Acute Stroke Imaging Research Roadmap

Max Wintermark
Gregory W. Albers
Andrei V. Alexandrov
Jeffry R. Alger
Roland Bammer
Jean-Claude Baron
Stephen Davis
Bart M. Demaerschalk
Colin P. Derdeyn
Geoffrey A. Donnan
James D. Eastwood
Jochen B. Fiebach
Marc Fisher
Karen L. Furie
Gregory V. Goldmakher
Werner Hacke
Chelsea S. Kidwell
Stephan P. Kloska
Martin Köhrmann
Walter Koroshetz
Ting-Yim Lee
Kennedy R. Lees
Michael H. Lev
David S. Liebeskind
Leif Ostergaard
William J. Powers
James Provenzale
Peter Schellinger
Robert Silbergleit
Alma Gregory Sorensen
Joanna Wardlaw
Ona Wu
Steven Warach

ABSTRACT: The recent "Advanced Neuroimaging for Acute Stroke Treatment" meeting on September 7 and 8, 2007 in Washington DC, brought together stroke neurologists, neuroradiologists, emergency physicians, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), industry representatives, and members of the US Food and Drug Administration (FDA) to discuss the role of advanced neuroimaging in acute stroke treatment. The goals of the meeting were to assess state-of-the-art practice in terms of acute stroke imaging research and to propose specific recommendations regarding: (1) the standardization of perfusion and penumbral imaging techniques, (2) the validation of the accuracy and clinical utility of imaging markers of the ischemic penumbra, (3) the validation of imaging biomarkers relevant to clinical outcomes, and (4) the creation of a central repository to achieve these goals. The present article summarizes these recommendations and examines practical steps to achieve them.

On September 7 and 8, 2007, the National Institute of Health, in conjunction with the American Society of Neuroradiology and the Neuroradiology Education & Research Foundation, sponsored a research symposium entitled *Advanced NeuroImaging for Acute Stroke Treatment*. The first day of the symposium was devoted to presentations that provided an overview of technical and clinical aspects of acute stroke imaging, including perfusion imaging. These presentations focused on topics that remain, to some extent, controversial and for which a higher degree of consensus is needed for research to proceed. For instance, the appropriate way to image the ischemic penumbra, ie, the region of hypoperfused—but not yet infracted—tissue at risk to proceed to infarction, and its exact role in triaging patients for therapy were debated. A number of issues with regard to study design and patient selection for clinical trials were also reviewed in detail. The second day consisted of 3 concurrent workshops, with 1 on each of the following major themes: (1) standardization of perfusion and penumbra imaging terminology and methodology, (2) trial design and patient selection for acute reperfusion therapy, and (3) development of multicenter collaborations and repositories to demonstrate that advanced stroke imaging improves acute stroke patients' outcomes. This report provides the salient points of the meeting, outlines the unresolved issues, and proposes the creation of a consortium that would greatly advance our efforts to overcome these issues. Specifically, this report provides recommendations for stroke imaging research in terms timing of imaging studies for acute stroke patients, perfusion imaging protocols, and development of a central repository for images that will facilitate answering of major unresolved questions. There are important aspects of acute stroke imaging that were not addressed during

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From the University of California, San Francisco (M.W.); Stanford University (G.W.A., R.B.), Palo Alto, Calif; University of Alabama Comprehensive Stroke Center (A.V.A.), Birmingham, Ala; University of California, Los Angeles (J.R.A.); Addenbrooke's Hospital Hills Road (J.-C.B.), Department of Neurology, Cambridge, UK; Department of Neurology (S.D.), Royal Melbourne Hospital, University of Melbourne, Australia; Mayo Clinic (B.M.D.), Phoenix, Arizona; Washington University (C.P.D.), St Louis, Mo; National Stroke Research Institute (G.A.D.), Austin Health, University of Melbourne; Department of Radiology (J.D.E., J.P.), Duke University Medical Center, Durham, NC; Charité University Hospital and Berlin NeuroImaging Center (BNIC) (J.B.F.), Berlin, Germany; University of Massachusetts Medical School (M.F.), Worchester, Mass; Massachusetts General Hospital (K.L.F., G.V.G., M.H.L., A.G.S., O.W.), Boston, Mass; Heidelberg University (W.H.), Germany; Georgetown University, Washington Hospital Center (C.S.K.), Washington, DC; Department of Clinical Radiology (S.P.K.), University of Muenster, Germany; Department of Neurology (M.K.), University Clinic at Erlangen, Germany; National Institute of Neurological Disorders and Stroke (W.K., S.W.), Bethesda, Md; Lawson Health Research Institute (T.-Y.L.), Canada; University Department of Medicine & Therapeutics (K.R.L.), Western Infirmary, University of Glasgow, UK; University of California, Los Angeles Stroke Center (D.S.L.); Center for Functionally Integrative Neuroscience (L.O.), Department of Neuroradiology, Aarhus, Denmark; Department of Neurology (W.J.P.), University of North Carolina at Chapel Hill; Department of Neurology (P.S.), University Clinic at Erlangen, Germany; University of Michigan (R.S.), Ann Arbor; and Western General Hospital (J.W.), Edinburgh, UK.

Correspondence to Max Wintermark, MD, University of California, San Francisco, Department of Radiology, Neuroradiology Section, 505 Parnassus Avenue, Box 0628, San Francisco, CA 94143-0628. E-mail Max.Wintermark@radiology.ucsf.edu

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Table 1: Recommended Acquisition Protocols for Perfusion-Weighted (PWI) and Diffusion-Weighted (DWI) MR Imaging

	PWI	DWI
Sequence	Single-shot gradient-echo echoplanar imaging	Single-shot diffusion-weighted spin-echo echoplanar imaging
Image acquisition parameters	TR≤1500 ms* TE=35 to 45 ms @ 1.5T TE=25 to 30 ms @ 3T flip angle α=60 to 90° @ 1.5T, 60° @ 3.0T	TR≥4000 ms but can be as high as needed to fit all slices TE minimum (partial Fourier) b=0 and 1000 sec/mm^2 (at least 3 orthogonal directions) eddy current correction (dual-spin echo or postprocessing)
	Parallel imaging and coil selected at the discretion of the site	
Image acquisition duration	90 to 120 seconds image acquisition started 10 seconds before initiation of injection to achieve at least 10 to 12 baseline images and also record slow uptake in stroke regions	90 to 260 seconds
Coverage and slice thickness	Whole brain coverage using ≥12 slices slice thickness 5 mm gap 0 to 1 mm* matrix size 128×128* phase-encoding along A/P direction field of view ≈24 cm	Whole brain coverage using ≥12 slices slice thickness 5 mm gap 0 to 1 mm matrix size 128×128 phase-encoding along A/P direction field of view ≈24 cm
Slice orientation	Parallel to hard palate	Parallel to hard palate (ideally perpendicular to the scanner bore)
Contrast material	Standard gadolinium-based contrast material	
Contrast volume	Single dose (for half-molar agent, ≈20 mL for 100 kg person) followed by 20 to 40 mL saline flush	
Injection rate	4 to 6 mL per second (power injector required) same injection rate for contrast and saline	
IV access	18 to 20 gauge IV line right antecubital vein preferred	
Miscellaneous	PWI can be performed before or after MR-angiography	

MRI scanner: 1.5T or 3T (MRI scanners with 512 image limit per series should be excluded).
*Interslice gap can be increased and matrix size can be decreased *to achieve whole-brain coverage* (TR can also be optimized to afford *entire brain coverage* but should be ≤1500 to 2000 ms).

the meeting, including the impact of advanced imaging findings on the management of acute stroke patients beyond acute penumbral salvage. These include identification of stroke subtype and mechanism (small vessel versus large vessel disease, atheroma versus dissection), large vessel patency status, and lesion volume, all of which have implications for acute and subacute management decisions. The specific issues pertinent to transient ischemic attacks and their imaging were not discussed either.

Recommended Timing for Research Imaging Studies in Acute Stroke Patients

As a research model for evaluating the efficacy of reperfusion therapies or other interventions, acute stroke patients enrolled in clinical trials should ideally undergo imaging at 4 time points. The respective contraindications to CT and MRI, and to iodinated and gadolinium contrast material, should of course be taken into consideration when selecting the imaging modality and implementing the recommended time points described below. The rationale for this imaging protocol is detection of (1) the initial parenchymal and vascular state, (2) the biological effect of the intervention, (3) the occurrence of early hemorrhagic transformation, and (4) the final tissue outcome.

1. At baseline, acute stroke patients should undergo either a "baseline" MRI or CT study.
   - Baseline MRI sequences should include: scout image, diffusion-weighted imaging (DW; Table 1), 3D time-of-flight MR-angiogram (MRA) of the intracranial arteries, gradient-recalled echo (GRE) imaging, perfusion-weighted imaging (PWI; Table 1), and T2-fluid attenuated inversion recovery (FLAIR). FLAIR images can be obtained before or after gadolinium administration. Delayed postgadolinium FLAIR images allow assessment for the presence of the Hyperintense Acute Reperfusion Marker (HARM) sign, possibly an indicator of early blood-brain barrier disruption. Time-of-flight or gadolinium-enhanced MRA to evaluate the cervical carotid and vertebral arteries should be obtained, either at baseline (if it does not delay treatment) or at any subsequent time point. Performing axial T1 fat-suppressed images of the neck is left to each site's discretion.
   - The baseline CT study should include: noncontrast CT, perfusion CT (PCT; Table 2), CT-angiography (CTA), and contrast-enhanced CT (PCT can be performed before or after CTA). CTA must include the intracranial and cervical arteries.
2. Typically 1 to 6 hours after treatment, patients enrolled in research protocols should undergo either an MRI or a CT study to assess for recanalization and reperfusion. Indeed, arterial occlusion is the first event in the chain of causality that leads to the stroke syndrome, perfusion and diffusion

Table 2. Recommended Acquisition Protocol for Perfusion-CT (PCT)	
Image acquisition rate	2 phases: 1st phase: 1 image per second, duration=30 to 45 seconds 2nd phase: 1 image per 2 to 3 seconds, duration=30 to 45 seconds Total duration of the acquisition at least 70 to 90 seconds
Gantry rotation	1 second per gantry rotation (up to every 3 seconds with "shuttle" or "toggle table" mode)
Image acquisition parameters	80 kVp, 100 mAs
Coverage and slice thickness	Maximal coverage possible based on CT scanner configuration (minimal coverage of 20 mm slab per contrast bolus injection preferable; two boluses is suggested to double coverage for all CT scanners with under 4 cm detector length unless precluded by contrast dose considerations) focus on supratentorial compartment/ anterior circulation 5- to 10-mm-thick slices field of view ≈24 cm
Slice orientation	Parallel to hard palate lowest slice through the proximal middle/anterior cerebral artery (above the orbits)
Contrast material	350 to 370 mg/mL iodinated contrast material high concentration, low/iso osmolar contrast preferred follow local guidelines for contrast-induced nephropathy prevention
Contrast volume	35 to 50 mL, followed by 20 to 40 mL saline flush
Injection rate	4 to 6 mL per second (power injector required) same injection rate for contrast and saline
IV access	18 to 20 gauge IV line right antecubital vein preferred (for anatomical reasons, reduces pooling of contrast, lowers the risk of extravasation and minimizes streak artifact at thoracic inlet in CTA portion)
Miscellaneous	PCT can be performed before or after CTA

imaging abnormalities, and ultimately infarction. For treatments aiming at the recanalization of the occluded artery, an appropriate assessment requires baseline and post-treatment assessment of arterial patency. The timing of the "reperfusion" scan should reflect a sufficient duration of the investigational therapy to demonstrate any effects. Ideally, the same modality (and MR field strength/CT parameters) should be used for the baseline and this "reperfusion" scan.

- The reperfusion/recanalization MRI study should include: scout image (no pregadolinium T1 required), DWI (Table 1), 3D time-of-flight MRA of the intracranial arteries, GRE, PWI (Table 1), and T2-FLAIR (FLAIR images can be obtained before or after gadolinium administration).
- The reperfusion/recanalization CT study should include: noncontrast CT, PCT (Table 2), and CTA, which can be limited to the intracranial arteries if the cervical arteries have been assessed at baseline (again, PCT can be performed before or after CTA).

If the patient has (1) undergone endovascular or intra-arterial (IA) therapy, or if the patient is (2) placed under continuous transcranial Doppler monitoring, and the recanalization (or persistent occlusion) status is known, then an MRA or CTA is not required, but may be obtained to assess for possible early reocclusion. PWI or PCT should be obtained in all cases to assess tissue reperfusion (or lack thereof, particularly considering the possibility of distal embolization after intraarterial therapy).

For treatments other than reperfusion therapies, such as hyperoxia, induced hypertension, or collateral flow augmentation, an "on-treatment" scan should be considered instead of the "posttreatment", "reperfusion" scan described above.

3. The third scan—either a noncontrast CT or GRE MRI of the brain—is a "safety scan" to assess the safety of investigational therapies, particularly with respect to the presence and degree of any hemorrhagic transformation. It may be obtained systematically or only in case of clinical worsening, typically between 24 and 72 hours after symptom onset.
4. A follow-up imaging study should be obtained to determine the final infarct volume. The appropriate timing for this follow-up scan is discussed below.

Recommended Perfusion Imaging Acquisition Protocols

Both PWI and PCT will be important components of the imaging studies collected from acute stroke patients and contributed to the central repository described below. The recommended imaging protocols for PWI and PCT are summarized in Tables 1 and 2. They are based on a consensus rather than solely evidence-based outcomes trials. The selected perfusion imaging parameters are based on first pass tracer kinetic models and intended to provide the optimal balance between requirements for maximization of image quality and image analysis along with the need to minimize contrast material dose and CT radiation dose. Although these protocols are already applied at the time points listed above at some institutions, their safety in terms of the total amount of contrast injected, the renal function, and the total radiation dose associated with the CT approach, requires further investigation.

Acute Stroke Imaging Central Repository

The development of standardized, integrated, clinically useful imaging paradigms in acute stroke will require consolidation of existing data, prospective collection of new data, and the development of tools to analyze data in a standardized fashion at the time of image acquisition. This process will also require the systematic accumulation of evidence that specific imaging markers at determined time points accurately predict radiographic and clinical outcomes. An Acute Stroke Imaging Consortium could provide the framework for linking international resources. This organization will require leadership on the part of a small group of respected neuroimagers with a track record in collaborative endeavors. Criteria for inclusion

in the consortium and definition of the structure for committees and representation will need to be established. A charge to the leadership of such a consortium will be to secure funding from public and private sources and to foster collaboration with imaging equipment manufacturers and stroke pharmaceutical/device companies.

An important initial step in effecting standardized analysis will be the creation of a central repository. This approach has been adopted by other organizations, as evidenced in acute stroke initiatives such as the American Heart Association's *Stroke - Get With the Guidelines* program,[1] the Centers for Disease Control and Prevention's (CDC) *Paul Coverdell National Acute Stroke Registry*,[2] and the NINDS *Specialized Program in Translational Research in Acute Stroke* (SPOTRIAS).[3] The Alzheimer Disease Neuroimaging Initiative (ADNI) group has successfully created an archive of imaging datasets publicly available for research images,[4] and there have also been nascent efforts to establish image repositories by SPOTRIAS,[3] the NIH Biomedical Informatics Research Network (BIRN),[5] the National Cancer Institute's *cancer Biomedical Informatics Grid* (caBIG),[6] and the International Consortium for Brain Mapping.[7] Investigators in Canada (*Canadian Stroke Network and Canadian Stroke Consortium*), Germany (*Stroke Competence Network*), United Kingdom and Scotland (*NeuroGrid* and *SINAPSE*),[8,9] France (VIRAGE), Japan (*Acute Stroke Imaging Standardization Group* - ASIST),[10] Taiwan, and the international investigators from the MR Stroke Collaborative Group[11] and the I KNOW[12] and VISTA[13] projects have also established imaging repositories or are in the process of doing so. A coordinated centralized resource building on these individual efforts would significantly benefit the field of acute stroke imaging.

The central repository should include a statistically meaningful number of imaging studies obtained in acute stroke patients admitted within 12 hours of symptom onset. In addition to these imaging studies, relevant metadata such as clinical information should be collected using standardized definitions, including (1) scores of clinical stroke severity, eg, NIH Stroke Scale, and other abstracted clinical parameters, (2) treatment records, (3) subsequent imaging studies, as well as information on (4) timing of symptom onset, admission, imaging studies, interventions, and clinical evaluations, and (5) the results of these evaluations indicative of functional outcome, eg, modified Rankin scores, Barthel Index scores, and cognitive scales. In addition, whenever possible, blood should be banked from a subset of patients for the assessment of biomarkers.

The concepts underlying image-guided selection of stroke patients for therapy are that (1) only patients with reversible ischemia are going to benefit from treatment, and (2) imaging can identify these patients. To validate these concepts, it will be important for the set of patients included in the central repository either (1) no treatment decision is based on imaging or (2) that matched control patients be identified in the case of image-guided treatment decisions, and that (3) all required imaging time points are obtained from all patients, including those deemed ineligible for treatment.

Documentation of early reperfusion (whether spontaneous or following therapy) is important because it strongly influences the appropriate predictive analysis and maximizes ability to test acute imaging paradigms. Patients who achieve early reperfusion are informative with regard to distinguishing penumbra from core; nonrecanalizing patients are informative with regard to distinguishing imaging benign oligemia from penumbra. Data would ideally be prospectively collected, but some retrospective data collected as part of existing networks and ongoing or completed trials, such as SPOTRIAS,[3] Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET),[11] MR RESCUE,[14] Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution (DEFUSE),[15] etc, would also be included in the imaging database, as long as the datasets satisfy the minimal requirements listed below in terms of imaging acquisition protocols and time points for imaging studies. Contributors to the repository will need to confirm consent of their patients and approval from their institutional review board to allow inclusion and utilization of anonymized data. The collected information (including the source or raw imaging data) will be deidentified. Also, the potential for unblinding during the analysis of the scans collected in the imaging repository will be considered.

The data collected in the repository will be made accessible to qualified researchers worldwide, based on the recommendations of a scientific committee that will evaluate proposed research projects. The confidentiality of patients' information will be rigorously protected. Contributors will be offered suitable reassurance over the uses to which their data may be put, the acknowledgement that they as individuals and their institutions will be granted for ensuing projects and developments, and an opportunity both to assist with the academic leadership of the consortium and to access the repository for projects of their own.

Adequate funding will be required to implement a data quality control program and to coordinate successful communication among participating sites. The cost of local study coordination, data collection, and image transfer will need to be compensated. The consortium will require financial resources to reimburse centers for performance of additional images or tests that are not otherwise clinically indicated, facilitate communication with sites and data transfer, organize regular investigator meetings, support centralized analysis, recruit services of dedicated stroke neuroimaging biostatisticians and technology assessment experts, and develop the technical infrastructure for the repository. Several mechanisms are available for potential funding through the NIH (U01), the Foundation for NIH, and the Institute of Medicine. Diverse partnerships will be explored with the NIH, private foundations, and industry.

Pilot Projects

As pilot studies for the proposed Acute Stroke Imaging Consortium, 3 "proof of concept" validation projects are proposed that would build on the optimized test dataset collected in the central repository.

Perfusion Imaging Processing

The first study would compare the different algorithms used to process PCT and PWI datasets. Many researchers believe that delay-insensitive or delay-compensated deconvolution methods that take recirculation into account, with automatic selection of 1 global or several local arterial input functions (AIF)

and of a venous output function (to correct for partial volume averaging in the AIF), are the most appropriate approach to process these datasets. However, a formal comparison with other analysis techniques (eg, nondeconvolution based or maximal slope methods) is required to demonstrate the superiority of this approach for predicting tissue fate and clinical outcome. This systematic comparison will also determine which parameters have, or do not have, a significant impact in terms of accurately representing acute perfusion status and predicting subsequent tissue outcome. Parameters studied will include cerebral blood flow, cerebral blood volume, and mean transit time, among others. The optimal method(s) should be most immune against slight raw image quality differences resulting from the use of different scanner hardware (ie, detector size configuration for multidetector CT scanners, magnetic field strengths, RF coils, scan parameters, injection protocols, and contrast agents used).

Imaging Prediction of Tissue Outcome

Still undetermined are the perfusion imaging parameters that indicate that tissue is at risk for infarction or that adequate reperfusion has taken place to prevent infarction. The "four scan" approach described above (baseline, 1 to 6 hours, 24 to 72 hours and final tissue outcome) will be used to develop, optimize, and validate imaging biomarkers of the infarct core and the ischemic penumbra. It will establish the value of baseline perfusion imaging in predicting final infarct size, using tissue fate as the outcome variable. Analysis will adjust for recanalization and reperfusion status, considered as a key determinant of tissue outcome and one that can be influenced by treatment. Different models of "operational" penumbra will be compared, and the optimal parameters (eg, cerebral blood flow, transit time, flow heterogeneity maps, etc) and optimal thresholds (eg, quantitative versus relative, gray matter versus white matter) to characterize the ischemic penumbra will be determined. Emphasis will be placed on quantitative approaches. A consensus on the appropriate timing for deciding on the final infarct volume will be developed. Similarly, standard definitions for recanalization (ie, changes in the degree of arterial patency) and reperfusion (ie, changes in the amount and spatial extent of perfusion changes) will be established before the final analysis. This analysis will incorporate patient characteristics at the time of scan acquisition, such as heart rate, blood pressure, glucose level, and hematocrit, which may have a significant impact on the distribution of contrast within collateral fields, and NIHSS which may reflect penumbral tissue shifting in and out of electric dysfunction. Imaging data in patients who have undergone reperfusion therapy and in those who have not will be analyzed separately to determine whether the results are the same for both groups.

Imaging Prediction of Clinical Outcome

One of the greatest challenges raised by pilot projects #1 and #2 is on the lack of consensus with respect to the optimal timing of outcome scans. Identification of key imaging biomarkers would facilitate the prediction of clinical outcome, define responders/nonresponders to therapy, and permit monitoring of the efficacy of stroke treatment. This would represent a significant advance in the field of stroke imaging.

The third study will determine the optimal timing to perform imaging (48 hours, 1 week, 2 weeks, 1 month, 2 months, 3 months) to predict clinical outcomes at varying time points in the course of stroke recovery (eg, 30 days, 3 months, 6 months, 12 months). Analysis will be stratified according to management (eg, conservative care, IV/IA thrombolysis, mechanical thrombectomy, collateral augmentation, or neuroprotective agents). The optimal imaging modality (MRI versus CT) should be identified (many researchers believe that T2-FLAIR is the current best imaging modality for the identification of final infarct, but this requires validation). Clinical outcomes will be documented using measures of global disability (eg, the Modified Rankin Scale [mRS]), instrumental activities of daily living (eg, Barthel Index [BI]), neurological deficit (eg, NIHSS), cognitive function (neuropsychological testing), and quality of life. All clinical outcome assessments should be undertaken in a standardized manner and blinded to imaging and vice versa. Inclusion of generic and stroke-specific quality of life scores, and measures that identify values important to the patient (patient-derived recovery targets), are considered critical. This plan is in harmony with the Patient-Reported Outcomes Measurement Information System (PROMIS), an NIH Roadmap initiative.[16] Cost-effectiveness analyses should be integrated into this and all future projects.

For this third pilot project, follow-up imaging studies will be obtained at multiple time points. All datasets should be contributed to the central repository.

Deliverables

The goals of these 3 pilot projects, based on the clinical and imaging data from the central repository, will be to provide investigators with:

1. A standard set of imaging sequences to be performed at specific time points.
2. A standardized image processing toolbox to analyze these imaging sequences and to extract quickly (ideally subminute but certainly <5 minutes) necessary information on the selection of acute stroke patients for acute therapies. This toolbox will include image registration and perfusion imaging software that will have the capacity to process both CT and MRI datasets in a reliable, reproducible, completely automated manner, and will have the ability to seamlessly process DICOM compatible data from any vendor's scanner. The developed software will be able to reliably identify patients who will benefit from a specific therapy—many researchers believe that this will involve segmentation of the infarct core and ischemic penumbra—and hence assist in treatment decisions in a relevant time window. Software performance will be expected not to deteriorate in the real world environments where the tool will be used. This toolbox will be developed in collaboration with imaging manufacturers, so that it can be integrated into their respective platforms, and will ultimately be made publicly or commercially available. This open source repository will facilitate software upgrades over time, as new postprocessing and analysis approaches develop. The data collected in the central repository will serve as a standard dataset to be used in benchmarking and validating these upgrades.

Overall, these deliverables will be accommodated in the clinical workflow of institutions using them and represent minimal impediment to enrollment of acute stroke patients in treatment protocols.

Next Steps

The deliverables outlined above, and the datasets stored in the central repository, will be available for further analyses. The initial focus will be on identifying the parameters that optimize the selection of acute stroke patients who benefit from reperfusion therapy. Other parameters of interest include aspects that will improve our understanding of collateral perfusion, including determinants of tissue fate and clinical outcome, and predictors of hemorrhagic transformation. A consensus on the definition of clinically meaningful hemorrhagic transformation will need to be developed.

At this stage, the efforts of the Acute Stroke Imaging Consortium will set the stage for 1 or more clinical trials. Indeed, the institutions contributing to the central repository will constitute a broad network of stroke care centers that could form the basis for an acute stroke trial/imaging network. They will all apply standardized imaging acquisition protocols, and use the same toolbox to process images and apply the same optimized criteria to interpret these processed images. This process will significantly minimize any source of variation other than the specific intervention (ie, drug or device) that will be tested in the clinical trial. The performance of the toolbox will be fully documented, facilitating sample size calculations for such trials. Initially, the identified imaging biomarkers will need to be validated in clinical trials with conventional clinical primary end points. Subsequently, it is anticipated that sample sizes will be reduced by the increased power afforded by the use of imaging biomarkers. In addition, if validated, the shorter follow-up periods that will be tested as part of the pilot projects will reduce loss to follow-up and minimize variation in clinical outcome due to unrelated events. This will greatly increase the feasibility and decrease the duration and cost of stroke treatment clinical trials.

Among the future stroke treatment clinical trials considered, particular interest has focused on 2 that have the potential to increase the proportion of acute stroke patients that are treated. The first trial is 1 of image-guided recanalization therapy in an extended time window (3 to 6 or 9 hours); the second one would assess image-guided recanalization therapy in wake-up stroke patients. Preliminary analysis (S.C. Johnston, personal communication, 2007) indicates that increasing the time window for acute reperfusion therapy from 3 hours to 6 hours could result in a 10-year societal benefit of $US 60 million. Neuroprotective agents and collateral enhancement could also be tested by the consortium, and future analyses should include attention to tissue repair, neurogenesis from stem cells, neurovascular remodeling, and stroke recovery.

Conclusion

Validation and widespread use of imaging for acute stroke patients' management will be facilitated by the establishment of an Acute Stroke Imaging Consortium, consisting of an international, multi-institutional stroke neuroimaging network. This consortium would provide an expertise structure in which methodological issues in stroke imaging can be addressed and consensus reached among different groups of researchers and care providers. Initially, the consortium would create a central repository of imaging studies and clinical data obtained from acute stroke patients and develop a standardized image analysis toolbox. These could subsequently benefit clinical trials of acute stroke treatments, including, but not limited to, treatment of stroke patients in an extended time window, treatment of patients with wake-up stroke or those with long intervals between the time last seen well and time of symptom discovery, and neuroprotective, collateral enhancement, and neuroplasticity-stimulating therapies. Ultimately, these efforts, combined with strategies to change patient/population behavior to promote earliest possible admission to hospital, should result in more acute stroke patients being appropriately treated and in an overall improvement of their outcome, as well as in reduced societal costs from economic disability. Collaboration between academia, the NIH, the FDA, and industry is integral to the successful realization of these aims.

Appendix

Contributors

Gregory W. Albers, MD, Stanford University; Andrei V. Alexandrov, MD, University of Alabama Comprehensive Stroke Center, Birmingham, Ala; Jeffry R. Alger, PhD, University of California, Los Angeles; Harvey J. Altman, MD, Mitsubishi Pharma America, Inc; Roland Bammer, PhD, Stanford University; Marc Barlow, GE Healthcare, Chalfont St. Giles, UK; Neil C. Barman, MD, Concentric Medical; Jean-Claude Baron, MD, Addenbrooke's Hospital Hills Rd, Department of Neurology, Cambridge, United Kingdom; William G. Barsan, MD, Department of Emergency Medicine, University of Michigan; Jim Beckett, Philips Medical Systems; Tamanna Bembenek, PhD, GE Healthcare; Carl Bjartmar, MD, PhD, Department of Neurology, International Clinical Research, H. Lundbeck A/S; Ken S. Butcher, MD, PhD, University of Alberta; Fernando Calamante, PhD, Brain Research Institute, Melbourne, Australia; Louis R. Caplan, MD, Beth Israel Deaconess Medical Center and Harvard Medical School; Trevor K. Carpenter, PhD, Western General Hospital, Edinbugh, United Kingdom; Neeraj Chopra, Siemens Medical Solutions USA Inc; William A. Copen, MD, Massachusetts General Hospital; Stephen Davis, MD, FRCP, Edin, FRACP, Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Parkville Victoria, Australia; Bart M. Demaerschalk, MD, MSc, FRCP(C), Mayo Clinic, Phoenix, Ariz; Colin P. Derdeyn, MD, Washington University; Rick M. Dijkhuizen, MD, PhD, University Medical Center Utrecht, Utrecht, The Netherlands; William P. Dillon, MD, University of California, San Francisco; Geoffrey A. Donnan, MD, FRACP, National Stroke Research Institute, Austin Health, University of Melbourne; Vincent Dousset, MD, CHU de Bordeaux - Université Victor Segalen Bordeaux, Service de Neuroradiologie, Hôpital Pellegrin, Bordeaux, France; James D. Eastwood, MD, Department of Radiology, Duke University Medical Center; Giora Z. Feuerstein, MD, Wyeth; Jochen B. Fiebach, MD, Charité University Hospital, Berlin, Germany, and Berlin NeuroImaging Center (BNIC), Berlin, Germany; David Fiorella, MD, PhD, Cleveland Clinic; Marc Fisher, MD, University of Massachusetts Medical School; Anthony J. Furlan, MD, University Hospitals Case Medical Center, Case Western Reseve University, Department of Neurology, Cleveland, Ohio; Karen L. Furie, MD, MPH, Massachusetts General Hospital; James Gantenberg, FACHE, Neuro-

radiology Education and Research Foundation and American Society of Neuroradiology; Gregory V. Goldmakher, MD, PhD, Massachusetts General Hospital; R. Gilberto Gonzalez, MD, PhD, Massachusetts General Hospital; Werner Hacke, MD, PhD, Heidelberg University; Maxim D. Hammer, MD, University of Pittsburgh Medical School Stroke Center; Randall T. Higashida, MD, University of California, San Francisco; Michael D. Hill, MD, MSc, FRCPC, HSF Alberta/NWT/NU Professorship Department of Clinical Neurosciences/Medicine/Community Health Sciences, Hotchkiss Brain Institute, University of Calgary, Canada; Ellen G. Hoeffner, MD, University of Michigan; Amie W. Hsia, MD, Washington Hospital Center Stroke Center, Washington, DC; S. Claiborne Johnston, MD, PhD, University of California, San Francisco, Department of Neurology; Tudor G. Jovin, MD, University of Pittsburgh Medical School Stroke Center and Center for Neuroendovascular Therapy; Markku Kaste, MD, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland; Chelsea S. Kidwell, MD, Goergetown University, Washington Hospital Center; Stephan P. Kloska, MD, Department of Clinical Radiology, University of Muenster, Germany; Martin Köhrmann, MD, Department of Neurology, University Clinic at Erlangen, Germany; Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke; Kohsuke Kudo, MD, PhD, Hokkaido University, Japan; Paul Kwon, Genentech; Meng Law, MD MBBS FRACR, Mount Sinai Medical Center, New York; Ting-Yim Lee, PhD, Lawson Health Research Institute, Canada; Kennedy R. Lees, MD, University Department of Medicine & Therapeutics, Western. Infirmary, University of Glasgow, United Kingdom; Michael H. Lev, MD, Massachusetts General Hospital; David S. 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