Experience in Imaging Core Lab and Independent Central Review

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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

- Imaging CRO (contract research organization) and Imaging core laboratory, and Independent Image Review Committee (IIRC)

- Experience in Acute ischemic stroke

- Summary & Recommendation
CRO

- Company that provides **support** to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

- **Imaging CRO:** CRO for Imaging service in Research

- **Imaging core laboratory** for Centralized imaging analysis

- **Independent Image Review Committee (IIRC)** for Centralized reading
Imaging biomarker

# Fund project (imaging biomarker)
Total = 6,229

Funding
Total = $3,452,186,291
Imaging biomarker

역할
- Predictive biomarker
- 약력학/약동학 평가
- 약리 메커니즘
- 유효성/독성 평가

장점
- 비침습적, 생체 내 현상
- 시간에 따라 반복적 관찰
- 개체수/피험자수 최소화
- 전임상-임상 연계

효과
- 피험자수 ↓
- 시험기간 ↓
- 개발비용 ↓

환자선별: 암밀로이드 PET으로 알츠하이머병 선별

약물 약동학 평가: Dynamic PET

약리작용 평가 (수용체 영상화)

유효성 평가 (CT, MR, PET)

독성 평가 (심장 MRI로 심 근독성)
Imaging CRO

Imaging support for multicenter clinical trials

<table>
<thead>
<tr>
<th>Services</th>
<th>Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Imaging protocol / charter</td>
<td>Quantitative Imaging Biomarkers Alliance</td>
</tr>
<tr>
<td>- Global standards</td>
<td>RSNA</td>
</tr>
<tr>
<td>- Site training</td>
<td>Guidance for Industry Standards for Clinical</td>
</tr>
<tr>
<td>- Site monitoring</td>
<td>Trial Imaging Endpoints</td>
</tr>
<tr>
<td>- Imaging acquisition</td>
<td>SAMSUNG</td>
</tr>
<tr>
<td>- QA/QC</td>
<td>삼성의료원</td>
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<tr>
<td>- Data management</td>
<td>서울아산병원</td>
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<td>- Post-processing</td>
<td>서울대학교병원</td>
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<tr>
<td>- Image analysis</td>
<td></td>
</tr>
<tr>
<td>- Central reading</td>
<td></td>
</tr>
</tbody>
</table>

Central Imaging Core Lab in clinical trials
CRO Team for multicenter trial

Project Manager
Imaging CRA
Imaging QC
IT manager
Radiologists
Regulation medicine
Site core lab service

- Investigator (Clinician)
- Imaging CRC
- Radiology Department
- Radiologist

- Coordinate imaging device & protocol
- Image acquisition
- Data anonymization & transfer
- Pre-study validation
- Local reading

Central core lab service

- Image Analyst Central Reader
- Image CRA
- IT system Manager
- Imaging physicist (PhD)

- Image protocol
- Site training/monitoring
- Imaging data management
- Image quality control
- Central reading
- Regulation/SOP
AIM : Asan Image Metrics

It is the first Central Imaging Core Lab in Korea that was established at Asan Medical Center to support all aspects of imaging use in clinical trials.

In clinical trials, we support to continue efficient, quick and accurate clinical trials through integrated consultation and imaging support services from imaging protocol plan to analysis.

Reliable Results
Reliable results by medical imaging professionals

Rapid Results
Rapid results by web-based process

High Quality
High quality with expertise in the latest imaging technique

Quick Facts about AIM

Our Services

Our Strength


12. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET, Lancet 2008): Alteplase의 6시간 연장 사용의 유효성 평가를 위한 연구로서 임상지표를 우선하여 영상바이오마커 지표가 Primary endpoint로서 사용되었음. Primary endpoint로서 DWI (baseline) 과 T2-weighted imaging (=FLAIR, 90 days after)사이의 뇌경색 부피 변화를 사용하였음. 정량적 영상 분석 소프트웨어를 이용하여 뇌경색 부피 변화를 측정하였음. PWI, MRA를 이용하여 관류 변화와 재개통 여부를 판정하였음.


## Imaging core lab & IIRC

2012 – 2018 Clinical trials for endovascular treatment in acute ischemic stroke

<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.</td>
<td>131: 75 (63.6: 36.4 %)</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.</td>
<td>133:49 (73.1: 26.9 %)</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.</td>
<td>189: 15 (92.6: 7.4 %)</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.</td>
<td>13: 54 (19.4: 80.6 % at 24 hours)</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>
Guidance

Clinical Trial Imaging Endpoint Process Standards
Guidance for Industry

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

April 2018
Clinical/Medical
Guidance

A. Choice of Imaging Modality

If an imaging-based primary endpoint is chosen for a phase 3 trial, the choice of the imaging modality (such as echocardiography versus single photon emission computerized tomography) may prove to be an especially important consideration. Imaging modality upgrades and malfunctions are sometimes unpredictable. Clinical sites may also experience unforeseen limitations on the use of the modality or modality-specific imaging drugs and processes, such as the interchange of certain contrast agents that may not affect typical diagnostic imaging but may alter trial-specific quantitative imaging measures.

➢ Protocol setting: Survey, Site training, Site monitoring
B. Is Centralized Image Interpretation Important for an Imaging-Based Primary Endpoint?

In clinical trials, images are interpreted either at the clinical site or at a centralized facility that
As compared to site-based image interpretations in multicenter clinical trials, a centralized image interpretation process may provide more verifiable and uniform reader training as well as ongoing management of reader performance, helping to ensure quality control of the images and the interpretations and to decrease variability in image interpretations, leading to a more precise estimate of treatment effect. Nevertheless, the overarching trial design features and the other previously described features may justify the use of site-based imaging interpretations even in large phase 3 multicenter clinical trials, so long as blinding of image interpretation to treatment can be assured or bias is otherwise controlled.

medicine, little imaging acquisition or interpretation variability is anticipated, and potential

➢ Independent image review committee (IIRC)
C. Should Image Interpretation Be Blinded to Clinical Data?

To determine whether image readers should be blinded to clinical information, sponsors should have knowledge of the underlying clinical condition, an understanding of the precedent for the use of imaging as a trial’s primary endpoint, and detailed insight into the trial’s unique image interpretation procedures (such as a plan for sequential locked-read image interpretation where an assessment cannot be altered versus an option for modification of prior image interpretations). In certain disease conditions, readers also should be blinded to the image acquisition date and/or knowledge of prior imaging observations. Again, we note that even if the image reader is aware of individual-level clinical information, blinding to treatment assignment is almost always critical.

- Independent image review committee (IIRC)
Guidance

D. How Often Should Imaging Evaluations Be Performed?

When a medical image serves as a trial’s primary endpoint, its timing and frequency of ascertainment depends upon the underlying condition being studied, the feasibility of the imaging schedule, and the overarching trial design features. For a trial using time point-based imaging measures as a primary endpoint, the frequency of imaging evaluations should be the same in all trial arms. Asymmetric imaging evaluation time points can introduce bias in the treatment effect assessment. For a primary endpoint that uses a time-to-event analytical approach, imaging evaluations should be performed at baseline and at sufficient frequency to provide a reasonably precise measure of the time to the expected clinical event.

➢ Imaging core lab / IIRC
Guidance

E. How Soon After Acquisition Should Images Be Interpreted?

In diagnostic medical imaging practice, images typically are interpreted on site within several hours following acquisition. In contrast, in clinical trials using centralized imaging interpretation, the interpretation may require a longer time frame. Therefore, image interpretation timing typically is more of a consideration when clinical trials use centralized imaging interpretation. When planning a clinical trial that uses an imaging primary endpoint, the turnaround time by a central image interpretation facility should be appropriate for the anticipated trial design. For example, prompt image interpretation may be an important consideration for trials that use centralized image interpretations as components of interim analyses, which may occur when imaging-based analyses are important to accommodate prespecified sample size adjustment plans. Similarly, image interpretation expediency may prove critical when centralized imaging interpretation is used to help control imaging quality; in this situation, the centralized imaging readers or an appropriately prespecified centralized imaging quality control process should promptly identify technical flaws that necessitate repeat imaging of a subject. In other circumstances, interpretation of batches of randomized images at specified intervals during a trial may be appropriate. Sponsors should consider the timeliness of centralized image interpretation when developing a clinical trial protocol that uses an imaging-based primary endpoint.

➢ Imaging core lab / IIRC, Quality assurance/Quality control
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

➢ Standardization
Guidance: 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
Guidance: 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
Imaging core lab

1. Protocol setting: Survey, Site training, Site monitoring
   - Standardization
   - Acquisition and transferring imaging data
   - Quality assurance/Quality control

2. Post-processing
   - Imaging analysis

3. Central reading
Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator

1. Outside Reader 3 – Consult or Evaluation
2. Image review committe (IRC)
3. Data & Safety monitoring board (DSMB)
Neuroprotective agent

1. Prospective, Randomized, Double-blinded, Phase IIa
2. 80 participants
3. Primary endpoint: CT
4. Secondary endpoint: SAE, mRS, sICH, NIHSS, Barthel index, Death rate, major systemic bleeding rate
5. Exploratory endpoint: DWI, GRE
6. Imaging CRO & Imaging core lab & IIRC
Primary outcome

- Safety and Efficacy of Novel Neuroprotective agent

- rtPA 표준 치료 시 NA주 투여 후 24시간 시점에 촬영한 뇌 CT 영상에서 유럽급성뇌졸중협력연구 (ECASS) I 과 II 기준에 따른 실질혈종 (Parenchymal hematoma)의 발생 비율

- Consultant for appropriate imaging protocol and analysis for evaluation of drug safety and efficacy
Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 GRE 영상에 확인된 출혈의 발생 건수 및 크기
- GRE와 DWI 영상을 통해 확인된 뇌출혈과 뇌경색의 변화 비율
1. Hemorrhagic transformation: BBB stabilizer → Prevent HT

1) Definition and classification → ECASS (4 classification)

2) Imaging modality: CT & MR

3) MR: GRE (SWI vs GRE)
   → The same imaging machine after Phantom

4) Measurement
   → Quantitative In-house Software
Hemorrhagic transformation

- The most critical risk of tPA

- HT
  - Autopsy: 38 – 71 %
  - CT: 13 – 43 %
  - Symptomatic: 0.6 – 20 %
  - HI vs PH: 9 % vs 3 % (in large cohort)

- European Cooperative Acute Stroke Study (ECASS) in 1990s

- Parenchymal hematoma $\propto$ poor clinical outcome

Neeb et al. Cerebrovasc Dis Extra 2013
ECASS I, II
Berger C et al. Stroke 2001
Hemorrhagic transformation

- **Predictors**
  - Massive infarction
  - Gray matter (abundant collateral → reperfusion injury)
  - Afib & Embolism
  - NIHSS ↑
  - Hyperglycemia
  - TC & LDLC ↓
  - Platelet ↓
  - Collateral ↓
  - Medication (tPA, warfarin)
  - Globulin ↑
  - Early CT signs
  - Albuminuria

Hemorrhagic transformation

- **Pathophysiology**
  - Unclear
  - Ischemia $\rightarrow$ ATP $\downarrow$ $\rightarrow$ Na-K ATPase alteration $\rightarrow$ cellular/metabolic imbalance $\rightarrow$ BBB disruption
  - Ischemia $\rightarrow$ strong inflammation $\rightarrow$ distorting normal cerebrovascular anatomy and physiology $\rightarrow$ **impairment of autoregulatory capacity**
  - **Recanalization** predispose to blood extravasation
  - tPA (neurotoxic?): degrade extracellular matrix integrity, BBB leakage...
Hemorrhagic transformation
Classification

ECASS I, II
Berger C et al. Stroke 2001
Hemorrhagic infarct type 1 (HI-1)

- Small petechiae along the margins of the infarct
- Smaller than 10 mm
Hemorrhagic infarct type 2 (HI-2)

✓ More confluent petechiae within the infarcted area

but without space-occupying effect

✓ > 10 mm

Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013
Parenchymal hematoma type 1 (PH-1)

- Hematoma in ≤ 30 % of the infarcted area with some slight space-occupying effect
- Round-shaped hypointensity (sometimes central hyperintensity)

Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013
Parenchymal hematoma type 2 (PH-2)

- Dense hematoma > 30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area

- Round-shaped hypointensity (possible central hyperintensity)

Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013
CT vs MR

1. Upward shift

2. Overestimation of PH

3. Variability
   (Inter- & Intra-)

Comparison of CT and Three MR Sequences for Detecting and Categorizing Early (48 Hours) Hemorrhagic Transformation in Hyperacute Ischemic Stroke

Marie-Cécile Arnould, Cécile B. Grandin, André Peeters, Guy Cosnard, and Thierry P. Duprez

BACKGROUND AND PURPOSE: Our goal was to compare the sensitivity of CT and three MR sequences in detecting and categorizing early (48 hours) hemorrhagic transformation (HT) in hyperacute ischemic stroke.

METHODS: Twenty-five consecutive patients with hyperacute ischemic stroke (<6 hours) without MR signs of cerebral bleeding at admission were included. Twenty-one underwent thrombolytic therapy. A standardized follow-up protocol, performed 48 hours after admission, combined brain CT scan and MR examination (1.5 T) including fast spinecho–fluid-attenuated inversion recovery (FSE-FLAIR), echo-planar spinecho (EPI-SE) T2-weighted, and EPI-gradient-recalled echo (GRE) T2*-weighted sequences. Both CT scans and MR images were obtained within a time span as possible between techniques (mean delay, 64 minutes). CT scans and MR images were independently rated as negative or positive for bleeding and categorized for bleeding severity (five classes) by two blinded observers. Prevalence of positive cases, intra- and interobserver agreement, and shifts in bleeding categorization between respective modalities and sequences were assessed.

RESULTS: Twelve patients (48%) were rated positive for HT on the basis of findings of at least one technique or sequence. From this subset of bleeding patients, seven (58%) had positive CT findings, nine (75%) had positive FSE-FLAIR and EPI-SE T2-weighted findings, and 12 (100%) had positive EPI-GRE T2*-weighted findings. CT had lower intra- and interobserver agreement for positivity than did MR imaging. Among the seven patients with positive CT and MR findings, only two had convergent ratings for bleeding category based on findings of two modalities. The five remaining had upward grading from CT to MR, which varied according to pulse sequence.

CONCLUSION: MR imaging depicted more hemorrhages and had higher intra- and interobserver agreement than did CT. The EPI-GRE T2*-weighted sequence demonstrated highest sensitivity. Equivocal upward shifts in bleeding categorization were observed from CT to MR imaging and between MR images.
### Intra- and inter observer agreement

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>FSE-FLAIR</th>
<th>EPI-SE T2</th>
<th>EPI-GRE T2*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observer 1:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First session</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Second session</td>
<td>6</td>
<td>9</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Consensus</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Intraobserver 1 $kappa$</td>
<td>0.780702</td>
<td>1</td>
<td>0.834437</td>
<td>1</td>
</tr>
<tr>
<td><strong>Observer 2:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First session</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Second session</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Consensus</td>
<td>4</td>
<td>9</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Intraobserver 2 $kappa$</td>
<td>0.752475</td>
<td>1</td>
<td>0.911032</td>
<td>1</td>
</tr>
<tr>
<td>Interobserver consensus</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Interobserver $kappa$</td>
<td>0.576271</td>
<td>1</td>
<td>0.911032</td>
<td>1</td>
</tr>
</tbody>
</table>

Arnould et al. AJNR 2004

### Kendall’s coefficient of concordance ($W$)

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 6)</th>
<th>Residents (n = 3)</th>
<th>Experts (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding categorization (HI-1, HI-2, PH-1, PH-2)</td>
<td>0.79</td>
<td>0.87</td>
<td>0.81</td>
</tr>
<tr>
<td>Distinction between HI and PH</td>
<td>0.82</td>
<td>0.91</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Kendall’s coefficient of concordance ($W$) was determined for the bleeding categorization and the distinction between HI and PH for all observers and for each group (3 residents and 3 experts). $W$ values of 0.6–0.8 indicated a substantial and of 0.81–1 an almost perfect degree of agreement.

Neeb et al. Cerebrovasc Dis Extra 2013
Intra- and inter observer agreement

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>T2*GRE</th>
<th>DWI</th>
<th>FLAIR</th>
<th>FLAIR DWI T2*GRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>group 1</td>
<td>group 2</td>
<td>group 1</td>
<td>group 2</td>
<td>group 1</td>
</tr>
<tr>
<td>Bleeding detection</td>
<td>0.66 (0.43–0.82)</td>
<td>0.59 (0.39–0.77)</td>
<td>0.80 (0.61–0.94)</td>
<td>0.75 (0.57–0.90)</td>
<td></td>
</tr>
<tr>
<td>Overall concordance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple $\kappa$</td>
<td>0.54 (0.42–0.64)</td>
<td>0.48 (0.34–0.59)</td>
<td>0.63 (0.50–0.76)</td>
<td>0.58 (0.45–0.69)</td>
<td></td>
</tr>
<tr>
<td>Weighted $\kappa$</td>
<td>0.70 (0.63–0.77)</td>
<td>0.68 (0.61–0.75)</td>
<td>0.74 (0.66–0.82)</td>
<td>0.75 (0.69–0.82)</td>
<td></td>
</tr>
<tr>
<td>Bleeding categorization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI1</td>
<td>0.60 (0.40–0.77)</td>
<td>0.42 (0.20–0.60)</td>
<td>0.34 (0.21–0.45)</td>
<td>0.42 (0.19–0.62)</td>
<td></td>
</tr>
<tr>
<td>HI2</td>
<td>0.50 (0.31–0.68)</td>
<td>0.44 (0.24–0.61)</td>
<td>0.56 (0.38–0.73)</td>
<td>0.47 (0.22–0.66)</td>
<td></td>
</tr>
<tr>
<td>PH1</td>
<td>0.43 (0.23–0.62)</td>
<td>0.34 (0.10–0.54)</td>
<td>0.61 (0.21–0.86)</td>
<td>0.54 (0.30–0.73)</td>
<td></td>
</tr>
<tr>
<td>PH2</td>
<td>0.41 (−0.03 to 0.78)</td>
<td>0.87 (0.49–1.00)</td>
<td>0.82 (0.38–1.00)</td>
<td>0.77 (0.54–0.94)</td>
<td></td>
</tr>
<tr>
<td>Distinction</td>
<td>0.66 (0.46–0.83)</td>
<td>0.51 (0.26–0.71)</td>
<td>0.83 (0.62–0.96)</td>
<td>0.78 (0.65–0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Renou et al. Cerebrovasc Dis 2010
HI 2

Confluent petechiae

Arnould et al. AJNR 2004
Extended debate

Spared tissue vs petechial HT

Arnould et al. AJNR 2004
2. Acute infarct

1) Definition: DWI restricted lesion

2) Presence or Absence

3) Anatomic location

4) Measurement: DWI (b1000 with ADC)

5) Semi-automated In-house software
3. New infarct or recurred infarct

1) Definition

- **New DWI restricted lesions** on follow-up outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.
- Although new DWI restriction occurs on follow-up image after no DWI restriction on initial images, the lesion is defined as **No New infarction** in case of occurrence in the perfusion territory which is the same with initial perfusion deficit.
3. New infarct or recurred infarct

2) Imaging modality: DWI

3) Measurement: The entire infarct core volume on F/U using In-house analysis software
4. Steno-occlusion

1) Definition: Revascularization

2) Imaging modality: CTA, MRA

3) Scoring: mTICI
Table 2: Varying definitions of TICI grades in the literature

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Grade 0</td>
<td>No flow</td>
</tr>
<tr>
<td></td>
<td>No canalization</td>
</tr>
<tr>
<td></td>
<td>Complete occlusion</td>
</tr>
<tr>
<td></td>
<td>No recanalization/reperfusion</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Minimal recanalization (&lt;20%)</td>
</tr>
<tr>
<td></td>
<td>Minimal flow (very slow) without significant flow distal to the occlusion site</td>
</tr>
<tr>
<td></td>
<td>Limited or no reperfusion</td>
</tr>
<tr>
<td></td>
<td>Distal movement of thrombus without reperfusion</td>
</tr>
<tr>
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<td>Perfusion past initial occlusion, but limited distal branch filling</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Partial recanalization—recanalization of some but not all of the occluded arteries</td>
</tr>
<tr>
<td></td>
<td>Incomplete recanalization/reperfusion</td>
</tr>
<tr>
<td></td>
<td>Near-normal flow, with flow distal to the occlusion but not filling the distal branches normally</td>
</tr>
<tr>
<td>Grade 2a</td>
<td>Perfusion of &lt;50% of the MCA distribution</td>
</tr>
<tr>
<td></td>
<td>Partial filling of the entire vascular territory</td>
</tr>
<tr>
<td></td>
<td>Partial perfusion with incomplete distal filling of &lt;50% of expected territory</td>
</tr>
<tr>
<td></td>
<td>Partial filling of the entire vascular territory</td>
</tr>
<tr>
<td>Grade 2b</td>
<td>Partial perfusion with incomplete distal branch filling of ≥50–99% of the expected territory</td>
</tr>
<tr>
<td></td>
<td>Complete filling, but the filling is slower than normal</td>
</tr>
<tr>
<td></td>
<td>Perfusion of half or greater of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>Grade 2c</td>
<td>Near-complete perfusion without clearly visible thrombus but with delay in contrast run-off</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Full perfusion with filling of all distal branches, including M3, M4</td>
</tr>
<tr>
<td></td>
<td>Normal flow</td>
</tr>
<tr>
<td></td>
<td>Partial recanalization with &gt;50% reperfusion</td>
</tr>
<tr>
<td></td>
<td>Full perfusion with normal filling of distal branches in a normal hemodynamic fashion</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Complete recanalization/reperfusion</td>
</tr>
</tbody>
</table>

Table 2. Modified Treatment in Cerebral Ischemia Scale

<table>
<thead>
<tr>
<th>mTICI Grades</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No perfusion</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion</td>
</tr>
<tr>
<td>Grade 2a</td>
<td>Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)</td>
</tr>
<tr>
<td>Grade 2b</td>
<td>Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; and mTICI, Modified Treatment in Cerebral Ischemia Scale.

J.E.Fugate et al. AJNR 2013
Osama O. Zaidat et al. Stroke 2013
1. Protocol setting: Survey & Site evaluation

- CT 프로토콜의 최소 충족 요건 (Full protocol 별점 점부)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Standard</th>
<th>CT 1 장비(서관5번방)</th>
<th>CT2 장비(서관 6번방)</th>
<th>CT 3 장비(등급실 CT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>제조업체 및 장비모델 명</td>
<td>-</td>
<td>SIEMENS SOMATOM Definition Edge</td>
<td>SIEMENS SOMATOM Definition Edge</td>
<td>SIEMENS SOMATOM Definition AS</td>
</tr>
<tr>
<td>Channel</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Slice thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Display FOV (DFOV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Table pitch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kernel, Reconstruction</td>
<td></td>
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</tr>
<tr>
<td>kVp, mAs, AEC</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
1. Protocol setting: Survey & Site evaluation

- MR DWI 프로토콜의 최소 충족 요건 (Full protocol 별첨 첨부)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Standard</th>
<th>MRI 1 장비(통관 3번방)</th>
<th>MRI 2 장비(응급실 MR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>재조합체 및 장비모델 명</td>
<td>-</td>
<td>Siemens Magnetom Avanto</td>
<td>Siemens Magnetom Avanto</td>
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<td>Tesla</td>
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<td>Coil</td>
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<tr>
<td>FOV</td>
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</tr>
<tr>
<td>Matrix</td>
<td></td>
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<tr>
<td>Resolution</td>
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<td>TE</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Slice thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gap thickness</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B-value 수</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Imaging CRO

1. Protocol setting: Imaging protocol standard

2. Standardization: Phantom (CT, DWI, GRE) with 3-month interval
1. **Protocol setting:** Imaging protocol standard

2. **Standardization**

3. **Site training:** Imaging acquisition & transfer

4. **Site monitoring:** QC/QA
### Brain CT

#### 최소 요구 사항

<table>
<thead>
<tr>
<th>Channel</th>
<th>4 channel 이상</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice thickness</td>
<td>5 mm 또는 그 이하</td>
</tr>
<tr>
<td>Display FOV (DFOV)</td>
<td>20 - 25 cm</td>
</tr>
<tr>
<td>Matrix</td>
<td>512 x 512 이상</td>
</tr>
<tr>
<td>Resolution</td>
<td>10 line pairs / cm 이상</td>
</tr>
<tr>
<td>Table pitch</td>
<td>2 이하 (Helical scanning일 경우)</td>
</tr>
<tr>
<td></td>
<td>대부분 1 (Sequential scanning)</td>
</tr>
<tr>
<td>Kernal</td>
<td>Manufacturer’s recommendation</td>
</tr>
<tr>
<td>KvP, mAS, AEC</td>
<td>Manufacture’s setting (60mGy 선량 이하에서 기기에 적합한 KvP, mAS, Automatic exposure control 기법 활용)</td>
</tr>
</tbody>
</table>
## DWI

### 최소 요구 사항

<table>
<thead>
<tr>
<th>Coil</th>
<th>8 ch 이상의 Head coil 혹은 NV coil</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOV</td>
<td>200 - 250 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>128 x 128 이상</td>
</tr>
<tr>
<td>Resolution</td>
<td>2.0x 2.0mm²</td>
</tr>
<tr>
<td>TR</td>
<td>2000 ms 이상</td>
</tr>
<tr>
<td>TE</td>
<td>110 ms 이하</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>4–6 mm</td>
</tr>
<tr>
<td>Gap thickness</td>
<td>0–2 mm</td>
</tr>
<tr>
<td>Number of b-value</td>
<td>2 이상</td>
</tr>
<tr>
<td>High b-value strength</td>
<td>700 – 1200 s mm⁻²</td>
</tr>
</tbody>
</table>
**T2* GRE**

- 최소 요구 사항

<table>
<thead>
<tr>
<th>Coil</th>
<th>8CH 이상의 Head coil 혹은 NV coil</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOV</td>
<td>200–250mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>128×128 이상</td>
</tr>
<tr>
<td>Resolution</td>
<td>2.0×2.0 mm²</td>
</tr>
<tr>
<td>TR</td>
<td>500–1000 ms</td>
</tr>
<tr>
<td>TE</td>
<td>16–32ms</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>4.0–6.0mm</td>
</tr>
<tr>
<td>Gap thickness</td>
<td>0–2.0mm</td>
</tr>
<tr>
<td>Average 수</td>
<td>1 이상</td>
</tr>
</tbody>
</table>
Imaging CRO

4. 페니지 종류 (총 3개)
   - CT 페니지: 1개
   - MR 페니지(DWI 페니지, GRE 페니지): 2개

사진 1. 1)DWI 페니지, 2)GRE 페니지, 3)CT 페니지

5. 로컬라이저 획득 방법.
   - 페니지 위를 항하도록 하여 해당 Coil 혹은 장바 태이블 중앙에 위치 시킴.
   - 페니지 번호(수직으로 각각의 영원번호)가 태이블 각 다리를 방향으로 항하게 위치시킴.
   - 페니지 상부에 각각의 십자선에 레이저 포인트를 일치시킴.
   - 로컬라이저 획득 파라미터는 각 기관의 protocol을 따른다.

사진 2. 1)DWI 페니지, 2)GRE 페니지, 3)CT 페니지
### Quality assurance/Quality control

<table>
<thead>
<tr>
<th>기관번호</th>
<th>대상자번호</th>
<th>Initial CT(DAY 0)</th>
<th>Follow-up CT(DAY 1)</th>
<th>Initial MRI(DAY 0)</th>
<th>Follow-up MRI(DAY 5)</th>
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</thead>
<tbody>
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<td>2016-12-27 / 2017-01-06</td>
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<td>2017-01-02 / 2017-01-06 / 2017-01-18</td>
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Image Transfer

➤ Anonymized imaging data and Transfer

영상 촬영 완료 후 2일 (근무일기준) 이내에 e-CRF로 전송

eCRF system

Easy File Upload

Quality Check
Charter Documentation

- 시험설계와 시험에서 영상의 역할에 대한 요약
- 표준화된 영상 획득 프로토콜
- 시험에 사용할 장비 및 소프트웨어의 표준화
- 영상 품질 및 장비 평가에 있어 각 기관의 방사선사의 역할
- 기관 적격성 평가 및 영상 품질 모니터링을 위한 절차 및 팬텀 영상 획득 방법
- 피험자 전 처치 및 촬영 자세 기준
- 영상 평가 일정
- 데이터 전송 및 보관, 관리 방법
- 표준화된 영상 획득용 의약품
- 영상 전송 및 수신된 내역에 대한 문서화 및 품질평가법
- 영상 디스플레이 및 판독 방법과 품질관리 절차
- 영상 데이터 보안화 절차
- 영상 증례 기록서
Imaging core lab

1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquisition & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
Quantitative imaging analysis

1. Infarct core volume measurement

2. Hemorrhagic transformation volume measurement
Infarct core volume segmentation

  - CT (infarction ≒ hypodensity, hemorrhage or not)
  - IV tPA beneficial? within 6 hrs of the onset of stroke
  - Try a time window of upto 6 hrs → Fail

- DIAS (Desmoteplase In Acute ischemic Stroke phase II, Stroke 2005)
  - MR (infarct lesion volume ≒ DWI abnormality)
  - IV Desmoteplase within 3 to 9 hrs improves outcome

- DEDAS (Dose Escalation study of Desmoteplase in Acute ischemic Stroke, Stroke 2006)
  - MR (infarct lesion volume ≒ DWI lesion)
  - CT (hemorrhage for exclusion)
  - IV Desmoteplase within 3 to 9 hrs improves outcome
Infarct core volume segmentation

• DIAS-2 (Desmoteplase In Acute ischemic Stroke phase III, Lancet Neurol 2009)
  ➢ MR (infarct lesion volume $\approx$ DWI abnormality), CT

• DEFUSE (Diffuseion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study, Ann Neurol 2006)
  ➢ MR (infarct lesion volume $\approx$ DWI high SI + ADC confirm)

• EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial, Lancet Neurol 2008)
  ➢ MR (infarct lesion volume $\approx$ DWI volume, no comment about ADC)

• DEFUSE 2 (Lancet Neurol 2012)- MRI can identify
  ➢ RAPID software
  ➢ MR (infarct lesion volume $\approx$ less than ADC $600\times100^{-6} \text{ mm}^2/\text{s}$)
Infarct core volume

- DWI high SI
- ADC low SI
- FLAIR high SI
- ADC pseudonormalization

→ Infarction volume is measured based on DWI high SI with reference to ADC
Infarct core/Hemorrhage volume

Datasharing.aim-aicro.com/strokevolumetry
Independent image review committee (IIRC)

1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquisition & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
6. Central reading
Independent image review committee (IIRC)

1. Mock training (모의고사) : around 20 ~ 30 cases
   1) Inter-observer agreement
   2) Reliability

2. Reading (수능) ➔ Actually, Independent
Independent image review committee (IIRC)
Independent image review committee (IIRC)
HI 2

→ HI 2?

PH 1

Renou et al. Cerebrovascular Dis 2010
Hemorrhagic infarct type 1 (HI-1)

✓ **Def.:** Small petechiae along the margins of the infarct

✓ < 1 cm (largest dimension)

✓ petechial hemorrhage:

  → gyral, dot-to-dot hemorrhage, cleft 有

✓ crowding (not confluent)
Hemorrhagic infarct type 2 (HI-2)

- Def.: More confluent petechiae within the infarcted area but without space-occupying effect

- ≥ 1cm (largest dimension)
- petechial hemorrhage:
  - gyral, dot-to-dot hemorrhage, cleft 有
- confluent (not crowding)
**Parenchymal hematoma type 1 (PH-1)**

✓ **Def.: Hematoma in ≤ 30 % of the infarcted area with some slight space-occupying effect**

✓ Hematoma (not gyral, not cleft, mass effect 有, ≥ 1cm)

✓ HI type 2와 혼갈릴때, hematoma는 3cm이상

✓ Midline shifting/Ventricular deformity (+) – 최우선 순위 아님.

✓ < 0.6 (largest dimension ratio)

→ based on each plane with largest area of hemorrhage/infarction
Parenchymal hematoma type 2 (PH-2)

✓ Def.: Dense hematoma > 30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area

✓ ≥ 0.6 (largest dimension ratio)

→ based on each plane with largest area of hemorrhage/infarction
### Independent image review committee (IIRC)

<table>
<thead>
<tr>
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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<td>Overall</td>
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<td>PsPD -&gt; PD</td>
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<td>PsP, PsP, PsP</td>
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<td>PsPD -&gt; NC</td>
<td>NC (Baseline 불분명)</td>
<td>PsP, PD, PD</td>
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- **AMC 1**: CR > NC  
  Postop, marginal enhancement는 CR
- **AMC 2**: PsP > PD
- **AMC 3**: PsP > PD ? compared 보편적으로PsP
- **AMC 5**: NC > NC  
  Postop, marginal enhancement는 CR
- **SNUBH 1**: PsP-PD > PsP-PsP
- **SNUBH 2**: psp-psp > PsP-PD
- **SNUBH 3**: PsP-PsP-CR >
- **SNUBH 4**: No baseline  
  PsP-NC or PR > PD
- **SNUBH 5**: Two lesion, PsP-PsP-PD
- **SNUBH 6**: 3선속 PsP < PsP-PsP-PD
- **SNUBH 7**: PsP-PsP-PD > PsP-PsP-PsP
- **SNUBH 8**: preCRT Baseline, NC-NC-PD
- **SNUBH 9**: Baseline, 연속 PsP
- **SNUBH 10**: preCRT Baseline, NC-NC-NC
- **SNUBH 11**: Postop, 가 Baseline, 연속 PsP
- **SNUBH 12**: PsP-PsP-PsP-NC
Independent image review committee (IIRC)

1. Pseudoprogression interval은 정확히 6 months로 계산한다. (제공된 CCRT termination 기준)
   
   Example: 2010−03−10 → 2010−09−10부터 progression, 2010−09−09는 pseudoprogression

2. Target lesion (1 cm 이상)은 nontarget (1 cm 미만)이 되어도 target에 기록
   
   Nontarget lesion은 target이 되어도 nontarget에 기록

   Target과 nontarget이 합쳐지는 경우, Target과 Nontarget을 동일하게 기록 및 판정.

3. RT field의 정의: RT field는 surgical cavity, nonenhancing T2W high signal intensity를 아우르면서 그 보다 조금 더 넓은 것으로 본다.


5. Seeding (1 cm 이상의 nodular lesion이 없는 이상)은 nontarget 으로 한다.

6. CR 후에 baseline과 동일부위 비슷한 크기의 lesion이 생겼다면 PD이다.
Outcomes

- Hemorrhagic transformation
- Infarction
Primary outcome

- rtPA 표준 치료 시 NA주 투여 후 24시간 시점에 촬영한 Brain noncontrast CT 영상에서 유럽급성뇌졸중협력연구 (ECASS) I 과 II 기준에 따른 실질혈종 (Parenchymal hematoma)의 발생 비율
1. Hemorrhagic transformation (yes/no)

2. Hemorrhagic transformation grade

- HI type I
- HI type II
- PH type I
- PH type II
1. Hemorrhagic transformation (yes/no)
2. Hemorrhagic transformation grade
   - HI type I
   - HI type II
   - PH type I
   - PH type II
Secondary outcome

➤ 5일 이내에 발생한 모든 두개내 출혈의 발생 비율

➤ 5일 이내에 DWI 영상에 확인된 뇌경색 크기의 증가 비율

➤ 5일 이내에 DWI 영상에 확인된 뇌경색의 재발 비율

➤ 5일 이내에 GRE 영상에 확인된 출혈의 발생 건수 및 크기

➤ GRE와 DWI 영상을 통해 확인된 뇌출혈의 변화 비율
MR (DWI-baseline)

1. Acute infarction (yes/no)
2. Acute infarction volume (Software)
1. New acute infarction (yes/no)
2. Acute infarction volume (Software)
Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 DWI 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 GRE 영상에 확인된 출혈의 발생 건수 및 크기
- GRE와 DWI 영상을 통해 확인된 뇌출혈의 변화 비율
1. Hemorrhagic transformation (yes/no)
2. Hemorrhagic transformation grade
   - HI type I
   - HI type II
   - PH type I
   - PH type II
3. Hemorrhage volume (Software)
1. New hemorrhagic transformation (yes/no)

2. Hemorrhagic transformation grade
   - HI type I
   - HI type II
   - PH type I
   - PH type II

3. Hemorrhage volume (Software)
Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator

1. Outside Reader 3 – Consult or Evaluation
2. Image review committe (IRC)
3. Data & Safety monitoring board (DSMB)
Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator

1. Outside Reader 3 – Consult or Evaluation
2. Image review committee (IRC)
3. Data & Safety monitoring board (DSMB)
Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator

1. Outside Reader 3 – External validation (German Radiologist)
2. Image review committe (IRC)
3. Data & Safety monitoring board (DSMB)
Image Review Flow

Site: Uploading subject’s images on eCRF:
- Initial & follow-up Brain CT / MRI & MRA

Imaging core lab: Quality check within 48 hours from uploading images
- As to adequate images according to the Imaging protocol
- As to adequate full series images
  ➔ Result: Pass or Recheck

1st & 2nd reviewers of IIRC will review the passed images
within 48 hours.
- Brain CT: for primary endpoint
- Brain MRI: for exploratory endpoint

If Pass, alarm email will be sent to IIRC members.

If the result of two reviewers is the same, alarm email will be sent to Imaging core lab for calculating lesion volume.

Imaging core lab: Lesion volume calculation by automatic program
1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquisition & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
6. Central reading
7. Report results

→ Phase IIb
1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquisition & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
6. Central reading
7. Report results

→ Phase IIb
Anti-coagulation

1. Prospective, Randomized, Phase II
2. 68 participants
3. Primary endpoint: Recurred infarct on DWI
4. Secondary endpoint: Hemorrhagic transformation on GRE, Recanalization on TOF-MRA
5. Imaging CRO & Imaging core lab & IIRC with imaging consult
Anti-coagulation

1. 에독사반(edoxaban)은 factor Xa를 선택적으로 저해하는 약물로서, 심방세동을 가진 환자에서 뇌경색 위험을 낮추는 데 있어 와파린과 비슷한 정도의 효능을 가지면서도, 출혈의 위험은 유의하게 낮은 새로운 경구용 항응고제(Novel oral anticoagulants, NOAC)이다. 에독사반은 factor Xa 저해 기능을 가지는 다른 NOAC들과 비교해서도 출혈 위험이 적은 것으로 알려져 있다.

2. 비판독성 심방세동에 의한 급성 허혈성 뇌졸중 환자에서 조기 에독사반 투여의 효과 및 안전성 평가를 위한 무작위배정, 평행대조, 다기관 예비 임상시험 (Early administration of edoxaban after acute ischemic stroke in patients with non-valvular atrial fibrillation: a randomized, multi-center, parallel-group trial (PILOT)

3. 가설: 비판막성 심방세동을 가진 급성 뇌경색 환자에서 에독사반의 조기 투여가 고식적 항응고제 투여에 비해 뇌경색의 이른 재발을 줄일 수 있다.

4. Phase II
Anti-coagulation

5. 다기관 뇌졸중 치료제 임상시험: 국내 3개 기관

6. 68 Participants

7. Primary endpoint: DWI (Recurred infarct 10-14 days after the onset)

8. Secondary endpoints
   1) Imaging indexes: GRE (Hemorrhagic transformation), TOF-MRA (Recanalization)
   2) Clinical indexes: NIHSS deterioration, mRS

9. Safety endpoints
   1) Symptomatic ICH
   2) Hemorrhage

10. Imaging CRO/Imaging core lab/IIRC
1. New infarct or recurred infarct

1) Definition: New separate restricted lesions on follow-up diffusion-weighted imaging (DWI) outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.

2) Classification: Local recurrent infarcts are defined as new lesions within the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging. Distant recurrent infarcts are defined as new lesions outside the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging. The initial perfusion is assessed primarily on angiography followed by perfusion-weighted imaging.
1. New infarct or recurred infarct

2) Primary outcome → eCRF (Anatomic and Vascular territory)

3) DWI → Standardization (Phantom), Presence or absence, local or distant, numbers

4) Measurement → Semi automated analysis in-house software
Experience 2

Consultant

2. Hemorrhagic transformation
   1) Definition and classification → ECASS
   2) Secondary outcome
   3) CT and MR → Discrepancy
   4) MR: Standardization (SWI vs GRE) → Same imaging modality between initial and F/U
   5) Measurement → Semi automated analysis in-house software
3. Infarct core

1) Definition or Criteria: b1000 after ADC correction

2) Secondary outcome

3) MR (DWI), ASPECT (X)

4) Measurement: DWI, Δ Infarc core volume

5) Semi automated analysis in-house software
4. Steno-occlusion

1) Definition: Recanalization

2) Secondary outcomes

3) MRA > CTA

4) Scoring: mAOL (MR RESCUE, ESCAPE)
Experience 2

### Table S3. Arterial Occlusive Lesion (AOL) Rating Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No recanalization of the primary occlusion lesion</td>
</tr>
<tr>
<td>I</td>
<td>Incomplete or partial recanalization of the primary occlusion lesion with no distal flow</td>
</tr>
<tr>
<td>II</td>
<td>Incomplete or partial recanalization of the primary occlusion lesion with any distal flow</td>
</tr>
<tr>
<td>III</td>
<td>Complete recanalization of the primary occlusion with any distal flow</td>
</tr>
</tbody>
</table>

### Table S4. Thrombolysis in Cerebral Infarction (TICI) Rating Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No perfusion</td>
</tr>
<tr>
<td>1</td>
<td>Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion</td>
</tr>
<tr>
<td>2a</td>
<td>Perfusion of less than 2/3 of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>2b</td>
<td>Perfusion of 2/3 or greater of the vascular distribution of the occluded artery</td>
</tr>
<tr>
<td>3</td>
<td>Full perfusion with filling of all distal branches</td>
</tr>
</tbody>
</table>

### Table S5. Thrombolysis in Myocardial Ischemia (TIMI) Rating Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No perfusion: absence of any antegrade flow beyond a coronary occlusion</td>
</tr>
<tr>
<td>1</td>
<td>Penetration without perfusion: faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed</td>
</tr>
<tr>
<td>2</td>
<td>Partial reperfusion: delayed or sluggish antegrade flow with complete filling of the distal territory</td>
</tr>
<tr>
<td>3</td>
<td>Complete perfusion: normal flow which fills the distal coronary bed completely</td>
</tr>
</tbody>
</table>
Anti-coagulation

1. Prospective, Randomized, Open-label, Phase IV

2. 220 participants

3. Primary endpoint: Leaflet thrombosis on Cardiac CT

4. Secondary endpoint: New infarct lesions on DWI

5. Imaging CRO & Imaging core lab & IIROC with imaging consult
Guidance

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 800-835-4700.

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

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April 2018
Clinical/Medical
Guidance

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 information that describe the standards generally employed by clinical practitioners. This guidance recommends additional imaging endpoint process standards that are more specific to clinical trials. Imaging process standards help sponsors ensure that imaging data are obtained in a manner that complies with a trial’s protocol, that the quality of imaging data is maintained within and among clinical sites, and that a verifiable record of the imaging process is created. Minimization of imaging process variability may importantly enhance a clinical trial’s ability to detect drug treatment effects.

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
Clinical Trial Imaging in Acute Ischemic Stroke

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
Clinical Trial Imaging in Acute Ischemic Stroke

1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquisition & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
6. Central reading
7. Report results

뇌졸중 임상시험 영상 기준 권고안 (with 식약처)
Summary & Recommendation

1. Role: Imaging CRO/core lab, IIRC

2. Standardization & Consultant: Characteristics of Imaging modalities

3. IIRC: Mock training/detailed reading point, Independent

4. Evidence and Documentation

5. Recommendation and Guidelines for clinical trial imaging in acute ischemic stroke is necessary.
경청해 주셔서 감사합니다.