Advance imaging and Standardization in acute stroke

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Funding: The research was supported by a grant from the Ministry of Food and Drug Safety in 2018 (No. 18182MFDS402).
Overview

- Advanced techniques in acute stroke MRI
  1) Fast imaging
  2) Metabolic imaging

- Clinical trial imaging in acute ischemic stroke:
  Recommendation & Guideline with Standardization
Fast scan for MRI

Six-Minute Magnetic Resonance Imaging Protocol for Evaluation of Acute Ischemic Stroke

Pushing the Boundaries

Kambiz Nael, MD; Rihan Khan, MD; Gagandeep Choudhary, MD; Arash Meshksar, MD; Pablo Villablanca, MD; Jennifer Tay, MD; Kendra Drake, MD; Bruce M. Coull, MD; Chelsea S. Kidwell, MD

Background and Purpose—If magnetic resonance imaging (MRI) is to compete with computed tomography for evaluation of patients with acute ischemic stroke, there is a need for further improvements in acquisition speed.

Methods—Inclusion criteria for this prospective, single institutional study were symptoms of acute ischemic stroke within 24 hours onset, National Institutes of Health Stroke Scale ≥3, and absence of MRI contraindications. A combination of echo-planar imaging (EPI) and a parallel acquisition technique were used on a 3T magnetic resonance (MR) scanner to accelerate the acquisition time. Image analysis was performed independently by 2 neuroradiologists.

Results—A total of 62 patients met inclusion criteria. A repeat MRI scan was performed in 22 patients resulting in a total of 84 MRIs available for analysis. Diagnostic image quality was achieved in 100% of diffusion-weighted imaging, 100% EPI-fluid attenuation inversion recovery imaging, 98% EPI-gradient recalled echo, 90% neck MR angiography and 96% of brain MR angiography, and 94% of dynamic susceptibility contrast perfusion scans with interobserver agreements (k) ranging from 0.64 to 0.84. Fifty-nine patients (95%) had acute infarction. There was good interobserver agreement for EPI-fluid attenuation inversion recovery imaging findings (k=0.78; 95% confidence interval, 0.66–0.87) and for detection of mismatch classification using dynamic susceptibility contrast-Tmax (k=0.92; 95% confidence interval, 0.87–0.94). Thirteen acute intracranial hemorrhages were detected on EPI-gradient recalled echo by both observers. A total of 68 and 72 segmental arterial stenoses were detected on contrast-enhanced MR angiography of the neck and brain with k=0.93, 95% confidence interval, 0.84 to 0.96 and 0.87, 95% confidence interval, 0.80 to 0.90, respectively.

Conclusions—A 6-minute multimodal MR protocol with good diagnostic quality is feasible for the evaluation of patients with acute ischemic stroke and can result in significant reduction in scan time rivaling that of the multimodal computed tomographic protocol. (Stroke. 2014;45:1985-1991.)

Key Words: magnetic resonance angiography ■ magnetic resonance imaging ■ perfusion imaging ■ stroke
Table 1. MR Imaging Protocol and Sequence Parameters

<table>
<thead>
<tr>
<th></th>
<th>DWI</th>
<th>EPI-FLAIR</th>
<th>EPI-GRE</th>
<th>CE-MRA</th>
<th>DSC</th>
</tr>
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<tbody>
<tr>
<td>TR/TE, ms</td>
<td>4600/65</td>
<td>10000/82</td>
<td>1860/48</td>
<td>3.3/1.2</td>
<td>1450/22</td>
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<tr>
<td>FA, °</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>25</td>
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<td>160</td>
<td>128</td>
<td>192</td>
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<td>128</td>
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<tr>
<td>FOV, mm</td>
<td>220</td>
<td>220</td>
<td>220</td>
<td>340</td>
<td>220</td>
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<tr>
<td>Slices (n×thickness), mm</td>
<td>30×4</td>
<td>30×4</td>
<td>40×3</td>
<td>120×0.8</td>
<td>30×4</td>
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<tr>
<td>GRAPPA</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Acquisition time, s</td>
<td><strong>58</strong></td>
<td><strong>52</strong></td>
<td><strong>56</strong></td>
<td><strong>22</strong></td>
<td><strong>90</strong></td>
</tr>
</tbody>
</table>
Ultra Fast Brain (GE Architect)

- DWI (Hyperband) → 00:10
- T2 SSFSE → 00:10
- T1 SPGR → 00:25
- T2 * GRE → 00:10
- 3D TOF (Hypersense) → 0:38
Simultaneous multi-slice imaging = Hyperband

Compressed sensing = Hypersense

3T
Techniques: Compressed sensing
Techniques: Multi-band

Simultaneous Multi-Slice Acceleration with blipped CAIPIRINHA

- Multiple slices excited simultaneously
- Blipped CAIPIRINHA applied during echo train
  Minimization of g-factor related SNR loss
- Slice GRAPPA based unaliasing
- Inplane GRAPPA based unaliasing
Techniques: Parallel imaging

\[ S = C \cdot I \]
\[ I = C^{-1} \cdot S \]

Coil Sensitivity Map:
- \( c_1(x,y) \)
- \( c_2(x,y) \)
- \( c_3(x,y) \)

\( I(x,y) \)

Courtesy of Kim PhD.
Fast scan for 1.5 T MRI

- Siemens Avanto 1.5T ER (5 min 8 s ~ 6min 43s) + 2 min (조영제)

<table>
<thead>
<tr>
<th></th>
<th>TR/TE/IR</th>
<th>FA</th>
<th>Matrix</th>
<th>FOV</th>
<th>Slices (nxthickness)</th>
<th>ETL</th>
<th>GRAPPA</th>
<th>NAV</th>
<th>Scan time</th>
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<tr>
<td>Localizer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 s</td>
</tr>
<tr>
<td>Scout</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 s</td>
</tr>
<tr>
<td>FLAIR 기존</td>
<td>9000/109/2500</td>
<td>150</td>
<td>256 x 190</td>
<td>210 x 184</td>
<td>20 x 5</td>
<td>21</td>
<td>1</td>
<td></td>
<td>128 s</td>
</tr>
<tr>
<td>FLAIR EPI</td>
<td>9000/101/2000</td>
<td>90</td>
<td>128 x 128</td>
<td>230 x 230</td>
<td>20 x 5</td>
<td>128 (EPI)</td>
<td>2</td>
<td></td>
<td>45 s</td>
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<tr>
<td>FLAIR ETL</td>
<td>9000/102/2500</td>
<td>150</td>
<td>192 x 192</td>
<td>210 x 184</td>
<td>20 x 5</td>
<td>32</td>
<td>2</td>
<td>1</td>
<td>74 s</td>
</tr>
<tr>
<td>FLAIR TR</td>
<td>5560/109/1930</td>
<td>150</td>
<td>256 x 256</td>
<td>210 x 184</td>
<td>20 x 5</td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>79 s</td>
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<tr>
<td>GRE 기존</td>
<td>690/16</td>
<td>15</td>
<td>256 x 205</td>
<td>210</td>
<td>20 x 5</td>
<td></td>
<td></td>
<td></td>
<td>141 s</td>
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<tr>
<td>GRE Parallel</td>
<td>765/26</td>
<td>20</td>
<td>192 x 163</td>
<td>220 x 220</td>
<td>20 x 5</td>
<td>3</td>
<td>1</td>
<td></td>
<td>54 s</td>
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<tr>
<td>GRE EPI</td>
<td>2260/48</td>
<td>90</td>
<td>192 x 192</td>
<td>230 x 230</td>
<td>20 x 5</td>
<td>192 (EPI)</td>
<td>2</td>
<td>10</td>
<td>29 s</td>
</tr>
<tr>
<td>DWI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>81 s</td>
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<tr>
<td>PWI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61 s</td>
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<tr>
<td>CE MRA 기존</td>
<td>3.67/1.31</td>
<td>30</td>
<td>240</td>
<td>340</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td></td>
<td>74 s</td>
</tr>
<tr>
<td>CE MRA</td>
<td>3.37/1.2</td>
<td>25</td>
<td>144</td>
<td>340</td>
<td>0.8</td>
<td>3</td>
<td>1</td>
<td></td>
<td>39 s</td>
</tr>
</tbody>
</table>

M.S.Chung, S.C. Jung et al. Eur Radiol 2018
Metabolic imaging beyond perfusion

- Research >> Clinical field
- Imaging should not delay treatments
- MRS
- Oxygen extraction fraction: SWI
- Hyperpolarized C13
- .....
CEST

- CEST (Chemical exchange saturation transfer)
- In vivo molecular imaging without exogenous contrast agents
- Chemical exchange: proton exchange between solute and water pool
- Signal amplification
- Amide proton transfer (APT)
pH weighted imaging

- Exchange rate ($k$): very pH dependent, pH↓ → $k$↓ (pH weighted MR imaging)
- Amide proton (APT)
- Amine proton (GluCEST)
Background: Role of pH-weighted imaging in stroke

Reversal
Amide Proton Transfer

MCAO model
pH weighte imaging

Orange: pHW deficit, Black: DWI deficit, Purple: PWI deficit
pH weighted imaging

- Significant correlation with lactate in linear regression: ADC, APT

Permanent occlusion model
Transient occlusion model
Human APT in acute stroke

1 day

6 days

34 days
Human APT in acute stroke

Acute: Acidosis
Subacute: Akalosis
Chronic: Neutral
Human APT in acute stroke

Surrogate biomarker?

<table>
<thead>
<tr>
<th></th>
<th>Onset time ≤96 h</th>
<th>Onset time 4 ~ 7 days</th>
<th>Onset time 8 ~ 21 days</th>
<th>Onset time ≥22 days</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment (n = 30)</td>
<td>Post-treatment (n = 12)</td>
<td>Pre-treatment (n = 13)</td>
<td>Post-treatment (n = 11)</td>
</tr>
<tr>
<td>Lesion</td>
<td>−1.13 ± 1.05</td>
<td>−0.33 ± 0.61</td>
<td>−0.75 ± 0.45</td>
<td>−0.30 ± 0.34</td>
</tr>
<tr>
<td>CNAWM</td>
<td>0.43 ± 0.50</td>
<td>0.46 ± 0.28</td>
<td>0.20 ± 0.26</td>
<td>0.19 ± 0.50</td>
</tr>
<tr>
<td>APTW contrast</td>
<td>−1.56 ± 1.01</td>
<td>−0.79 ± 0.51</td>
<td>−0.95 ± 0.46</td>
<td>−0.49 ± 0.32</td>
</tr>
<tr>
<td>NIHSS</td>
<td>6.3 ± 4.2</td>
<td>3.2 ± 1.6</td>
<td>5.5 ± 3.7</td>
<td>3.1 ± 1.4</td>
</tr>
</tbody>
</table>

|                     | Pre-treatment (n = 12)             | Post-treatment (n = 7) |
| Lesion              | −0.05 ± 0.69                       | 0.82 ± 0.79            |
| CNAWM               | 0.27 ± 0.57                        | 0.21 ± 0.35            |
| APTW contrast       | −0.31 ± 0.57                       | 0.61 ± 0.59            |
| NIHSS               | 2.4 ± 0.8                          | 1.6 ± 0.6              |

Lu Yu et al. Frontiers in Neurology 2019
Human APT in acute stroke: Repeatability

![Diagram showing scan sequences and time intervals for normal, glioma, and stroke conditions.](image-url)
### Human APT in acute stroke: Repeatability

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Patients with glioma</th>
<th>Patients with stroke</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>19</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>Number of male subjects</strong></td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>53.8 ± 13.4</td>
<td>53.6 ± 10.9</td>
<td>68.5 ± 8.7</td>
</tr>
<tr>
<td><strong>Imaging interval (intersession, days)</strong></td>
<td>3.5 ± 0.5</td>
<td>3.7 ± 0.2</td>
<td>Less than 1 day</td>
</tr>
<tr>
<td><strong>Supratentorial locations</strong></td>
<td>19</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infratentorial locations</strong></td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Lesion size (mL)</strong></td>
<td>-</td>
<td>28.7</td>
<td>6.6</td>
</tr>
<tr>
<td><strong>ROI size (mL)</strong></td>
<td>0.2</td>
<td>28.7</td>
<td>6.6</td>
</tr>
</tbody>
</table>
**Human APT in acute stroke: Repeatability**

<table>
<thead>
<tr>
<th></th>
<th>Supratentorial</th>
<th>Glioma</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>wCV (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>27.4 (21.8, 35.6)</td>
<td>16.1 (12.6, 21.3)</td>
<td>15.0 (11.4, 20.6)</td>
</tr>
<tr>
<td>Intrasession</td>
<td>23.7 (17.3, 34.5)</td>
<td>12.0 (8.5, 18.1)</td>
<td>11.8 (8.1, 18.8)</td>
</tr>
<tr>
<td>Intersession† (1 vs. 3)</td>
<td>30.4 (22.0, 45.0)</td>
<td>15.7 (11.1, 23.8)</td>
<td>16.2 (11.0, 26.0)</td>
</tr>
<tr>
<td>Intersession* (2 vs. 3)</td>
<td>27.8 (20.2, 40.9)</td>
<td>19.8 (14.0, 30.2)</td>
<td>16.7 (11.4, 26.8)</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.85 (0.68, 0.94)</td>
<td>0.96 (0.91, 0.99)</td>
<td>0.93 (0.82, 0.98)</td>
</tr>
<tr>
<td>Intrasession</td>
<td>0.83 (0.55, 0.93)</td>
<td>0.97 (0.90, 0.99)</td>
<td>0.95 (0.83, 0.99)</td>
</tr>
<tr>
<td>Intersession† (1 vs. 3)</td>
<td>0.78 (0.43, 0.91)</td>
<td>0.95 (0.84, 0.98)</td>
<td>0.87 (0.54, 0.96)</td>
</tr>
<tr>
<td>Intersession* (2 vs. 3)</td>
<td>0.77 (0.40, 0.91)</td>
<td>0.91 (0.74, 0.97)</td>
<td>0.86 (0.55, 0.96)</td>
</tr>
</tbody>
</table>
### Human APT in acute stroke: Repeatability

<table>
<thead>
<tr>
<th></th>
<th>wCV (%)</th>
<th>Supratentorial</th>
<th>Infratentorial</th>
<th>Supra- + Infratentorials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>27.4 (21.8, 35.6)</td>
<td>32.7 (25.9, 42.9)</td>
<td>34.0 (28.7, 41.0)</td>
</tr>
<tr>
<td>Intrasession</td>
<td></td>
<td>23.7 (17.3, 34.5)</td>
<td>26.9 (19.6, 39.5)</td>
<td>28.3 (22.5, 36.8)</td>
</tr>
<tr>
<td>Intersession† (1 vs. 3)</td>
<td></td>
<td>30.4 (22.0, 45.0)</td>
<td>33.7 (24.3, 50.4)</td>
<td>35.4 (27.9, 46.7)</td>
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<tr>
<td>Intersession* (2 vs. 3)</td>
<td></td>
<td>27.8 (20.2, 40.9)</td>
<td>37.6 (27.0, 57.0)</td>
<td>38.3 (30.1, 50.8)</td>
</tr>
<tr>
<td>ICC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.85 (0.68, 0.94)</td>
<td>0.44 (−0.18, 0.76)</td>
<td>0.84 (0.72, 0.91)</td>
</tr>
<tr>
<td>Intrasession</td>
<td></td>
<td>0.83 (0.55, 0.93)</td>
<td>0.46 (−0.43, 0.80)</td>
<td>0.84 (0.69, 0.92)</td>
</tr>
<tr>
<td>Intersession† (1 vs. 3)</td>
<td></td>
<td>0.78 (0.43, 0.91)</td>
<td>0.40 (−0.40, 0.76)</td>
<td>0.74 (0.49, 0.86)</td>
</tr>
<tr>
<td>Intersession* (2 vs. 3)</td>
<td></td>
<td>0.77 (0.40, 0.91)</td>
<td>0.15 (−1.14, 0.67)</td>
<td>0.70 (0.43, 0.84)</td>
</tr>
</tbody>
</table>
임상시험 영상활용

Imaging Biomarker (Pubmed)

Imaging biomarker AND Clinical trial

# Fund project (imaging biomarker)

Total = 6,229

Funding

Total = $3,452,186,291
Clinical trial imaging in Stroke


- 뇌졸중 임상시험에 있어서 영상 획득과 해석에 대한 Consensus 및 권고안 제시

- 뇌졸중 임상시험의 영상 조건: Speed, Standardization, Quality control, Reproducibility, Centralization
Clinical trial imaging in Stroke

Table 1. General Requirements for Imaging in Stroke Clinical Trials

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Speed</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Standardization</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Quality control</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Reproducibility</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Centralization</strong></td>
<td>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</td>
</tr>
</tbody>
</table>

⇒ Reliability ↑↑
Standardization in Acute Ischemic Stroke

Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

Consensus Recommendations and Further Research Priorities

Conclusions—Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals, and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials. (Stroke. 2016;47:1389-1398. DOI: 10.1161/STROKEAHA.115.012364.)

Max Wintermark, MD, MAS; for the Stroke Imaging Research (STIR) and VISTA-Imaging Investigators*

Background and Purpose—The Stroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5 to 6, 2015 in Washington, DC. The purpose of this roadmap was to focus on the role of imaging in future research and clinical trials.

Methods—This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration to discuss STIR priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials.

Results—The imaging session summarized and compared the imaging components of the recent positive endovascular trials and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch, and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials.
Clinical trial imaging in Acute ischemic stroke

- 2012 ~ 2018
- Randomized, Multi-center clinical trials in endovascular treatment for acute cerebral ischemic stroke
## IIRC, Imaging core lab, Standardization

<table>
<thead>
<tr>
<th>Trial nickname</th>
<th>Independent image review and core laboratory</th>
<th>Reviewers</th>
<th>Standardization</th>
<th>*CT: MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAWN</td>
<td>Used</td>
<td></td>
<td>Same imaging modality is encouraged to be used during follow-up. 131: 75 (63.6: 36.4 %)</td>
<td></td>
</tr>
<tr>
<td>DEFUSE 3</td>
<td>Used</td>
<td></td>
<td>The baseline and follow-up imaging should be performed with DEFUSE 3 protocol, which is installed at all study sites. 133:49 (73.1: 26.9 %)</td>
<td></td>
</tr>
<tr>
<td>PISTE</td>
<td>Used</td>
<td>3 Neuroradiologists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASTER</td>
<td>Used</td>
<td>2 + 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THERAPY</td>
<td>Used</td>
<td>1 Neuroradiologist</td>
<td>Nonenhanced thin-section (≤ 2.5 mm) CT</td>
<td></td>
</tr>
<tr>
<td>THRACE</td>
<td>Used</td>
<td>4 Neuroradiologists for CT and MR, 3 Interventional neuroradiologists for DSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>Used</td>
<td>2+1</td>
<td>Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer. 189: 15 (92.6: 7.4 %)</td>
<td></td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Used</td>
<td></td>
<td>NECT and CTA protocols were presented. 13: 54 (19.4: 80.6 % at 24 hours)</td>
<td></td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Used</td>
<td>Neuroradiologist/Stroke neurologist</td>
<td>The imaging protocols will follow current international consensus guidelines. Standard CT and MR protocols were presented.</td>
<td></td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>Used</td>
<td>Two neuroradiologists</td>
<td></td>
<td>24: 94 (20 : 80 %)</td>
</tr>
<tr>
<td>MR RESCUE</td>
<td>Used</td>
<td></td>
<td>MR RESCUE protocols were presented.</td>
<td></td>
</tr>
<tr>
<td>SYNTHESIS</td>
<td>Used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMS III</td>
<td>Used</td>
<td>3 CT experts (including one neuroradiologist was mandatory)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWIFT</td>
<td>Used</td>
<td>2 neurointerventionalists</td>
<td>It is preferred that whether CT or MR is taken at baseline, the same imaging modality should be obtained at follow-up.</td>
<td></td>
</tr>
<tr>
<td>TREVO 2</td>
<td>Used</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Standardization

- The process of implementing and developing technical standards based on the consensus of different parties

1. Technical Standards: Imaging Protocols
2. Different Parties: Vendors, Scanners, Softwares
3. Consensus: Figuring out common protocols for all vendors, scanners, softwares → Standardization

Courtesy of 김인성 Ph.D.
QIBA (Quantitative Imaging Biomarkers Alliance)

1) In 2007, RSNA organized the Quantitative Imaging Biomarkers Alliance® (QIBA) to unite researchers, healthcare professionals and industry to advance **quantitative imaging** and the use of **imaging biomarkers in clinical trials and clinical practice**.

2) QIBA seeks to **improve** the value and practicality of **quantitative imaging biomarkers** by **reducing variability** across devices, sites, patients and time

Oncology imaging
Standardization
Standardization in acute stroke imaging

- QIBA (Quantitative Imaging Biomarkers Alliance)
- Oncology imaging

- Urgent circumstance in acute ischemic stroke
- Balancing between standardization and critical pathway
Clinical trial imaging in Stroke

Table 1. General Requirements for Imaging in Stroke Clinical Trials

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed</td>
<td>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.</td>
</tr>
<tr>
<td>Standardization</td>
<td>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.</td>
</tr>
<tr>
<td>Quality control</td>
<td>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.</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>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.</td>
</tr>
<tr>
<td>Centralization</td>
<td>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.</td>
</tr>
</tbody>
</table>

→ Reliability ↑ ↑
Clinical trial imaging in Stroke

Imaging support for multicenter clinical trials

- Imaging protocol / charter
- Global standards

- Site training
- Site monitoring

- Imaging acquisition

- QA/QC
- Data management

- Post-processing
- Image analysis
- Central reading

Central Imaging Core Lab in clinical trials
Clinical trial imaging: Standards

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1890 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologies Evaluation and Research (CBER)

August 2011
Clinical/Medical

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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April 2018
Clinical/Medical
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Clinical trial imaging: Standardization

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in optimizing the quality of imaging data obtained in clinical trials intended to support approval of drugs and biological products. This guidance focuses on imaging acquisition, display, archiving, and interpretation process standards that we regard as important when imaging is used to assess a trial’s primary endpoint or a component of that endpoint.

Considerable standardization already exists in clinical imaging. There are a variety of sources, including picture archiving and communication systems and the Digital Imaging and Communications in Medicine (DICOM) formats for the handling and transmission of clinical imaging data. Standardization, while important for all clinically used measures, becomes essential for an imaging endpoint used in a clinical trial to reduce variability and to ensure interpretability of the results. The extent of trial-specific standardization may vary depending upon how standardized the local imaging procedures are (e.g., routine bone X-rays (relatively standardized) versus bone mineral density (more variability across sites)). This guidance does not address approaches for...
F. What Procedures Should Be Standardized for an Imaging-Based Clinical Trial Primary Endpoint?

No single set of detailed imaging process standards is readily applicable to every clinical trial because the trials differ in design and objectives. When usual medical practice imaging process standards are acceptable in a trial, the plans for the use of such standards should be stated in the clinical protocol. Determinations on what to standardize beyond these expectations should be driven by consideration of the imaging processes that might introduce variability and inaccuracy to the endpoint and by consideration of the other items outlined below. When determining the
Clinical trial imaging: Standardization

- Imaging modality availability and the modality’s technical performance variation across trial sites

- Performance features of the imaging modality at the trial sites or any other locations where subjects may undergo imaging

- Qualifications of the imaging technologists and any special technological needs for the trial

- Proposed imaging measures’ reliance on phantoms and/or calibration standards to ensure consistency and imaging quality control among clinical sites

- Any unique image acquisition features of the trial design, including subject positioning, anatomical coverage of imaging, use of contrast, timing of imaging, importance of subject sedation, and scanner settings for image acquisition

- Image quality control standards, including those specifying the need for repeat imaging to obtain interpretable images
Clinical trial imaging: Standardization

- Procedures for imaging display and interpretation, including technical variations in reader display stations
- Nature of the primary endpoint image measurement, including the importance of training image readers in trial-specific quantification methods
- Extent that image archiving could be important to the trial’s conduct, monitoring, and data auditing
- Potential for imaging modality upgrades or modality failures, as well as the potential variation in imaging drugs (such as contrast agents) across trial sites
- Precedent for use of the imaging-based primary endpoint measure in investigational drug development, especially previously observed imaging methodological problems
뇌졸중 영상 적합 팬텀

NIST/ISMRM system phantom

NIST/RSNA/NCI diffusion phantom

NIST/UCSF/NCI system phantom
뇌졸중 영상 적합 팬텀

영상바이오마커 선정 내부 물질 협의 팬텀 디자인

내부 물질 협의 팬텀 주문 제작 표준물질 공식인증

센터소개

의료용합표준센터는 2025년 세계적으로 의료측정표준 분야의 연구를 선도하는 대표적인 연구센터가 되기 위하여 기본 물리량에 소급한 의료기기 측정표준 확립, 의료영상 정량화를 통한 재현성과 신뢰성이 확보된 영상 측정기술 개발, 정밀측정 기술을 기반으로 새로운 의료진단 및 치료기술 개발 연구를 통해 의료 빅데이터 영역화를 추구하고 있습니다.

표준연, 의료기기 성능 평가하는 모듈형 팬텀 세계 첫 개발

<조회한 한국표준과학연구원 의료용합측정표준센터 박사가 새로 개발한 'MOMA 팬텀' 모듈 물성을 시험하고 있다.>
뇌졸중 영상 적합 패턴

뇌졸중 표준화 패턴을 위한 영상바이오마커 선정: DWI, GRE (T2*), T1

K-Stroke-Block (KSB) 패턴과 QIBA 및 NIST/ISMRM system 패턴과의 차별점

1. Spatial resolution 측정 가능

2. Cost-effective 패턴

3. GRE 동시에 측정 가능 패턴

4. 레고블럭방식의 패턴: 다양한 영상 바이오마커 선정 및 조합 가능
뇌졸중 영상 적합 팬텀

NIST (National Institute of Standards and Technology) 공인 물질
가격 경쟁력 (미국 제품의 반값)
조립이 용이하고 맞춤형 디자인 가능
분석 소프트웨어

1. 국내: 소프트웨어 개발이 진행중 (자동 정량화 분석 소프트웨어가 주류, DWI-PWI mismatch 위주, 해외 소프트웨어에 비해 가격이 낮으나 개별 연구자에게는 여전히 높을 수도 있음.)

2. 해외: 다수의 글로벌 회사 및 연구자들이 다양한 분석 소프트웨어를 판매 (편리한 UI, 고가)
분석 소프트웨어

http://datasharing.aim-aicro.com/strokevolumetry?language=en
분석 소프트웨어

http://datasharing.aim-aicro.com/strokevolumetry?language=en
Clinical trial imaging in Acute ischemic stroke: Standards

- 쇠졸중 치료 약물 임상시험에서의 영상 바이오마커의 기준안을 제시한다.

1. 쇠졸중 영상 바이오마커 표준화 팬텀

2. 쇠졸중 영상 바이오마커 분석 소프트웨어

3. 쇠졸중 영상 바이오마커의 촬영, 전송, 분석 등의 기준
Clinical trial imaging in Acute ischemic stroke: Standards

급성 뇌졸중 임상시험 영상의 글로벌 동향
조사 보고서

2018. 10

저작: 서울아산병원 영상의학과/
음산대학교 의과대학/

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국문보고서: 본 보고서는 정부(식품의약품안전처, 18182교량402)의 중역연구개발사업의 자원을 받아 수
행된 연구일.
영문보고서: This work was supported by the grant of Ministry of Food and Drug Safety
(18182MFS402).
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저자: 서울아산병원 영상의학과/
울산대학교 의과대학/

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영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).
Clinical trial imaging in Acute ischemic stroke: Standards

- Infarct core을 반영하는 영상: CT, MR (DWI, PWI-CTP)
- Hemorrhagic transformation/Hematoma를 반영하는 영상: CT, MR (GRE)
- Steno-occlusion을 반영하는 영상: CTA, MRA, DSA
- 영상 촬영 기준 및 팬텀 사용
- 최소한의 Standardization
- Independent centralized reading and analysis
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경청해 주셔서 감사합니다.