-level reperfusion as measured on catheter angiography.

Table 6. Required Characteristics for the Dataset to be Used in Analysis to Calibrate Acute CTP to Acute DWI Abnormality

A maximum delay of 2 h between the CTP and the DWI studies
 Criteria for satisfactory data will be concurrent CTA (NCT assumed) and MRA to confirm lack of recanalization between exams
 For cases where no baseline occlusion can be detected on the initial CTA, then follow-up MRP will be required to confirm the absence of reperfusion; ideally, MRI data should contain both MRA and MRP

CTA indicates computed tomography angiography; CTP, perfusion imaging with computed tomography; MRA, MR angiography; MRP, perfusion imaging with MRI; and NCT, noncontrast computed tomography.

volume of ischemic core and penumbra independently of the underlying algorithms. This calibration step does not address the accuracy of the software packages for prediction of the tissue fate. Also, as mentioned above, this calibration process does not assess or recommend how to use ischemic core and penumbra information for prognosis, prediction of response to treatment, and selection of patients for reperfusion therapy.

This calibration process will involve acute CT and MRI datasets to determine optimal parameters or thresholds to determine ischemic core and penumbra in 2 groups of patients: 1 with no revascularization and 1 with early revascularization (Table 7). The baseline dataset will include an advanced CT dataset: NCT (ideally with clot imaging), CTP, CTA (ideally dynamic CTA), and an MRI dataset: DWI, MRP, FLAIR, gradient recalled echo or susceptibility-weighted imaging, MRA. In the first group, patients should demonstrate persistent occlusion on follow-up CTA or MRA or complete lack of revascularization (persistent CTP or MRP lesion of similar size to baseline). In the second group (early revascularization), the issue is the timing of documentation of revascularization. The purest group is evidence of complete revascularization on DSA after clot retrieval. But it is also important to assess and compare ischemic core parameter(s) or threshold(s) after intravenous tissue-type plasminogen activator lysis. It is therefore, desirable to have a second almost pure group with evidence of complete revascularization between 2 and 8 hours after intravenous tissue-type plasminogen activator lysis initiation. Finally, a third less pure group with evidence of complete revascularization on CTA/MRA between 8 and 24 hours after revascularization initiation would also be acceptable. Because the STIR calibration process will consist of comparing the results of different software packages using the same dataset, the limitations of the less pure dataset will be the same for all the software packages, and the comparison will be fair.

Final infarct volume needs to be assessed in both groups of patients. Final infarct volume assessment is a challenging issue because of the initial variation in the volumes of imaging abnormalities, contributed to by the superimposed edema in the initial phase and atrophy in the later phase, and because of logistic issues. Patients with persistent, complete, proximal occlusion have a very poor outcome and may be deceased by day 7. STIR pragmatic recommendation for the purpose of this calibration process is to use DWI (preferred) or NCT obtained between 18 and 36 hours to define the lesion to be used as the reference for the analyses described above. The 18- to 36-hour DWI is significantly associated with later infarct volume and is much easier to obtain than very late imaging (eg, day 30).⁶¹

The fourth recommended analysis aims at standardizing collateral assessment, whether it is on angiographic data or noninvasive CTP/MRP data. Ideally, the collected dataset would be identical to the pure DSA group in the second recommended analysis. The underlying idea is to define the most accurate measure of collateral flow on noninvasive imaging datasets. The reference standard would be the DSA, and the tested imaging modalities would be the CTA or MRA performed prior and within 60 minutes of DSA, with confirmation of lack of recanalization between DSA and CTA/MRA. For this analysis, patients with baseline CTA and patients with baseline MRA will be analyzed as separate groups. Collateral assessment may be more accurate from time-resolved (or at least multi-phase) CTA data compared with static (single time point) CTA. This similarly applies to static MRA. Ideally, concurrent CTP or DWI/MRP should be obtained to assess quantitative perfusion measures against collateral status on DSA and noninvasive angiography.

For all the above-recommended analyses, we will need a combination of sensitivity and specificity from receiver operator characteristic curve analysis. At this time, we are not recommending any specific level of sensitivity or

Table 7. Summary of Imaging Data Characteristics to be Collected for Software Calibration and Collateral Assessment

Baseline imaging study	NCT/CTP/(dynamic) CTA or DWI, MRP, FLAIR, T2* GRE or SWI, and MRA
Revascularization imaging study, to confirm revascularization for the ischemic core calibration	DSA after clot retrieval or NCT/CTA (ideally dynamic/multiphase) and CTP between 2 and 24 h after treatment or DWI/FLAIR/GRE or SWI/MRA and MRP between 2 and 24 h after treatment
Follow-up imaging study to determine the infarct volume	18- to 36-hour DWI (preferred regardless of baseline imaging modality) or 18- to 36-hour NCT

CTA indicates computed tomography angiography; CTP, perfusion imaging with computed tomography; GRE, gradient recalled echo; MRA, MR angiography; MRP, perfusion imaging with MRI; NCT, noncontrast computed tomography; and SWI, susceptibility-weighted imaging.

specificity to be achieved. Rather, we are recommending the 4 analyses detailed above be performed for all perfusion software packages available and the results published so as to serve as the initial benchmark. It is likely that the benchmark levels of sensitivity or specificity will increase over time, reflecting continuous improvements in the perfusion software packages.

For all datasets, a spread of the baseline imaging is needed in various time windows after stroke onset (eg, 0–3, 3–4.5, 4.5–6, 6–12 hours). Similarly, a diverse population is desired, with patients who were not treated, patients treated with intravenous thrombolysis, and patients treated with intra-arterial revascularization. All the datasets collected should ideally have appropriate clinical information collected as part of the protocol. If possible, National Institutes of Health Stroke Scale scores at all imaging time points, mRS at day 90, time of onset, and acute treatment should be collected.

In terms of the imaging protocols used, 2 approaches can be considered. One would be to harmonize acquisition protocols as much as possible and for STIR to provide guidelines (as done previously).^{62,63} However, a second, more pragmatic approach is to accept a broad range of acquisition protocols. A good enough software should be able to deal with a broad range of image acquisition protocols. This makes the results more generalizable, but this approach requires validation.

The data submitted to the STIR repository should be anonymized and undergo a rigorous quality control process before being accepted into the repository, to ensure compliance with minimum basic acquisition standards.

Stroke Neuroimaging Network and Coordinating/Data Center

Similar to continuously evolving software tools, STIR recognizes that imaging techniques will continue to advance on the acquisition side as well. Promising emerging imaging techniques for providing even greater understanding into stroke sequelae include noninvasive measurement of cerebral blood flow (eg, arterial spin labeling MRI,^{64,65} oxygen extraction fraction MRI,⁶⁶ pH-weighted MRI,⁶⁷ vessel size imaging,^{68,69} vascular space occupancy MRI,⁷⁰ cerebrovascular reactivity measured with MRI,⁷¹ diffusion kurtosis MRI,⁷² diffusion-tractography,⁷³ resting-state fMRI (functional magnetic resonance imaging),^{74–76} dual-energy CT,⁷⁷ and positron emission tomography and single photon emission CT tracers to assess inflammatory processes). New imaging techniques offer practical benefits such as less invasive methods that allow for repeat assessments or less motion sensitive approaches which are critical for imaging agitated and noncompliant patients who make up the majority of the acute stroke population. New contrast agents may offer practical benefits of patients' exposure to less iodine or gadolinium. Beyond the likely increased specificity and sensitivity of identifying patients who may benefit from novel pathways for acute intervention, advanced imaging techniques can also potentially be used for trials of stroke prevention to assess vulnerable carotid atherosclerotic plaque and identify patients at high risk of stroke. Advanced imaging has also been posited to be potentially of use for monitoring functional changes in the brain recovery process and, therefore, may be used to evaluate physical and neurocognitive therapy after stroke.^{78,79}

Although advanced neuroimaging techniques have the potential to impact all stages of stroke patient management, the practical translation of these potentially transformative techniques from research to clinical settings currently faces many challenges. Some of these include limited support for developing advanced imaging techniques in clinical trial environments and logistic issues on their feasibility in acute trial settings. Pragmatic issues, such as scan duration, are important, especially in the acute revascularization trials as described above. For evaluating patients without pressing time constraints, for example, chronic stroke patients and transient ischemic attack patients, longer acquisitions may be feasible, and automatic motion correction would be extremely useful in this setting.

Critical to the acceptance of new techniques will be their performance. Depending on the patient population under investigation, there are many possible criteria by which new imaging techniques can be evaluated. As described above, for acute stroke patients, imaging techniques are typically evaluated on their ability to predict lesion volumes on follow-up imaging as a reference standard. The equivalent for at-risk patients would be prediction of future strokes. For acute stroke or at-risk patients, additional evaluation criteria should include prediction or measurement of clinical response to intervention or medication such as gray matter volume measurement relative to the contralateral unaffected brain could be evaluated against neurocognitive testing and be used for prediction of cognitive outcomes and response to rehabilitation therapy.⁸⁰ Ultimately, any new technique will need to impact clinical management of these patients, whether by making the imaging study less invasive or providing additional information on potential tissue salvage, tissue at risk or risk of complication with treatment. In addition, the evaluation of the use of new imaging techniques for patient selection or as a biomarker of safety or efficacy of new treatments should follow the recommendations described above.

For translating new techniques from research settings to clinical settings, several study designs are possible. After the initial validation at a single site or small number of sites, the consensus is that multicenter, multi-vendor studies would be the most appropriate for successful translation of new techniques to nonacademic hospital centers. There is still debate on whether to limit evaluation of new techniques to current state of the art technology (eg, 3 Tesla scanners) or to emphasize generalizability (eg, include 1.5 Tesla MRI scanners). For evaluating the clinical use of new advanced imaging techniques, both acquisition and processing techniques, and contrast administration techniques will need to be standardized by expert panels, as is currently done for arterial spin labeling by the Perfusion Study Group of the International Society for Magnetic Resonance in Medicine and the European consortium arterial spin labeling in Dementia (funded through a grant from the European Union COST [Cooperation in Science and Technology] agency).

Mechanisms are, therefore, needed to translate and test advanced imaging methods across centers, to encourage the use of advanced imaging in acute settings, to stimulate closer academic-industry collaborations (such as for the Alzheimer Disease Neuroimaging Initiative <http://www.adni-info.org/>),⁸¹ and to promote the retrospective and prospective collection

and pooling of imaging data, such as the one to create the STIR repository described above.

The 2 logistic priorities for promoting translation of new imaging research are (1) population of the STIR imaging data repository with links to clinical metadata, and (2) establishment of a stroke trial imaging network.

Regarding the first priority, STIR recommends that worldwide government agencies can provide funding to centers to acquire a standard dataset using a common institutional review board–approved imaging-based study protocol matching the description above in the section about the STIR calibration process. Also, some government-funded acute stroke clinical trials could be required to collect a minimal basic imaging dataset, in addition to the clinical Common Data Elements. Promoting imaging as a required data element in some trials, and making these data available to the stroke community through a repository, would accelerate testing of the use of advanced imaging for stroke research.

The second priority, an international stroke trial imaging network, will provide the infrastructure that facilitates advanced neuroimaging-based studies. An imaging network comprising international experts could track the clinical and imaging capabilities of potential participating centers (ie, contact information for neurologists, neuroradiologists, interventionalists, imaging physicists and emergency physicians, ability to do acute CT, CTA, MRI, as well as the number of acute stroke patients seen per year). In addition, scanner details (ie, 1.5 Tesla MRI, 3 Tesla MR, manufacturer and software version) should be recorded. Having this information readily available will provide an easy mechanism for identifying potential centers that are capable of integrating advanced imaging into stroke clinical trials. Currently, every imaging-based multicenter trial repeats the same process for identifying eligible centers with the required technical capabilities to perform the study before startup. Having a centralized, regularly updated database of center capabilities could streamline the process and ultimately accelerate startup of these studies. Establishment of a stroke trial imaging network with a central coordinating/data group has the potential of both immediate and long-term impact on stroke research and public health by creating an infrastructure that reduces redundancy and increases efficiency of stroke imaging research, thereby allowing investigators to concentrate on clinical and scientific questions rather than implementation issues. In addition, such centers can promote scientific collaboration and education in a distributed fashion, and further advance software reuse, and data and model sharing.

Finally, worldwide governmental funding agencies can use their unique position to work with industry and academia to promote public–private partnerships to facilitate the distribution of proprietary techniques and software across multiple platforms and accelerate standardization and translation of advanced imaging technologies.

Conclusions

The 2 main achievements of the STIR II are to provide specific terminology for acute stroke imaging, and a modified TICI scale. General guidance about the use of imaging in the design of stroke clinical trials is also provided.

The 3 main recommendations of STIR II for stroke imaging research directions include

- the establishment of a STIR calibration process for measuring ischemic core and penumbral software,
- populate the STIR clinical and imaging data repository to facilitate the STIR calibration process, and
- the creation of a stroke neuroimaging network able to keep track of the clinical and imaging capabilities of centers (ie, contact information for neurologists, neuroradiologists, interventionalists, imaging physicists and emergency physicians, ability to do acute CT, CTA, CTP, MRI, MRP, MRA, as well as the number of acute stroke patients seen per year).

Collaboration among academia, industry, and funding and regulatory agencies is integral to the successful realization of these aims.

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KEY WORDS: angiography ■ clinical trial ■ computed tomography ■ consensus ■ imaging ■ magnetic resonance imaging ■ stroke ■ thrombolysis

Appendix:

STroke Imaging Research (STIR) group:

Co-Chairs: Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center)

Steering Committee: Gregory W. Albers (Stanford University School of Medicine), Stephen M. Davis (Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne), Geoffrey A. Donnan (The Florey Institute of Neuroscience and Mental Health), Marc Fisher (University of Massachusetts School of Medicine), Anthony J. Furlan (University Hospitals Case Medical Center, Case Western Reserve University), James C. Grotta (Department of Neurology, University of Texas Health Science Center), Werner Hacke (Department of Neurology, University of Heidelberg), Dong-Wha Kang (Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine), Chelsea Kidwell (Department of Neurology and the Stroke Center, Georgetown University), Walter J. Koroshetz (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Kennedy R. Lees (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary), Michael H. Lev (Massachusetts General Hospital and Harvard Medical School), David S. Liebeskind (UCLA Stroke Center), A. Gregory Sorensen (Siemens), Vincent N. Thijs (Laboratory of Neurobiology, Vesalius Research Center, VIB, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), University of Leuven (KU Leuven), Department of Neurology, University Hospital Leuven), Götz Thomalla (University Medical Center Hamburg-Eppendorf), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Joanna M. Wardlaw (Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV))

Coordinator: Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH))

Imaging assessment of ischemic core and salvageable tissue:

Co-Chairs: Joseph P. Broderick (Department of Neurology, University of Cincinnati Neuroscience Institute), Michael H. Lev (Massachusetts General Hospital and Harvard Medical School), Mark W. Parsons (Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle)

Members: Richard I. Aviv (University of Toronto and Sunnybrook Health Science Centre), Keith Heberlein (Siemens), Srinivas Kidambi (Bayer), Chelsea Kidwell (Department of Neurology and the Stroke Center, Georgetown University), Walter J. Koroshetz (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Kohsuke Kudo (Department of Diagnostic Radiology, Hokkaido University Hospital), Rüdiger von Kummer (Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden), Maarten G. Lansberg (Stanford University School of Medicine), Ting-Yim Lee (The University of Western Ontario), David S. Liebeskind (UCLA Stroke Center), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), John Metellus (Siemens), Heiko Meyer (Siemens), Keith Muir (Institute of Neurosciences & Psychology, University of Glasgow, Southern General Hospital), Timothy Nicholson (TAMS), Leif Østergaard (Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark), Salvador Pedraza (Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta), Betsy Rose (Bracco Imaging), Howard A. Rowley (Department of Radiology, University of Wisconsin School of Medicine and Public Health), Makoto Sasaki (Institute for Biomedical Sciences, Iwate Medical University), Efrat Shefer (Philips), Saad Sirohey (GE), Sri Swaminathan (Philips), Götz Thomalla (University Medical Center Hamburg-Eppendorf), Kim van de Ven (Philips), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Ona Wu (Massachusetts General Hospital and Harvard Medical School), Faith Yao (Bayer), Albert J. Yoo (Massachusetts General Hospital and Harvard Medical School)

Imaging assessment of revascularization:

Co-Chairs: Andrew M. Demchuk (Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary), Joanna M. Wardlaw (Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh)

Members: Richard I, Aviv (University of Toronto and Sunnybrook Health Science Centre), Mark Bowman (GE), Colin P. Derdeyn (Washington University School of Medicine), Salvatore Desena (Bayer), Brian Frake (Vital Images), James C. Grotta (Department of Neurology, University of Texas Health Science Center), Keith Heberlein (Siemens), Olav Jansen (University of Kiel, Institute of Neuroradiology, Kiel, Germany), Tudor G. Jovin (Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute and UPMC Center for Neuroendovascular Therapy), Srinivas Kidambi (Bayer), Walter J. Koroshetz (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Rüdiger von Kummer (Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden), David S. Liebeskind (UCLA Stroke Center), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Grant Mair (Division of Neuroimaging Sciences, Western General Hospital, University of Edinburgh), Bijoy K. Menon (Calgary Stroke Program, Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada), John Metellus (Siemens), Heiko Meyer (Siemens), Robert Mikulik (Neurology Department, International Clinical Research Center, St. Anne's Hospital), Timothy Nicholson (TAMS), Salvador Pedraza (Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta), Christian H. Riedel (Department of Neuroradiology, University of Kiel), Betsy Rose (Bracco Imaging), Makoto Sasaki (Institute for Biomedical Sciences, Iwate Medical University), Efrat Shefer (Philips), Saad Sirohey (GE), Olaf Such (Philips), Sri Swaminathan (Philips), Thomas A. Tomsick (Department of Radiology, University of Cincinnati Medical Center), Georgis Tsivgoulis (Comprehensive Stroke Center, Department of Neurology, University of Alabama at Birmingham, Second Department of Neurology, School of Medicine, University of Athens), Kim van de Ven (Philips), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Philip M White

(Institute for Ageing and Health, Newcastle University), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Faith Yao (Bayer), Albert J. Yoo (Massachusetts General Hospital and Harvard Medical School), Herman Zeumer (University of Kiel, Institute of Neuroradiology, Kiel, Germany)

Imaging of stroke complications:

Co-Chairs: Jochen B. Fiebach (Academic Neuroradiology, Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin), Jens Fiehler (University Medical Center Hamburg-Eppendorf, Hamburg, Germany), David S. Liebeskind (UCLA Stroke Center)

Members: Richard I. Aviv (University of Toronto and Sunnybrook Health Science Centre), Charles Bisordi (GE), Mark Bowman (GE), Bruce C. V. Campbell (Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne), Trevor C. Carpenter (Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh), Salvatore Desena (Bayer), Brian Frake (Vital Images), Keith Heberlein (Siemens), Srinivas Kidambi (Bayer), Chelsea Kidwell (Department of Neurology and the Stroke Center, Georgetown University), Kohsuke Kudo (Department of Diagnostic Radiology, Hokkaido University Hospital), Ting-Yim Lee (The University of Western Ontario), Richard Leigh (Johns Hopkins University School of Medicine), David S. Liebeskind (UCLA Stroke Center), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), John Metellus (Siemens), Heiko Meyer (Siemens), Timothy Nicholson (TAMS), Leif Østergaard (Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark), Salvador Pedraza (Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta), Betsy Rose (Bracco Imaging), Efrat Shefer (Philips), Saad Sirohey (GE), Olaf Such (Philips), Sri Swaminathan (Philips), Kim van de Ven (Philips), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Faith Yao (Bayer)

Image-guide clinical trials of ischemic stroke:

Co-Chairs: Kennedy R. Lees (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary), Keith Muir (Institute of Neurosciences & Psychology, University of Glasgow, Southern General Hospital), Tudor G. Jovin (Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute and UPMC Center for Neuroendovascular Therapy)

Members: Olubunmi Afonja (Bayer), Jeffrey R. Alger (UCLA Stroke Center), Richard I. Aviv (University of Toronto and Sunnybrook Health Science Centre), James Beckett (Philips), Charles Bisordi (GE), Mark Bowman (GE), Joseph P. Broderick (Department of Neurology, University of Cincinnati Neuroscience Institute), Andrew M. Demchuk (Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary), Colin P. Derdeyn (Washington University School of Medicine), Salvatore Desena (Bayer), Jochen B. Fiebach (Academic Neuroradiology, Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin), Jens Fiehler (University Medical Center Hamburg-Eppendorf, Hamburg, Germany), Marc Fisher (University of Massachusetts School of Medicine), Brian Frake (Vital Images), Anthony J. Furlan (University Hospitals Case Medical Center, Case Western Reserve University), James C. Grotta (Department of Neurology, University of Texas Health Science Center), Werner Hacke (Department of Neurology, University of Heidelberg), E. Clarke Haley Jr (Department of Neurology, University of Virginia), Keith Heberlein (Siemens), Srinivas Kidambi (Bayer), Chelsea Kidwell (Department of Neurology and the Stroke Center, Georgetown University), Walter J. Koroshetz (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Maarten G. Lansberg (Stanford University School of Medicine), Michael H. Lev (Massachusetts General Hospital and Harvard Medical School), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Patrick Lyden (Cedars-Sinai Medical Center), John Metellus (Siemens), Heiko Meyer (Siemens), Timothy Nicholson (TAMS), Mark W. Parsons (Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle), Salvador Pedraza (Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta), Betsy Rose (Bracco Imaging), Howard A. Rowley (Department of Radiology, University of Wisconsin School of Medicine and Public Health), Peter D. Schellinger (Johannes Wesling Klinikum Minden), Efrat Shefer (Philips), Saad Sirohey (GE), Olaf Such (Philips), Sri Swaminathan (Philips), Vincent N. Thijs (Laboratory of Neurobiology, Vesalius Research

Center, VIB, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), University of Leuven (KU Leuven), Department of Neurology, University Hospital Leuven), Götz Thomalla (University Medical Center Hamburg-Eppendorf), Kim van de Ven (Philips), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Joanna M. Wardlaw (Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Faith Yao (Bayer), Albert J. Yoo (Massachusetts General Hospital and Harvard Medical School)

Advanced neuroimaging for stroke:

Chair: Ona Wu (Massachusetts General Hospital and Harvard Medical School)

Members: Jeffry R. Alger (UCLA Stroke Center), Richard I. Aviv (University of Toronto and Sunnybrook Health Science Centre), Roland Bammer (Stanford University School of Medicine), Charles Bisordi (GE), Mark Bouts (University Medical Center Utrecht), Mark Bowman (GE), Trevor C. Carpenter (Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh), William A. Copen (Massachusetts General Hospital and Harvard Medical School), Salvatore Desena (Bayer), Brian Frake (Vital Images), Keith Heberlein (Siemens), Joseph Helpert, Jeroen Hendrikse (University Medical Center Utrecht), Jens Jensen (Medical University of South Carolina), Srinivas Kidambi (Bayer), Kohsuke Kudo (Department of Diagnostic Radiology, Hokkaido University Hospital), Lawrence L. Latour (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Richard Leigh (Johns Hopkins University School of Medicine), Weili Lin (Biomedical Research Imaging Center and Departments of Radiology, Neurology, Biomedical Engineering and School of Pharmacy, University of North Carolina at Chapel Hill), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Patrick Lyden (Cedars-Sinai Medical Center), John Metellus (Siemens), Heiko Meyer (Siemens), Michael Moseley (Stanford University School of Medicine), Timothy Nicholson (TAMS), Matthias van Osch (Leiden University Medical Center), Leif Østergaard (Center of Functionally Integrative Neuroscience,

Aarhus University Hospital, Aarhus, Denmark), Mark Parsons (Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle), Salvador Pedraza (Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta), Betsy Rose (Bracco Imaging), Peter Schramm (University Medicine Goettingen), Efrat Shefer (Philips), Saad Sirohey (GE), Olaf Such (Philips), Sri Swaminathan (Philips), Kim van de Ven (Philips), Peter van Zijl (Johns Hopkins University School of Medicine), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Faith Yao (Bayer), Greg Zaharchuk (Stanford University School of Medicine)

Standardization of the stroke imaging terminology:

Co-Chairs: Rüdiger von Kummer (Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden), Michael H. Lev (Massachusetts General Hospital and Harvard Medical School)

Members: Roland Bammer (Stanford University School of Medicine), Jean-Claude Baron (INSERM U894, Sorbonne Paris Cité and Dept of Clinical Neurosciences, University of Cambridge), Søren Christensen (Stanford University School of Medicine), Anthony J. Furlan (University Hospitals Case Medical Center, Case Western Reserve University), Kohsuke Kudo (Department of Diagnostic Radiology, Hokkaido University Hospital), David S. Liebeskind (UCLA Stroke Center), Howard A. Rowley (Department of Radiology, University of Wisconsin School of Medicine and Public Health), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Lawrence R. Wechsler (Department of Neurology, University of Pittsburgh School of Medicine)

Standardized assessment of ischemic core and penumbral imaging methods:

Chair: Mark W. Parsons (Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle)

Members: Andrew Bivard, Joseph P. Broderick (Department of Neurology, University of Cincinnati Neuroscience Institute), Bruce C. V. Campbell (Departments of Medicine and Neurology, Melbourne Brain Centre at Royal Melbourne Hospital, University of Melbourne), Søren Christensen (Stanford University School of Medicine), James C. Grotta (Department of Neurology, University of Texas Health Science Center), Ting-Yim Lee (The University of Western Ontario), David S. Liebeskind (UCLA Stroke Center), Marie Luby (National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)), Howard A. Rowley (Department of Radiology, University of Wisconsin School of Medicine and Public Health), Peter D. Schellinger (Johannes Wesling Klinikum Minden), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Lawrence Wechsler (Department of Neurology, University of Pittsburgh School of Medicine), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Ona Wu (Massachusetts General Hospital and Harvard Medical School), Albert J. Yoo (Massachusetts General Hospital and Harvard Medical School)

Consensus Thrombolysis in Cerebral Infarction (TICI) scale for revascularization in acute ischemic stroke trials:

Co-Chairs: David S. Liebeskind (UCLA Stroke Center), Albert J. Yoo (Massachusetts General Hospital and Harvard Medical School), Andrew M. Demchuk (Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary), Tudor G. Jovin (Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute and UPMC Center for Neuroendovascular Therapy)

Members: Gregory W. Albers (Stanford University School of Medicine), Joseph P. Broderick (Department of Neurology, University of Cincinnati Neuroscience Institute), Pooja Khatri (Department of Neurology, University of Cincinnati), Michael H. Lev (Massachusetts General Hospital and Harvard Medical School), Jay Mocco, Jeffrey L. Saver (UCLA Stroke Center), Thomas A. Tomsick (Department of Radiology, University of Cincinnati Medical Center), Rüdiger von Kummer (Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität

Dresden), Steven J. Warach (Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center), Max Wintermark (Department of Radiology, Neuroradiology, University of Virginia & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV)), Osama O. Zaidat (Department of Neurology, Neurosurgery, and Radiology, Medical College of Wisconsin and Froedtert Hospital)

STIR & VISTA-Imaging members endorsing the Stroke Imaging Research Roadmap II: All STIR & VISTA-Imaging authors of the roadmap, all STIR & VISTA-Imaging participants of working groups and task forces, plus

Harris A. Ahmad (BioClinica, Inc.)

Ken S. Butcher (University of Alberta)

Leeanne M. Carey (The Florey Institute of Neuroscience and Mental Health)

Jan Willem Dankbaar (UMC Utrecht)

Antoni Dávalos, (Hospital Germans Trias I Pujol)

Bart M. Demaerschalk (Mayo Clinic)

Xavier Golay (UMC Utrecht)

Randall Higashida (University of California, San Francisco Medical Center)

Karl-Olof Lovblad (Geneva University Hospitals)

Carlos A. Molina (Hospital Vall d'Hebron)

Thanh G. Phan (Monash Medical Centre)

Volker Pütz (University Clinics Dresden)

Pascal Salazar-Ferrer (Vital Images)

Peter Schramm (University Medicine Goettingen)

Joshua S. Shimony (Washington University in St. Louis)

Aneesh B. Singhal (Massachusetts General Hospital and Harvard Medical School)

Jamal Smyej (Lundbeck A/S)

Marianne van Walderveen (Leiden University Medical Center)

Birgitta Velthuis (UMC Utrecht)

STAIR participants endorsing the Stroke Imaging Research Roadmap II:

All STAIR authors of the roadmap, all STAIR participants of working groups and task forces, plus

Johannes Boltze (Fraunhofer IZI)

Antoni Dávalos (Hospital Universitari Germans Trias i Pujol)

Philip B. Gorelick (Saint Mary's Health Care)

Argye Beth Hillis (John Hopkins University)

Bernard Ravina (Biogen Idec)

Richard D. Scheyer (Daiichi Sankyo Pharma Development)

Thomas A. Tomsick (University of Cincinnati Medical Center)