

A S A N
M E D I C A L
C E N T E R

Clinical trial imaging in Acute ischemic 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

- Clinical trial imaging in Acute ischemic stroke: Review
- Experience as Imaging CRO (contract research organization)
- Recommendation vs Guideline

신약개발



| | | |
|--------------------|---------------------|----------------------|
| 임상 수요에 맞는 타겟 발굴 | 약물에 반응성이 좋은 환자군 선별 | 인허가 규정에 맞는 개발전략 |
| 메커니즘 기반 개발 전략 | Proof of Concept 검증 | |
| 빠른 의사결정 (Go/No-Go) | 효율적 독성 예측 시스템 | 규제기관과의 적극적 정보 공유와 교류 |
| 전임상시험의 예측력 제고 | 새로운 임상시험 방법론 | |

Biomarkers (Imaging, -Omics)

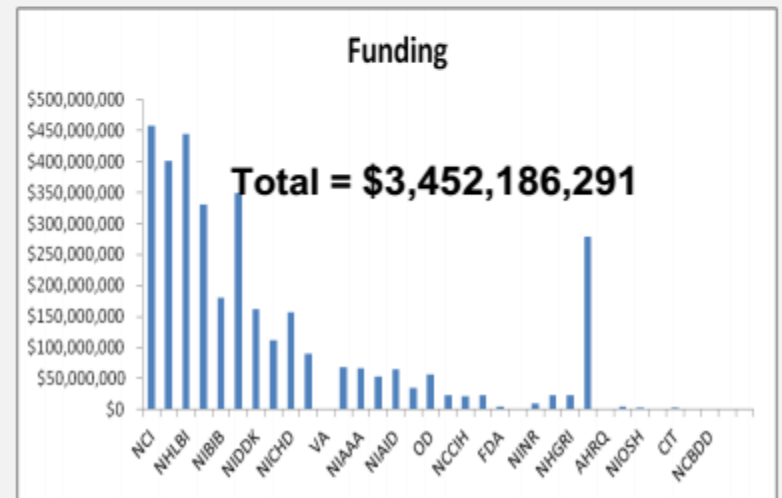
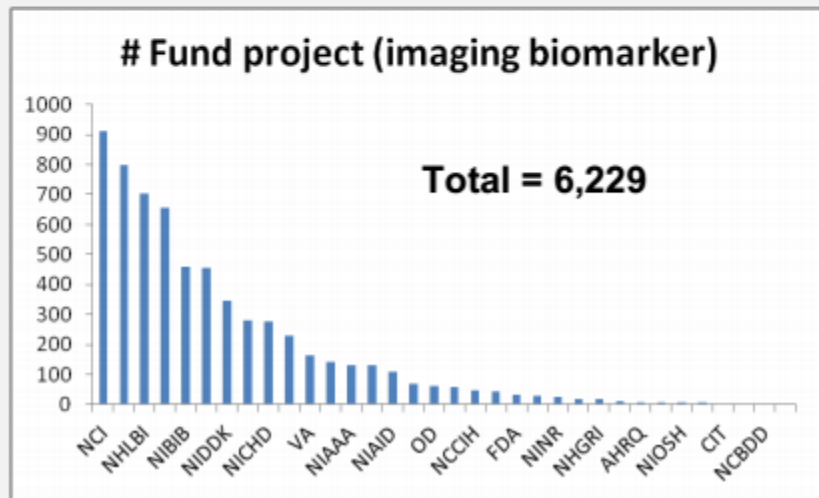
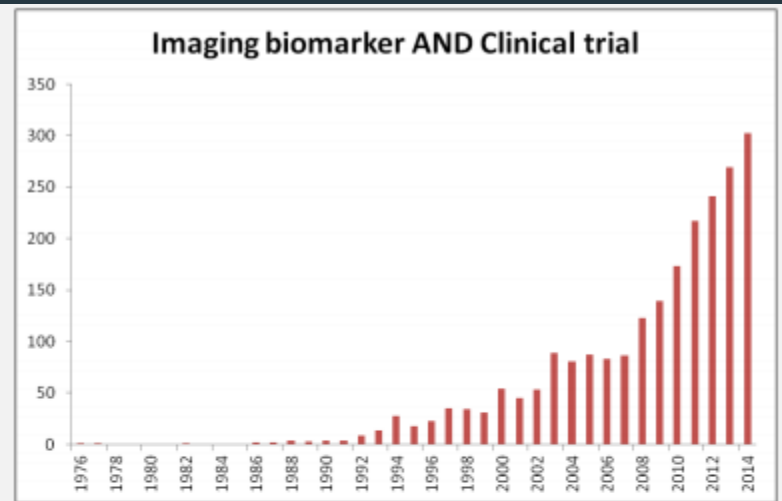
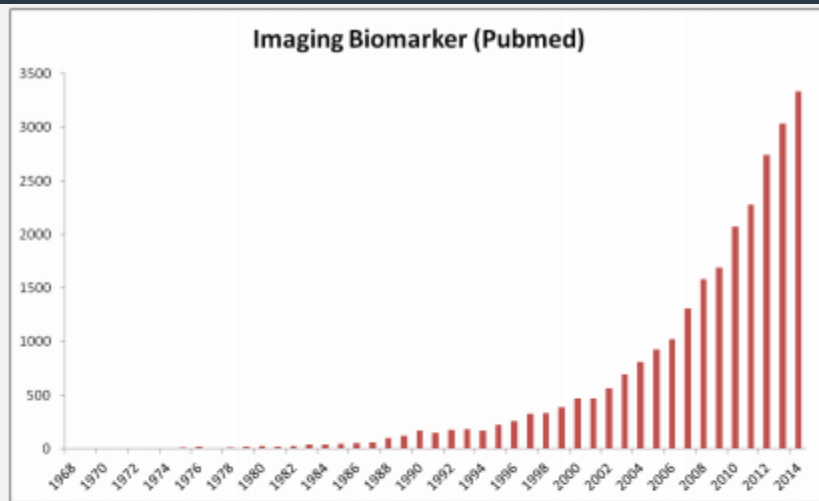
Advanced Clinical Trial

Animal Model

Toxicology

NICHE MARKET

Imaging biomarker



Imaging biomarker

역할

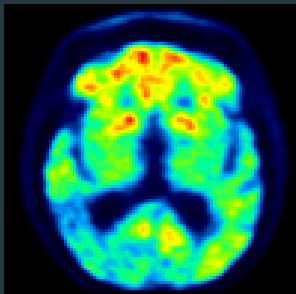
- Predictive biomarker
- 약력학/약동학 평가
- 약리 메커니즘
- 유효성/독성 평가

장점

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

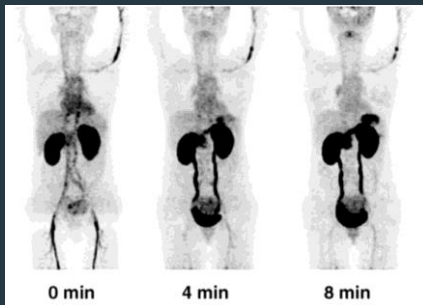
효과

- 피험자수 ↓
- 시험기간 ↓
- 개발비용 ↓

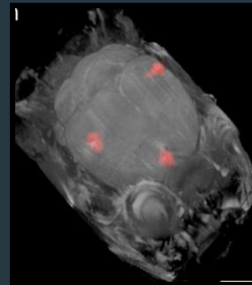


환자선별

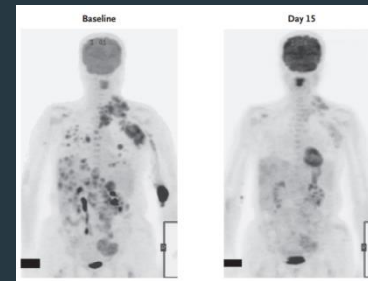
:아밀로이드 PET으로
알츠하이머병 선별



약물 약동학 평가
: Dynamic PET



약리작용 평가
(수용체 영상화)



유효성 평가
(CT, MR, PET)



독성 평가
(심장 MRI 로
심근독성)

임상시험에서의 영상 활용

| Phase | 목적 | 영상의 활용도 |
|---------------|---|---|
| 0상 | 극미량의 약물에 방사성표지를 하여 인체에 주입 후 약물의 분포(약동학) 및 수용체 포화도(약력학) 등을 평가함 | 약동학 약력학 |
| 개념증명 (I, IIa) | 소수의 환자에서 안전성(독성)을 확인하는 동시에 약리기전, 유효성을 평가. | 약리기전 평가 (Proof of mechanism 또는 Proof of concept) |
| IIb | 약효 입증 유효용량 확인/용량-반응 양상 유효성/안전성의 균형적 검토 | 대리종결점 PK/PD 모델링 |
| III | 충분한 환자에서 유효성/안전성 확립 장기투여시 안전성 검토 약물상호작용 및 특수 환자군 용량 정립 | 대리종결점 |

Clinical trial imaging in Acute ischemic stroke

1. European Cooperative Acute Stroke Study (ECASS, JAMA 1995), The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS, NEJM 1995): 급성 뇌경색 환자에서의 IV alteplase의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 **noncontrast CT**를 **약물 적용 환자군 선정**과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 noncontrast CT는 **Safety parameters**로서 사용됨.
2. The European Atrial Fibrillation Trial Study Group (NEJM 1995): Nonrheumatic atrial fibrillation환자에서 뇌졸중의 리스크를 줄이기 위한 항응고제의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 항응고제의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 **Safety parameters**로서 **noncontrast CT**를 이용함.
3. Low-molecular-weight Heparin for the treatment of acute ischemic stroke (NEJM 1995): 뇌졸중 환자에서 low-molecular-weight Heparin의 유효성 평가를 위한 연구로서 Primary outcome은 임상지표를 사용하였고 **Secondary outcome**으로서 low-molecular-weight Heparin의 합병증 (예: 뇌경색 후 뇌출혈)을 밝히고자 하였으며 **noncontrast CT**를 이용하여 뇌경색 후 뇌출혈을 객관적으로 평가하고자 하였고 **Independent image review system**을 도입하였음.
4. The Multicenter Acute Stroke Trial-Europe Study Group (MAST-E, NEJM 1996): 중대뇌동맥의 중등도 이상의 뇌졸중 환자에서 IV streptokinase의 유효성 평가를 위한 연구로서 Primary·Secondary outcome은 임상지표였으며 **noncontrast CT**를 **Safety parameters**와 **환자 배제 기준**으로서 사용함. **Independent image review system**을 도입하여 noncontrast CT상 뇌경색과 뇌출혈을 평가하였음.

Clinical trial imaging in Acute ischemic stroke

5. ECASS II (Lancet 1998): 급성 뇌졸중 환자에서 IV alteplase의 6시간까지의 연장 사용에 관한 유용성 평가를 위한 연구로서 noncontrast CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 **noncontrast CT는 Safety parameters**로서 사용됨. **Noncontrast CT가 환자 선정의 전면에 나온 연구이며** 뇌경색, 뇌출혈의 검출 뿐 아니라 뇌경색의 부피를 정량적으로 분석하였음.
6. Phenylpropanolamine and the Risk of Hemorrhagic stroke (NEJM 2000): Phenylpropanolamine (식욕 억제 및 감기 치료제)의 hemorrhagic stroke 발생에 미치는 영향을 평가한 연구로서 subarachnoid hemorrhage와 intracerebral hemorrhage 검출에 noncontrast CT를 이용하였음.
7. Pravastatin therapy and the Risk of Stroke (NEJM 2000): Pravastatin의 stroke risk 감소에 대한 유효성 평가를 위한 연구로서 **CT, MR, Angiography를 Ischemic stroke, Hemorrhagic stroke의 진단과 분류에 이용**하였음.
8. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS, Stroke 2005): 급성 뇌졸중 환자에서 Desmoteplase의 9시간까지의 연장 사용에 대한 유효성 평가를 위한 연구로서 **DWI, TOF-MRA, FLAIR, PWI**의 MR 영상 검사가 **환자 선정 및 outcome에서 주요한 역할**을 수행함. **Primary outcome**으로서 **PWI의 정량적 감소와 MRA의 재개통 소견**을 사용하였고 유효성 평가의 **다른 outcome**으로서 **DWI의 뇌경색 범위의 변화**를 이용하였음. DWI은 뇌경색의 진단 및 부피 측정을 위해 사용되었고 **FLAIR는 만성적 허혈성 병변 검출에 사용**하였음.

Clinical trial imaging in Acute ischemic stroke

9. Recombinant Activated Factor VII for Acute Intracerebral hemorrhage (NEJM 2005): 급성 뇌출혈 환자에서의 Recombinant Activated Factor VII의 유효성 평가를 위한 연구로서 **Noncontrast CT상 뇌출혈 부피의 변화를 Primary outcome으로 사용**하였음. Digital CT 정보를 imaging core lab으로 전송하여 Neuroradiologist에 의한 Independent image review system을 이용하여 Primary outcome을 분석하였음.
10. The Dose Escalation of Desmoteplase in Acute Stroke (DEDAS, Stroke 2006): 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 **MRI를 Primary efficacy endpoint로 사용**하였고 **Safety endpoint로서 noncontrast CT**를 이용하였음. **DWI**를 이용한 **정성적·정량적 뇌경색 부피 분석**, **MRA**를 이용한 **혈관의 재개통 분석**, **관류 MR**을 이용한 **정량적 관류 분석**, **Noncontrast CT**를 이용한 **뇌출혈 발생률**을 연구의 주요 결과로서 보고하였음. Imaging core lab과 Independent image review system을 통한 정성적·정량적 분석을 시행하였음.
11. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE, Ann Neurol 2006): 급성 뇌졸중 환자에서 **MRI profile과 임상지표를 직접적으로 비교**하는 연구로서 **DWI, DSC PWI, FLAIR, GRE, MRA, T1-weighted imaging**을 이용하여 정성적·정량적 분석을 시행하였음.
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 소프트웨어**를 이용하여 뇌경색 부피 변화를 측정하였음. PWI, MRA를 이용하여 관류 변화와 재개통 여부를 판정하였음.

Clinical trial imaging in Acute ischemic stroke

13. The Factor Seven for Acute Hemorrhagic Stroke (FAST, NEJM 2008): 급성 뇌출혈 환자에서 Recombinant activated factor VII의 유효성 평가를 위한 연구로서 **Primary endpoint**로서 **Noncontrast CT**를 이용한 뇌출혈 부피 변화를 이용하였음. **정량적 영상 분석 소프트웨어**를 이용하여 뇌출혈 부피 변화 결과를 산출하였음.
14. DIAS II (Lancet Neurol 2009): 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 **환자 선정과 Secondary outcome**을 위하여 **CT와 MR**을 사용하였음. 환자 선정을 위해 **DWI과 PWI**을 이용한 **희생가능한 반음영의 정량적 분석**을 시행하였고 **Secondary outcome**을 위하여 **DWI과 noncontrast CT**를 이용한 **뇌경색 부피 분석**을 하였음. 치료에 의한 혈관의 재개통여부를 위해 MR 혹은 CT angiography를 이용하였으며 Safety outcome으로서 Noncontrast상의 뇌출혈 발생을 사용하였음. **Imaging core lab**과 함께 정량적 영상분석이 이용되었음.
15. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke (NEJM 2012): 급성 뇌졸중 환자에서 IV Tenecteplase의 유효성 평가를 위한 연구로서 **환자 선정을 위해 CT angiography**를 이용하여 혈관의 폐색 정도와 여부를 평가하였고 **CT perfusion**을 이용하여 뇌경색 병변 범위와 관류상태를 평가하였음. **Primary outcome**으로서 **관류 영상**을 통한 관류 상태 변화를 측정하였고 **Secondary outcome**으로서 **뇌경색 부피 변화와 혈관 재개통 분석**을 하였으며 **Secondary imaging safety outcome**으로서 **뇌출혈 양 변화를 영상 검사를 통하여 분석**하였음. MR 검사로서는 **GRE, FLAIR, DWI, PWI, MRA**가 사용되었음. **Imaging core lab**과 **Independent image review system**을 통한 정성적·정량적 분석을 시행하였으며 정량적 영상 분석을 위해서 **Commercial software**를 사용하였음.

Clinical trial imaging in Acute ischemic stroke

1. Role of Imaging ↑
2. Imaging as Main outcomes ↑
3. Independent imaging review ↑
4. Centralized imaging analysis and reading ↑
5. Infarct size (DWI/NCCT), Hemorrhage (NCCT/GRE)

Clinical trial imaging in Acute ischemic stroke

Choosing a Hyperacute Stroke Imaging Protocol for Proper Patient Selection and Time Efficient Endovascular Treatment: Lessons from Recent Trials

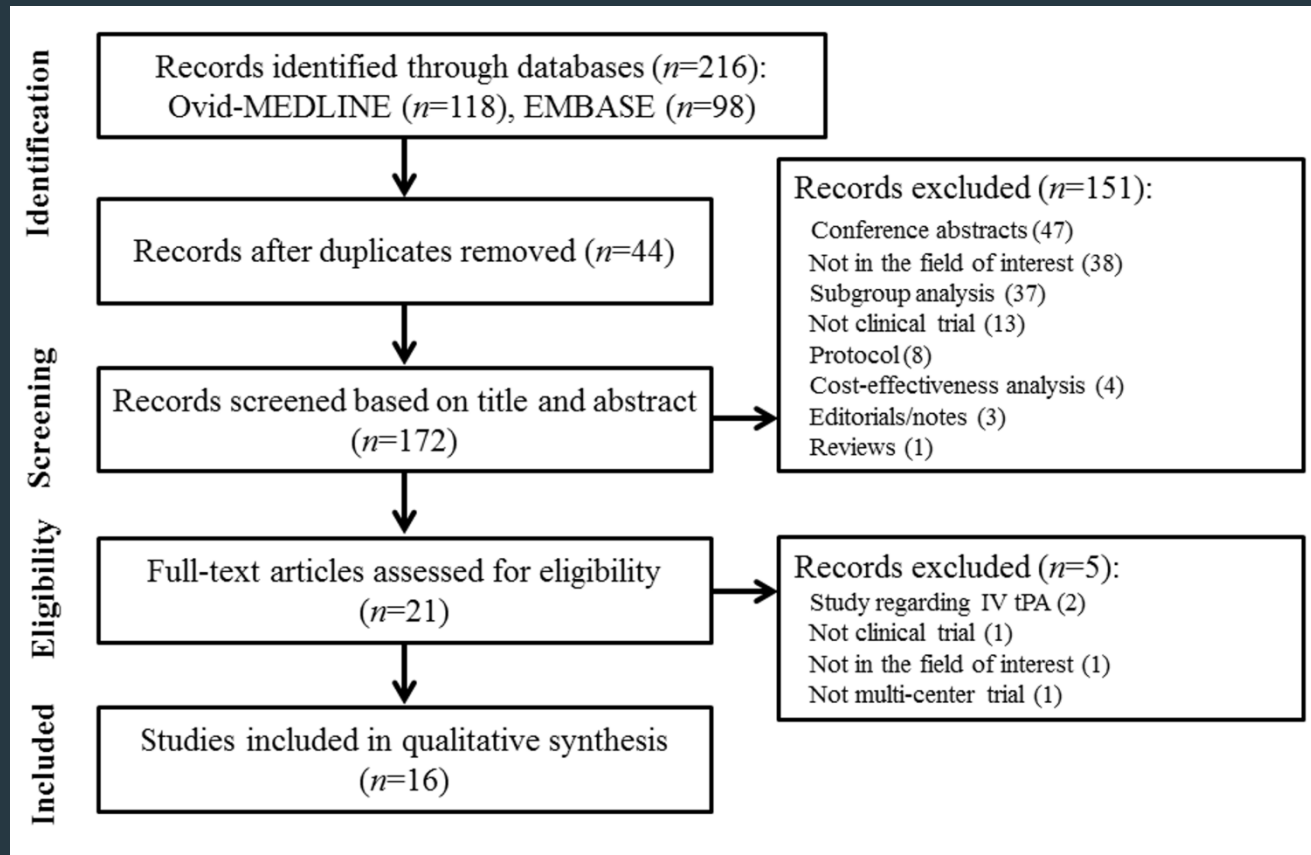
Introduction

Since about 1995, intravenous recombinant tissue plasminogen activator has been a gold standard for patients with acute ischemic stroke.^{1,3} For a diagnosis of acute ischemic stroke, non-contrast computed tomography (CT) was the only essential test beyond a clinical assessment based on history of illness, timing of last seen normal and neurological examination to rule out mimics and determine if disabling deficits.^{1,2} Intravenous tissue plasminogen activator (tPA) has since been shown to have limited efficacy in the setting of proximal large artery occlusions.^{4,5} Unfortunately, endovascular treatment with first generation devices failed to prove its efficacy⁶⁻⁸ until the advent of newer thrombectomy devices known as stent retrieval devices which resulted in a series of successful randomized clinical trials all published in 2015.^{9,13}

Several factors influenced the success of these recent endovascular treatment (Table 1). Retrievable stents such as (Solitaire FR [Medtronic, Irvine, CA, USA] and Trevo [Stryker, Kalamazoo, MI, USA]) were a leap in technology that achieved much higher rates of successful reperfusion than the older technology such as Merci (Concentric Medical, Mountain View, CA, USA) or intra-arterial thrombolytic delivery.^{14,15} Trials also mandated time targets for imaging to groin puncture and imaging to reperfusion which forced trial centres to focus on unnecessary delays and improve efficiencies. Initial CT to intra-arterial puncture times less than 1 hour were achieved in some these trials.^{10,11} Patient selection insured that all subjects had proximal intracranial occlusions and small or medium sized infarct cores of irreversible injury at time of baseline imaging. This selection used either a noncontrast CT (Alberta Stroke Program Early CT score [ASPECTS] based), CT angiography (CTA) collaterals or CT per-

Clinical trial imaging in Acute ischemic stroke

- 2012 ~ 2018
- Randomized, Multi-center clinical trials in endovascular treatment for acute cerebral ischemic stroke



| Author | Publication year | Trial nickname | No. of patients (n) | No. of centers | Purpose | ^a Inclusion time (hours) | Eligibility | |
|---------------------------|------------------|----------------|---------------------|----------------|--|-------------------------------------|--|---|
| | | | | | | | Inclusion | Inclusion: Neuroimaging |
| Nogueira RG, et al. (5) | 2018 | DAWN | 206 | 26 | Efficacy of EVT | 6-24 | 1) Ineligible or failed respond to IVT, 2) NIHSSs 10-42 | 1) Mismatch between clinical and infarct volume on CT or MR, 2) Occlusion of intracranial ICA or M1 on CTA or MRA |
| Albers GW, et al. (6) | 2018 | DEFUSE 3 | 182 | 38 | Efficacy of EVT | 6-16 | NIHSSs \geq 6 | ^b 1) Mismatch between infarct volume and penumbra on CT or MR, 2) Occlusion of ICA and M1 on CTA or MRA |
| Muir KW, et al. (12) | 2017 | PISTE | 65 | 10 | Efficacy of EVT | 6 | NIHSSs \geq 6 | Occlusion of intracranial ICA, M1, or single M2 on CTA or MRA |
| Lapergue B, et al. (13) | 2017 | ASTER | 381 | 8 | Comparison of Aspiration and Stent retrieval | 6 | | Occlusion of intracranial ICA, M1, or M2 on CTA or MRA |
| Mocco J, et al. (14) | 2016 | THERAPY | 108 | 36 | Efficacy of EVT | | NIHSSs \geq 8 | 1) Occlusion of intracranial ICA and MCA on CTA and Thrombus > 8 mm on CT |
| Bracard S, et al. (15) | 2016 | THRACE | 414 | 26 | Efficacy of EVT | 5 | NIHSSs 10-25 | Occlusion of intracranial ICA, M1, or upper 1/3 BA on CTA or MRA |
| Saver JL, et al. (7) | 2015 | SWIFT PRIME | 196 | 39 | Efficacy of EVT | 6 | NIHSSs 8-29 | Occlusion of intracranial ICA and M1 on CTA or MRA (TICI 0-1) |
| Jovin TG, et al. (8) | 2015 | REVASCAT | 206 | 4 | Efficacy of EVT | 8 | 1) Ineligible or failed respond to IVT, 2) NIHSSs \geq 6 | Occlusion of intracranial ICA or M1 on CTA, MRA, or DSA (TICI 0-1) |
| Goyal M, et al. (9) | 2015 | ESCAPE | 316 | 22 | Efficacy of EVT | 12 | NIHSSs > 5 | 1) Infarct core (small: ASPECTS 6-10) on NECT, 2) Occlusion of carotid T/L and M1/Immediate M2 on CTA, ^c 3) Moderate-to-good collaterals (filling of 50 % or more of MCA) on CTA, 3) Groin puncture \leq 60 min after NECT and CT-to-recanalization time \leq 90 min |
| Campbell BC, et al. (10) | 2015 | EXTEND-IA | 70 | 14 | Efficacy of EVT | 6 | | 1) Occlusion of ICA, M1, or M2 on CTA or MRA, 2) Infarct core volume (< 70 ml on CTP-CBF or DWI), ^b 3) Mismatch between infarct core and penumbra on CT or MR |
| Berkhemer OA, et al. (11) | 2015 | MR CLEAN | 500 | 16 | Efficacy of EVT | 6 | NIHSSs \geq 2 | Occlusion of intracranial ICA, M1-2, A1-2 on CTA, MRA, DSA, or TCD |
| Kidwell CS, et al. (16) | 2013 | MR RESCUE | 127 | 22 | Efficacy of EVT and penumbral imaging | 8 | 1) Ineligible or failed respond to IVT, 2) NIHSSs 6-29 | 1) Occlusion of ICA, M1-2 on CTA or MRA, 2) Multimodal CT or MR (MR RESCUE protocol) |
| Cicone A, et al. (17) | 2013 | SYNTHESIS | 362 | 24 | Efficacy of EVT | 6 | | |
| Broderick JP, et al. (18) | 2013 | IMS III | 656 | 58 | Efficacy of EVT | 5 | NIHSSs \geq 10 or 8-9 with occlusion of ICA or M1 or BA | Occlusion of ICA or M1 or BA on CTA in NIHSSs 8-9 |
| Saver JL, et al. (19) | 2012 | SWIFT | 113 | 18 | Efficacy and Safety of Solitaire | 8 | 1) Ineligible or failed respond to IVT, 2) NIHSSs 8-30, | Occlusion of M1, M2, ICA, BA, or VA on DSA (TIMI 0-1) |
| Nogueira RG, et al. (20) | 2012 | TREVO 2 | 178 | 27 | Efficacy and Safety of Trevo | 8 | 1) Ineligible or failed respond to IVT, 2) NIHSSs 8-29 | Occlusion of M1, M2, ICA, BA, or VA on DSA |

Clinical trial imaging in Acute ischemic stroke

| Trial nickname | Eligibility | Outcomes | | | | Conclusion |
|----------------|---|------------------------------|---|--|--|---------------|
| | Exclusion: Neuroimaging | Primary | Secondary | Safety | Imaging | |
| DAWN | 1) Intracranial hemorrhage, 2) Significant mass effect and midline shift, 3) Intracranial tumor on CT or MR, 4) Steno-occlusion or Tortuosity of cervical ICA on CTA or MRA | ^d mRS | Clinical indexes, Infarct core volume, Recanalization, Reperfusion, | 1) Death (90 days), 2) SICH (24 hours), 3) NIHSSs increase, 4) SAE | Included in Second outcomes | Positive |
| DEFUSE 3 | 1) ASPECTs < 6 on NECT, 2) Significant mass effect and midline shift on 3) Intracranial tumor on CT or MR, 4) ICA dissection of cervical ICA, 5) ≥ 1 vascular territory infarct on CTA or MRA | ^d mRS | Clinical index | 1) Death (90 days), 2) SICH (36 hours), 3) SAE | 1) Infarct core volume, 2) Recanalization 3) Reperfusion | Positive |
| PISTE | 1) Intracranial hemorrhage, 2) Infarct (> 1/3 MCA hypodensity), 3) Occlusion of extracranial ICA or BA | ^d mRS | Clinical indexes, Recanalization | 1) Death (90 days), 2) ICH (24 hours), 3) Procedural complication | ^f Reperfusion | Negative |
| ASTER | Occlusion of Cervical carotid artery | Revascularization | Clinical indexes, Revascularization, Time to successful revascularization | 1) Procedural complication, 2) Intracranial hemorrhage (24 hours) | Included in Primary and Secondary outcomes | No difference |
| THERAPY | 1) Significant mass effect with midline shift, 2) Infarct (acute ischemic change) > 1/3 of MCA territory, 3) intracranial hemorrhage, 4) Intracranial tumor, 5) Ipsilateral extracranial steno-occlusion, 6) Preexisting arterial injury | ^d mRS | Clinical indexes, Infarct core volume | 1) SAE, 2) SICH (24 hours), 3) Death (90 days) | Included in Second outcomes | Negative |
| THRACE | 1) Steno-occlusion of ipsilateral cervical carotid artery, 2) Intracranial hemorrhage, 3) Intracranial tumor, 4) Mass effect with midline shift on CT or MR | ^d mRS | Clinical indexes | 1) Death (90 days), 2) Hemorrhage (24 hours), 3) Procedural complication | None | Positive |
| SWIFT PRIME | 1) ASPECTs < 6 on NECT or DWI, ^{b2}) > 1/3 MCA territory or > 100 cc in other vascular territory (hypodensity on CT or hyperintensity on MR), 3) Intracranial hemorrhage, 4) Mass effect, 5) Intracranial tumor on CT or MR, 6) Occlusion of BA or PCA, 7) Occlusion or Dissection of cervical ICA on CTA or MRA | ^d mRS | Clinical indexes, Revascularization, Reperfusion | 1) SAE, 2) SICH (27 hours) | Included in Second outcomes and ^e Infarct core volume | Positive |
| REVASCAT | 1) Intracranial hemorrhage, 2) Significant mass effect and midline shift, 3) Intracranial tumor, 4) Steno-occlusion of cervical ICA on CTA, MRA or DSA, 5) Infarct volume (ASPECTs < 7 on CT; ASPECTs < 6 on DWI) | ^d mRS | Clinical indexes, Infarct core volume, Revascularization, Recanalization | 1) Death (90 days), 2) SICH (90 days), 3) Procedural complication, 4) SAE | Included in Second outcomes | Positive |
| ESCAPE | 1) Infarct core (moderate to large: ASPECTs 0-5) on NCCT, 2) Infarct core on CTA or CTP (moderate to large: no or minimal collaterals in a region greater than 50 % of MCA territory compared to contralateral side on CTA, low CBV and very low CBF ASPECT < 6 [≥8 cm coverage] or low CBV and very low CBF > 1/3 MCA territory[<8 cm coverage] on CTP), 3) Suspected intracranial dissection, 4) Chronic intracranial occlusion | ^d mRS | Clinical indexes, Reperfusion, Recanalization | 1) Death, 2) SICH, 3) Malignant infarct, 4) Procedural complication | Included in Second outcomes | Positive |
| EXTEND-IA | 1) Infarct volume (hypodensity > 1/3 MCA territory) on NECT, 2) Intracranial hemorrhage on CT or MR, 3) Difficulty or inability to access to cerebral arteries (proximal stenosis, dissection) | Reperfusion, NIHSSs (3 days) | Clinical indexes, ^f Infarct core volume, Recanalization | 1) Death, 2) SICH, 3) Parenchymal hematoma | Included in Primary and Secondary outcomes | Positive |
| MR CLEAN | Intracranial hemorrhage on CT or MR | ^d mRS | Clinical indexes, Infarct core volume, Reperfusion, Recanalization | 1) Neurologic deterioration, 2) SICH, 3) Procedural complication, 4) SAE (death) | Included in Second outcomes | Positive |

Clinical trial imaging in Acute ischemic stroke

| Trial nickname | Eligibility | Outcomes | | | | Conclusion |
|----------------|---|------------------|---|---|------------------------------|------------|
| | Exclusion: Neuroimaging | Primary | Secondary | Safety | Imaging | |
| MR RESCUE | 1) Intracranial hemorrhage, 2) cervical carotid steno-occlusion on CTA or MRA | ^d mRS | Clinical indexes, Infarct core volume, Reperfusion, Revascularization | 1) Death (90 days), 2) ICH (7 days), 3) SAE | Included in Second outcomes | Negative |
| SYNTHESIS | 1) Intracranial hemorrhage, 2) Intracranial tumor except small meningioma, 3) Acute infarct (may be > 4.5 hours after onset) | ^d mRS | Clinical indexes | 1) Hemorrhage, 2) Infarct, 3) death, 4) NIHSSs \geq 4 increase, 5) Extracerebral events at 7 days | None | Negative |
| IMS III | 1) Infarct (> 1/3 of MCA territory), 2) Intracranial hemorrhage, 3) Significant mass effect with midline shift, 4) Intraparenchymal tumor, 5) Baseline CTA without evidence of an arterial occlusion | ^d mRS | Clinical indexes, Infarct core volume, Reperfusion, Recanalization | 1) Death, 2) Hemorrhage, 3) Major complication d/t nonintracerebral bleeding, 4) Recurrent stroke, 5) Device or procedural complication | Included in Second outcomes | Negative |
| SWIFT | 1) Infarct volume (> 1/3 MCA territory or > 100 cc of volume), 2) Intracranial hemorrhage, 3) Intracranial tumor or mass effect on CT or MR, 4) Complete cervical carotid occlusion, carotid dissection on DSA | Recanalization | Clinical indexes, Time to Successful recanalization | 1) SICH, 2) Death 3) SAE | Included in Primary outcomes | Positive |
| TREVO 2 | 1) Infarct volume (> 1/3 MCA territory or > 100 cc of volume), 2) Intracranial hemorrhage, 3) Significant mass effect with midline shift, 4) Intracranial tumor on CT or MR, 5) Cervical carotid steno-occlusion including excessive tortuosity | Reperfusion | Clinical indexes, Time to Successful reperfusion, Asymptomatic SICH | 1) Death, 2) SICH, 3) SAE, 4) Device or procedural complication | Included in Primary outcomes | Positive |

Infarct core volume and hemorrhagic transformation in the outcomes

| Trial nickname | Infarct core volume | | | | Hemorrhagic transformation |
|----------------|---------------------|--------------------------------------|-----------------------|--|----------------------------|
| | Baseline | 24 hours | 5-7 days or discharge | Definition | Classification |
| DAWN | DWI, CTP | DWI, NECT | | RAPID (with semi-automated algorithm using manual lesion outlining; CTP -CBF, < 30 % of contralateral normal tissue; DWI, based ADC) Manually outlining hypodense lesion (NECT) | ECASS |
| DEFUSE 3 | DWI, CTP | MR (DWI), CT | | RAPID | ECASS |
| PISTE | | | | | ECASS (PH1, 2), SITS-MOST |
| ASTER | | | | | ECASS |
| THERAPY | CT | CT | | ASPECTs | ECASS |
| THRACE | | | | | ECASS |
| SWIFT PRIME | DWI, CTP | ^a DWI/FLAIR/MRP, NECT/CTP | | RAPID (DWI[ADC], < 620 X 10 ⁶ mm ² ; CTP-CBF, > 70 % reduced region) | ECASS |
| REVASCAT | DWI, NECT | DWI, NECT | | Quantomo | ECASS, SITS-MOST |
| ESCAPE | | | | | |
| EXTEND-IA | CTP | DWI, NECT | | RAPID (CTP-CBF, automated ischemic core volume < 30 % of normal tissue), DWI or NECT (manually outlined) | SITS-MOST |
| MR CLEAN | NECT, CTP | | NECT | Semi-automated algorithm for CT hypodensity | ECASS |
| MR RESCUE | DWI (MRP), CT | | FLAIR, CT | Study-specific predictive model on baseline, Hyperintensity (FLAIR), Hypodensity (CT) | ECASS |
| SYNTHESIS | | | | | Study specific definitions |
| IMS III | CT | CT | | ASPECTs, digital measurement | ECASS |
| SWIFT | | | | | ECASS |
| TREVO 2 | | | | | ECASS, SITS-MOST |

Revascularization, Reperfusion, Recanalization

| Trial nickname | Revascularization | | | Reperfusion | | | Recanalization | | |
|----------------|-------------------|----------------|--------------|-----------------------|--------------------------------|--|----------------|----------------|------------------------------------|
| | Imaging | Time interval | Definition | Imaging | Time interval | Definition | Imaging | Time interval | Definition |
| DAWN | | | | DSA | Post-procedure | mTICI (2b-3) | CTA or MRA | 24 hours | No, Partial, or Complete |
| DEFUSE 3 | | | | 1) CTP or MRP, 2) DSA | 1) 24 hours, 2) Post-procedure | 1) Reduction (>90%) in perfusion lesion volume with Tmax > 6s, 2) mTICI (2b-3) | CTA or MRA | 24 hours | Complete or not |
| PISTE | | | | DSA | Post-procedure | mTICI (2b-3) | CTA or MRA | 24 hours | IST-3 CTA score |
| ASTER | DSA | Post-procedure | mTICI (2b-3) | | | | | | |
| THERAPY | | | | | | | | | |
| THRACE | | | | | | | | | |
| SWIFT PRIME | DSA | Post-procedure | mTICI (2b-3) | CTP or MRP | 27 hours | Reduction (\geq 90%) in perfusion lesion volume | | | |
| REVASCAT | DSA | Post-procedure | mTICI (2b-3) | | | | CTA or MRA | 24 hours | Patent or Occluded |
| ESCAPE | | | | DSA | Post-procedure | TICI (2b-3) | CTA | 2-8 hours | mAOL (2-3) |
| EXTEND-1A | | | | CTP or MRP | 24 hours | RAPID (Reduction [%] in perfusion lesion volume with T max > 6 s) | CTA or MRA, | 24 hours | TIMI (2-3) |
| MR CLEAN | | | | DSA | Post-procedure | mTICI (2b-3) | CTA or MRA | 24 hours | mAOL (2-3) |
| MR RESCUE | CTA or MRA | 7 days | TICI (2a-3) | CTP or MRP | 7 days | Reduction (\geq 90%) in perfusion lesion volume with Tmax > 6s | | | |
| SYNTHESIS | | | | | | | | | |
| IMS III | | | | DSA | Post-procedure | TICI (2-3) | CTA > MRA | 24 hours | Partial or Complete recanalization |
| SWIFT | | | | | | | DSA | Post-procedure | TIMI (2-3) |
| TREVO 2 | | | | DSA | Post-procedure | TICI (2-3) | | | |

Revascularization, Reperfusion, Recanalization

- Revascularization, recanalization and reperfusion: interchangeably.
- **Revascularization** reflects **all treatment-related flow improvement**, including **local** arterial recanalization and reperfusion of the **downstream** territory.
- **Recanalization** is required for **antegrade** tissue reperfusion but may **not** be necessary for reperfusion in **distal** regions (36, 37).
- Revascularization and reperfusion seem to be interchangeable terms while recanalization seems to focus on the restoration of proximal vessel patency.

IIRC, Imaging core lab, Standardization

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

Summary

Appropriate eligibility criteria and outcomes should be selected based on clinical and imaging indexes.

→ Thorough review of previous studies may be helpful for planning a study.
Accordingly, this review may be helpful.

Imaging indexes: detailed criteria in infarct core volume and revascularization are not standardized. Therefore, neuroimaging prefers to be archived using the same imaging protocols and analyzed by an independent image review committee and imaging core laboratory.


→ Requirement (or encouragement) for the same imaging modality in the comparisons of outcomes seems reasonable and realistic because the same imaging protocol can be difficult in urgent circumstances.

This review may help each researcher to appropriately use neuroimaging biomarkers for observational studies as well as clinical trials in acute ischemic stroke like a consultant.



Neuroimaging in Acute ischemic Stroke: Role and Recent Advances

급성 허혈성 뇌졸중에서의 뇌 영상 검사의
최신 지견과 역할

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Neuroimaging plays a key role in assessing the detection of acute hemorrhage, diagnosis of infarct core, detection of steno-occlusive arteries, mismatch between infarct core and penumbra, and collateral circulation in patients with acute cerebral ischemic stroke. The recent announcement of randomized clinical trials that demonstrated the usefulness of intra-arterial mechanical thrombectomy and the guidelines of 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke from American Heart Association/American Stroke Association led to a larger role of neuroimaging and required new neuroimaging strategy for acute cerebral ischemic stroke. In this review, we summarize the recommendation on neuroimaging from the 2018 Guidelines, and review pros and cons between CT and MR and fast scanned stroke MR. Based on the new guidelines and recent research, we discuss the appropriate neuroimaging strategy for acute cerebral ischemic stroke patients.

Index terms Stroke; Neuroimaging; **Computed Tomography, X-Ray**; Magnetic Resonance Imaging

서론

급성 허혈성 뇌졸중은 신경학적 후유증을 유발하여 장애와 심할 경우 사망에 이를 수 있는 가장 흔한 신경학적 질환이다. 급성 허혈성 뇌졸중에서 1995년 The National Institute of Neurological Disorders recombinant tissue-type plasminogen activator trial 임상시험(NINDS rtPA) 이후 정맥 내 혈전 용해술(intravenous recombinant tissue-type plasminogen activator trial, IV tPA)은 유일하게 입증된 재관류 치료방법이었다(1). 하지만 정

Received September 5, 2018

Revised October 16, 2018

Accepted October 26, 2018

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Imaging CRO

Imaging support for multicenter clinical trials

- Imaging protocol / charter
- Global standards



**Guidance for Industry
Standards for Clinical Trial
Imaging Endpoints**

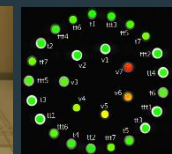
- Site training
- Site monitoring



- Imaging acquisition



- QA/QC
- Data management



- Post-processing
- Image analysis
- Central reading



**High Quality
Imaging
Service**

Central Imaging Core Lab in clinical trials

CRO Team for multicenter trial



저장: dicom 형식 전환,
anonimization



Centralized
Database



Qa/QC분석
Data 분석



표준화된 공개
소프트웨어

Project Manager

Imaging CRA

Imaging QC

IT manager

Radiologists

Regulation medicine

Site core lab service

Investigator
(Clinician)

Imaging CRC

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

Radiology
Department

Radiologist

Central core lab service

Image Analyst
Central Reader

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

Image CRA

IT system
Manager

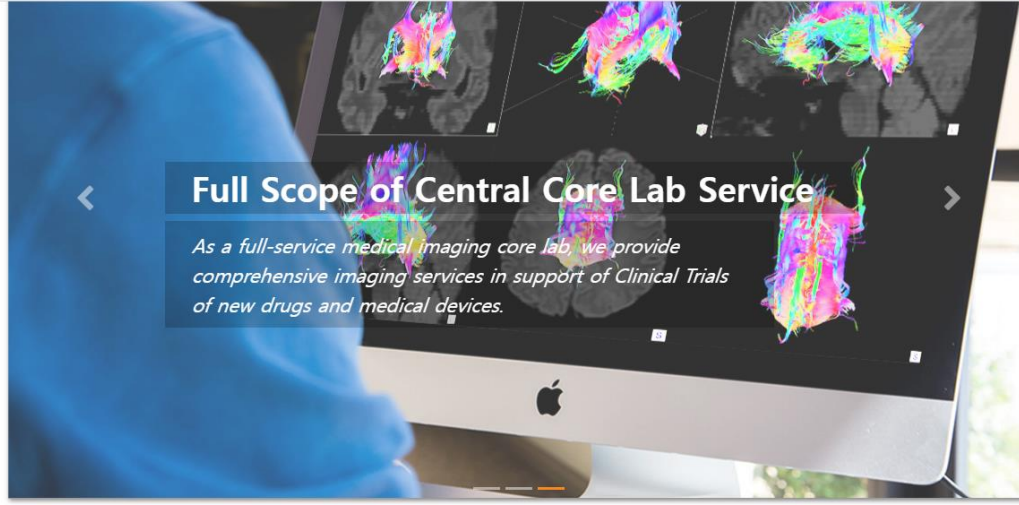
Imaging physicist
(PhD)



AIM : Asan Image Metrics

It is the first Central Imaging Core Lab in Korea that was established by 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.



Full Scope of Central Core Lab Service

As a full-service medical imaging core lab, we provide comprehensive imaging services in support of Clinical Trials of new drugs and medical devices.

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



Reliable Results
Reliable results by medical imaging professionals



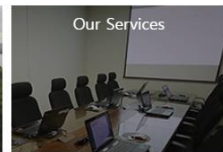
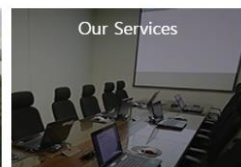
Rapid Results
Rapid results by web-based process



High Quality
High quality with expertise in the latest imaging technique



Standard Process
Global standardized process for FDA



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)

Edoxaban

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. 비관독성 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: 비관독성 심방세동을 가진 급성 뇌경색 환자에서 에독사반의 조기 투여가 고식적 항응고제 투여에 비해 뇌경색의 이른 재발을 줄일 수 있다.
4. Phase II

Edoxaban

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

Consultant

1. Infarct core

1) Definition or Criteria

2) Main outcomes

3) Modality and Methods: CT vs MR, ASPECT vs Quantitative

4) Measurement: noncontrast CT, CTP, DWI, PWI

5) Semi- or Fully automated analysis software

Consultant

2. Hemorrhagic transformation

1) Definition and classification

2) Safety outcome

3) CT vs MR

4) MR: Standardization (SWI vs GRE)

5) Measurement & Methods

Consultant

3. New infarct or recurred infarct

1) Definition and classification

2) Main outcomes

3) MR: DWI, FLAIR/T2W

4) Measurement

5) Semi- or Fully automated analysis software

Consultant

4. Steno-occlusion

1) **Definition: Reperfusion, Revascularization, Recanalization**

2) **Main/ Exploratory outcomes**

3) **CTA, MRA, DSA**

4) **Scoring: mAOL, mTICI, TICI, TIMI**

Consultant

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.

Consultant

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

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

Consultant

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

Consultant

4. Steno-occlusion

1) Definition: Recanalization

2) Secondary outcomes

3) MRA > CTA

4) Scoring: mAOL (MR RESCUE, ESCAPE)

Table S3. Arterial Occlusive Lesion (AOL) Rating Scale⁸

| Score | Definition |
|-------|---|
| 0 | No recanalization of the primary occlusion lesion |
| I | Incomplete or partial recanalization of the primary occlusion lesion with no distal flow |
| II | Incomplete or partial recanalization of the primary occlusion lesion with any distal flow |
| III | Complete recanalization of the primary occlusion with any distal flow |

Table S4. Thrombolysis in Cerebral Infarction (TICI) Rating Scale³

| Score | Definition |
|-------|---|
| 0 | No perfusion |
| 1 | Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion |
| 2a | Perfusion of less than 2/3 of the vascular distribution of the occluded artery |
| 2b | Perfusion of 2/3 or greater of the vascular distribution of the occluded artery |
| 3 | Full perfusion with filling of all distal branches |

Table S5. Thrombolysis in Myocardial Ischemia (TIMI) Rating Scale⁷

| Score | Definition |
|-------|---|
| 0 | No perfusion: absence of any antegrade flow beyond a coronary occlusion |
| 1 | Penetration without perfusion: faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed |
| 2 | Partial reperfusion: delayed or sluggish antegrade flow with complete filling of the distal territory |
| 3 | Complete perfusion: normal flow which fills the distal coronary bed completely |

AiCRO Home Study

Subjects list << Edoxaban_1_0

Add New Subject

Subject information

Subject No. R1-008
Initial SDS*
Site 순천향대학교서울병원
Subject Status

Visit Form

Screening
-- select visit --
Screening
baseline(D0-1)
Follow-up(D10-14)
Off-protocol (Unscheduled)

Customer service

Icon Explanation

Icons for subject data input

- NO DATA No data entered
- SAVE Currently entering
- QUERY Unresolved query
- ON HOLD On Hold
- DATA LOCKED Data Locked

Icons for image process

- NO IMAGE No image uploaded
- WAITING FOR QC Waiting for QC
- QC COMPLETED QC completed
- UNRESOLVED QC Unresolved QC
- NO IMAGE TO BE ANALYZED No image to be analyzed
- WAITING FOR ANALYSIS Waiting for analysis
- WAITING FOR MODERATE Waiting for moderate
- ANALYSIS COMPLETED Analysis completed

AiCRO Home Study

dynamics79 (Seung Chai Jung) | My Page | Logout

AiCRO Home Study

Baseline(D0-1) view 0

Edoxaban_1_0

Stenosis_Description

Subject Number R1-008
Subject Initial SDS*

Stenosis Description

Anal_com

Analysis Complete - select

I.DWI for Acute infarction

| | | | |
|---|---|--|--|
| 1 | Is there an infarction on baseline MRI? | <input type="radio"/> Yes <input type="radio"/> No | |
| If yes, please fill the below items. | | | |
| 2-1 | Right | <input type="checkbox"/> ICA <input type="checkbox"/> ACA <input type="checkbox"/> MCA superior <input type="checkbox"/> MCA inferior <input type="checkbox"/> MCA subcortical(Perforators) <input type="checkbox"/> PCA <input type="checkbox"/> VA/BA/AICA/PICA | |
| | Left | <input type="checkbox"/> ICA <input type="checkbox"/> ACA <input type="checkbox"/> MCA superior <input type="checkbox"/> MCA inferior <input type="checkbox"/> MCA subcortical(Perforators) <input type="checkbox"/> PCA <input type="checkbox"/> VA/BA/AICA/PICA | |
| 2-2 | Right | <input type="checkbox"/> Frontal <input type="checkbox"/> Parietal <input type="checkbox"/> Temporal <input type="checkbox"/> Occipital <input type="checkbox"/> Insula <input type="checkbox"/> Subcortical(Corona radiate /Internal capsule /Basal ganglia) <input type="checkbox"/> Thalamus <input type="checkbox"/> Midbrain <input type="checkbox"/> Pons <input type="checkbox"/> Medulla <input type="checkbox"/> Cerebellum | |
| | Left | <input type="checkbox"/> Frontal <input type="checkbox"/> Parietal <input type="checkbox"/> Temporal <input type="checkbox"/> Occipital <input type="checkbox"/> Insula <input type="checkbox"/> Subcortical(Corona radiate /Internal capsule /Basal ganglia) <input type="checkbox"/> Thalamus <input type="checkbox"/> Midbrain <input type="checkbox"/> Pons <input type="checkbox"/> Medulla <input type="checkbox"/> Cerebellum | |

II.GRE for hemorrhagic transformation.

| | | | |
|---|--|---|--|
| 1 | Is there a hemorrhagic transformation? | <input type="radio"/> Yes <input type="radio"/> No | |
| 2 | If yes, Hemorrhagic transformation grade | <input type="radio"/> HI type I <input type="radio"/> HI type II <input type="radio"/> PH type I <input type="radio"/> PH type II | |

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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 – 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 committee (IRC)

3. Data & Safety monitoring board (DSMB)

Trial & Imaging



Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Trial = Best Management

- Control
- Equipoise



Cancer Trial 에서 Imaging은 핵심 역할

- Surrogate endpoint
- Pharmacodynamic biomarker



Trial Imaging은 종합학문

- Whole body
- Whole imaging process
- Business & development
- Regulation
- Science
- IT platform

기준과 시스템 필요성

- 미국 FDA는 2015년 임상시험에서 영상을 활용하는 절차에 대한 지침을 발표함.
- QIBA, ACR, NCI 의 support !

Guidance for Industry Standards for Clinical Trial Imaging Endpoints

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)



제약회사

CRO

임상시험 실시기관

기준과 시스템 필요성

- ▶ 신약개발 임상 시험에 특화된 영상 데이터의 처리에 대한 표준을 제시한다.
- ▶ 영상 처리의 표준은 시험 의뢰자로 하여금 영상 데이터가 임상시험 프로토콜에 의거해 얻어지고, 영상 데이터의 임상시험 기준을 충족하며, 검증된 영상 처리과정에 대한 확신을 가질 수 있도록 도와준다.
- ▶ 표준화된 절차에 기반해 영상 처리 과정에서의 변동 혹은 편차를 최소화하는 것은 약효 평가를 위한 임상 시험의 신뢰성을 높이는 데 매우 중요한 요소이다.

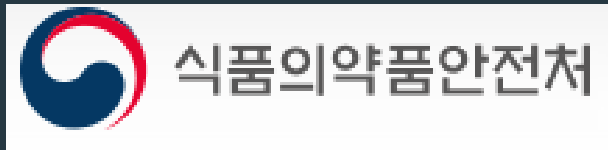
기준과 시스템 필요성

국내 00 제약회사

항암제 임상시험 완료



실태조사(Inspection)



식약처 지적사항

- 영상 관독자의 적격성이 평가되었는가?
- 영상 관독이 독립적이었는가?
- 영상 관리 시 GCP 규정을 철저히 준수했는가?

“ 기준? 지침? 가이드라인? & 시스템 ”

기준과 시스템 필요성



지침에 맞는 영상관리 및 영상평가

영상 관리 시스템 활용

영상 바이오마커 선정

- 각 임상시험에 맞는 영상 바이오마커 선정
 - 항암제: CT/MRI의 크기 측정, RECIST, etc
 - 골다공증 치료제: DEXA
 - ADPKD 치료제: Total kidney volume
 - 골관절염 치료제: X-ray, MRI
 - Etc.

체크포인트

- 영상 바이오마커가 정말 병적 현상과 직접적인 연관이 있어 약효를 평가할 수 있는가?
- 규제 기관에서 영상 바이오마커를 인정하는가?

영상 바이오마커 선정

- 영상정보 또는 해석의 신뢰도는 다양함
 - 신뢰도 높은 정보: X-ray 골절, CT의 암 진단 및 크기 측정
 - 모호한 정보: 대뇌 피질의 XXX 수용체 분포와 활성화도
- 약효 평가의 도구로 사용하려면 영상 정보가 의미하는 바가 명확하고 인체 내부의 정상적, 병적 현상과 직접적인 연관성이 있어야 한다.

→ 적격성 (Qualification)

- 규제기관의 승인
학계의 consensus

Evidentiary process of linking a biomarker with biological processes and clinical end points

영상 장비/프로토콜 확립

- 영상의 획득, 저장 및 해석의 방법의 편차
 - 약효 평가의 신뢰성과 정확성을 감소시키는 요인
 - **표준화 (Standardization)** 된 장비/프로토콜 필요
- 신약 평가시에는?
 - 임상진료에서 표준화된 영상 사용 (X-ray의 대퇴골절, CT의 암 크기). 이 경우에도 각 기관 영상의 표준화 유무 확인 절차는 필요함.
 - 개별 **임상시험에 특화된 시험-맞춤형 (trial-specific)** 영상 처리 표준 지침 마련

장비/프로토콜 선정시 고려 사항

- 임상 시험기관 별 영상 장비의 성능과 관리/운영의 기술적 차이
- 영상기술자의 수준 보장 및 임상시험에 특화된 영상기술의 가능 여부
- 각 기관들 간의 일관성과 영상 품질 관리를 보장하기 위해 phantom 및 calibration 스탠다드가 필요한 지 여부
- 시험에 특화된 고유의 영상 획득 방법 (피험자 위치, 영상의 해부학적 범위, 조영제의 사용, 영상 타이밍, 피험자 진정상태의 중요성, 영상 획득을 위한 스캐너 설정 포함)
- 판독 가용성 확보를 위해 반복 영상의 필요성의 명시를 포함하는 영상 품질 관리 표준
- 영상의 디스플레이 지침과 판독 절차
- 일차 판정변수로 사용되는 이미징 바이오마커의 성격 및 특성 및 시험에 특화된 영상 판독자의 정량적 측정을 위한 training 필요성 여부
- 시험의 수행, 모니터링 및 데이터 심사에 영향을 미치는 영상 기록보관의 기간 및 범위
- 영상 장비의 업그레이드 또는 오류의 가능성과 전체 시험기관에 걸친 (조영제와 같은) 영상 의약품의 변경 가능성
- Investigational drug development에서 영상 소견이 일차 평가변수로 사용된 경우, 영상 기법에서 발행한 문제점 등의 선례

전문 영상관리

Guidelines? Recommendation?

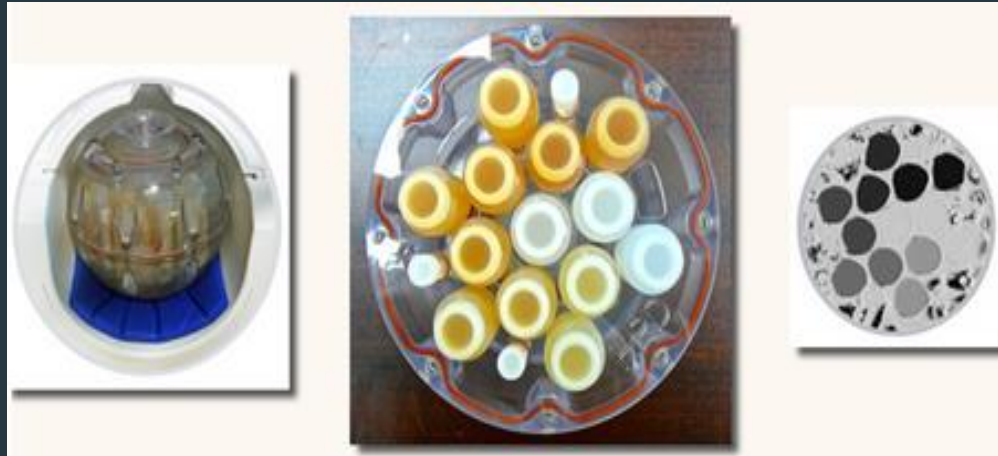
➤ 뇌졸중 치료 약물 임상시험에서의 영상 바이오마커의 기준안을 제시한다.

1. 뇌졸중 영상 바이오마커 표준화 팬텀
2. 뇌졸중 영상 바이오마커 분석 소프트웨어
3. 뇌졸중 영상 바이오마커의 촬영, 전송, 분석 등의 기준

뇌졸중 영상 적합 팬텀

1. CT 팬텀: 미국 표준 팬텀인 AAPM CT Performance phantom 혹은 ACR Phantom으로 표준화 가능
2. DWI MR 팬텀: QIBA 팬텀이 글로벌 스탠다드 (단점: 촬영의 불편, 해상도 평가 어려움, GRE추가 평가 불가, 비싼 가격 US \$ 4,000)
3. GRE MR 팬텀: NIST/ISMRM system 팬텀 (NIST에 의한 내부 물질 공인, 비싼 가격 US \$ 20,000)

뇌졸중 영상 적합 팬텀



NIST/ISMRM system phantom NIST/RSNA/NCI diffusion phantom NIST/UCSF/NCI system phantom

NIST/ISMRM system phantom

Labels: T₁ array, Resolution inset, T₂ array, Proton density array, Fiducial array, Slice profile inset

NIST/RSNA/NCI diffusion phantom

Wide range of diffusion

NIST/UCSF/NCI system phantom

Fat suppression with T₁ relaxation phantom

Labels: No Fat suppression, Spectral Fat suppression, Heavy Mineral oil, Olive oil

Signal from silicone shell is suppressed.

뇌졸중 영상 적합 팬텀



영상바이오마커 선정
내부 물질 협의
팬텀 디자인



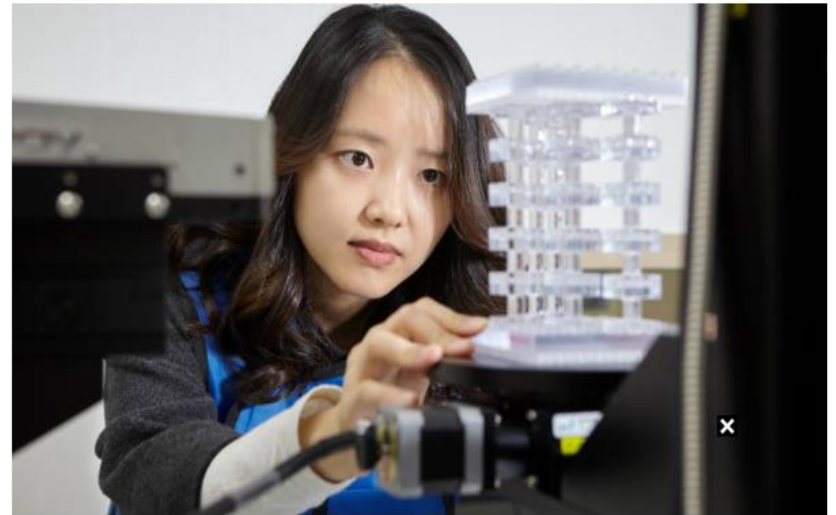
내부 물질 협의
팬텀 주문 제작
표준물질 공식인증

센터소개

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

전자 신문

표준연, 의료기기 성능 평가하는 모듈형 팬텀 세계 첫 개발



<조효민 한국표준과학연구원 의료융합측정표준센터 박사가 새로 개발한 'MOMA 팬텀' 모듈 물성을 시험하고 있다.>

뇌졸중 영상 적합 팬텀

➤ DWI Phantom

1) PVP (polyvinylpyrrolidone): 1순위 물질, QIBA phantom, 국제기준 충족

- Aqueous solution: 0 to 50 % w/w to obtain ADC values from 0.1×10^{-3} to 1.1×10^{-3} mm²/s at 0°C

- Long-term stability > 15 months (Pierpaoli et al, 2009)

2) PEG (polyethylene glycol) with T1/T2 modifier

- PEG은 농도조절을 통해 diffusivity를 조절가능함

- T1/T2 modifier로 gadobutrol이 사용가능 (Gatidis et al, 2014).

뇌졸중 영상 적합 팬텀

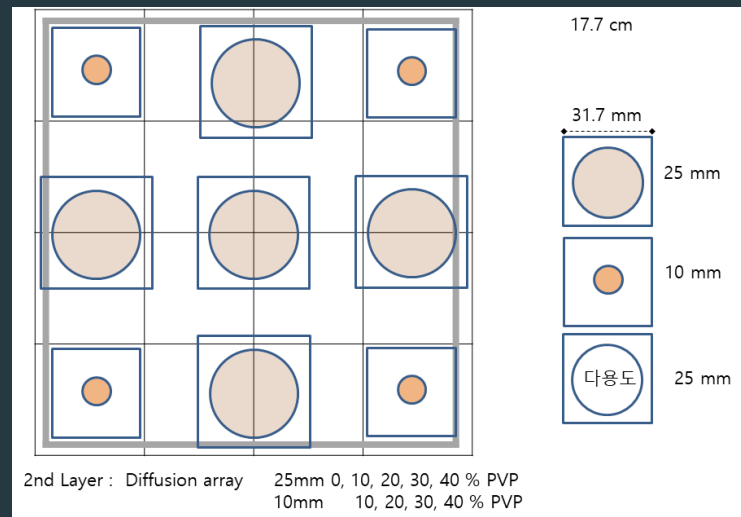
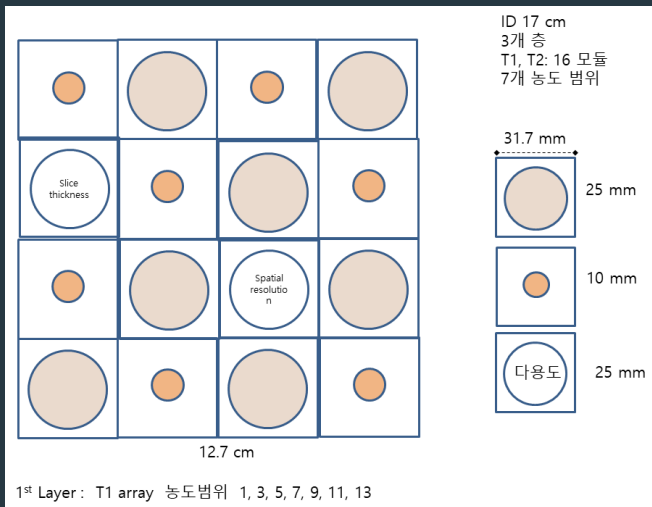
- ▶ 뇌졸중 표준화 팬텀을 위한 영상바이오마커 선정: DWI, GRE (T2*), T1
- ▶ K-Stroke-Block (KSB) 팬텀과 QIBA 및 NIST/ISMRM system 팬텀과의 차별점

1. Spatial resolution 측정 가능

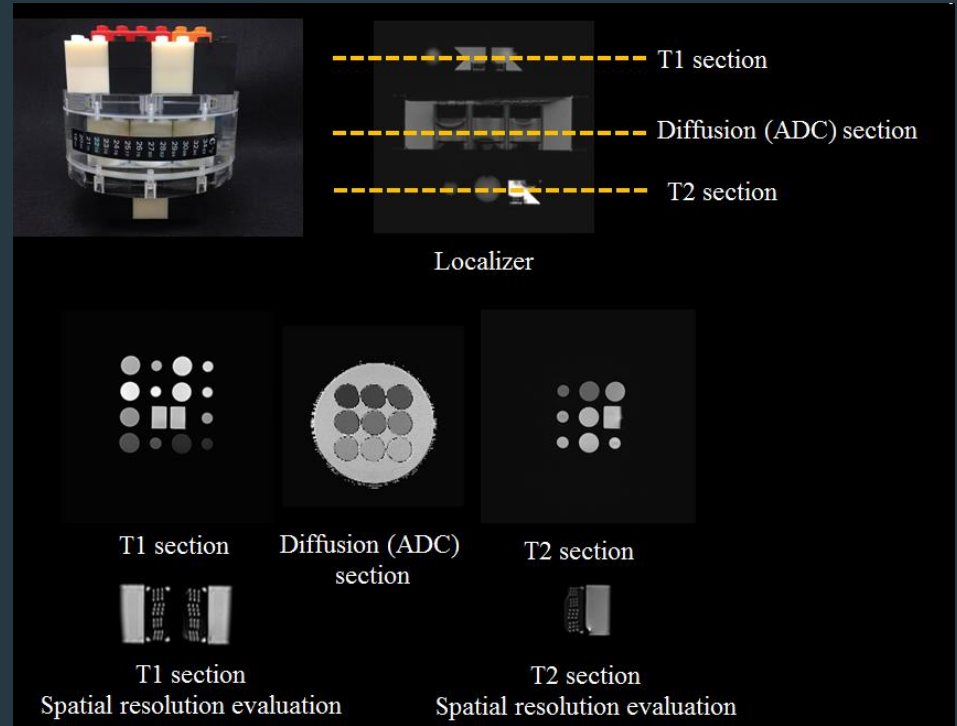
2. Cost-effective 팬텀

3. GRE 동시 측정 가능 팬텀

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



뇌졸중 영상 적합 팬텀



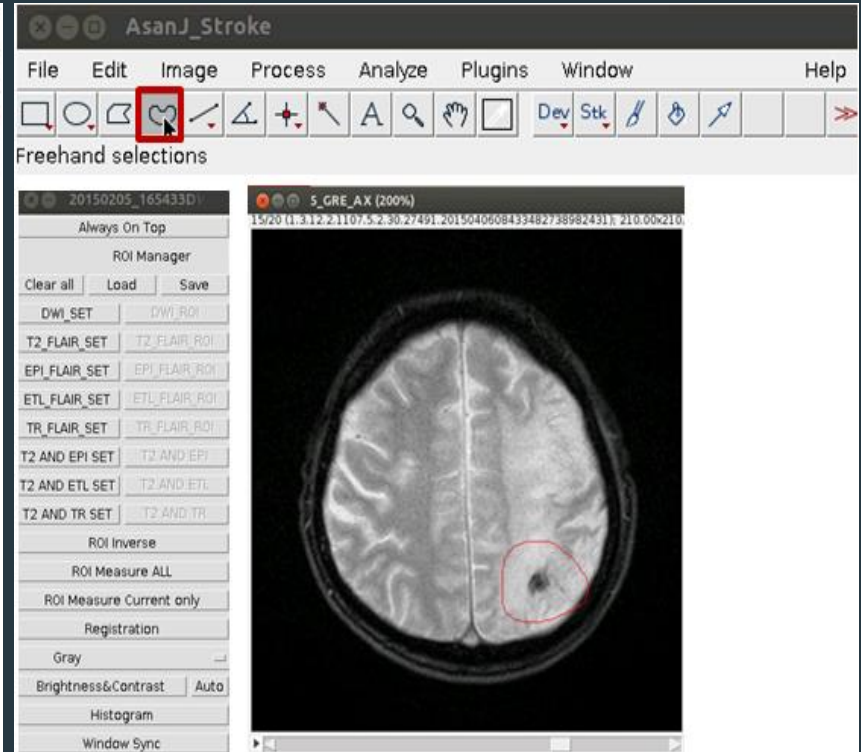
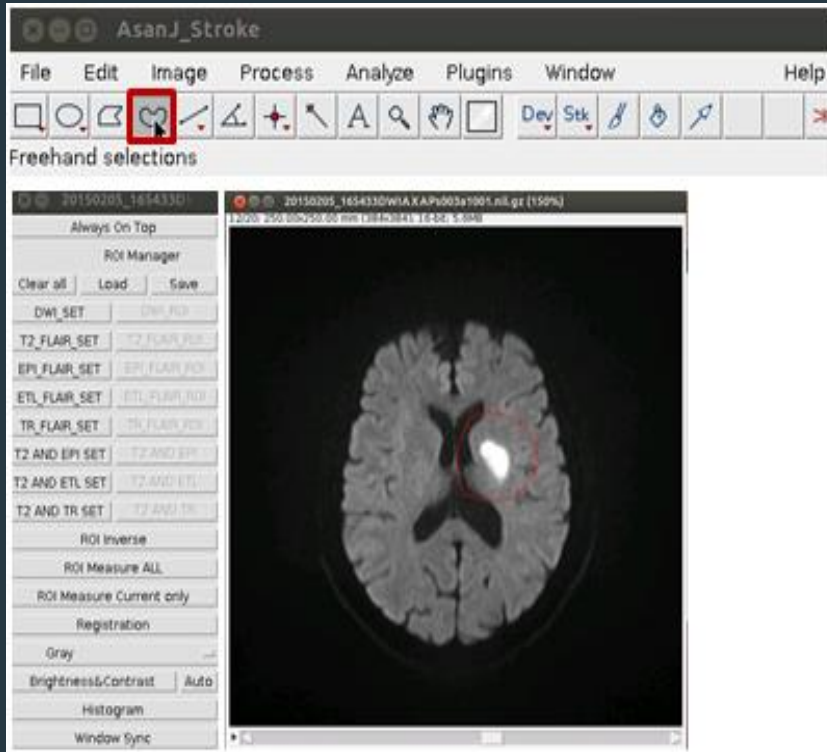
NIST (National Institute of Standards and Technology) 공인 물질
가격 경쟁력 (미국 제품의 반값)
조립이 용이하고 맞춤형 디자인 가능

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



Datasharing.aim-aicro.com/strokevolumetry

분석 소프트웨어

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ASANJ_Stroke.exe

현재 보기

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Guidelines? Recommendation?

급성 뇌졸중 임상시험 영상의 글로벌 동향 조사 보고서

2018. 10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

국문표기: 본 보고서는 정부(식품의약품안전처, 18182임상평402)의 용역연구개발사업의 지원을 받아 수행된 연구임.

영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).

목차

1. 뇌경색 약물 유효성 평가를 위한 글로벌 다기관 연구 고찰 3
2. 2018년 미국 뇌졸중 협회 뇌영상 가이드라인 8
3. 뇌영상 가이드라인상의 영상바이오마커 10
4. 뇌졸중 치료 약물 유효성 평가 11
5. 뇌종양 임상시험의 바이오이미징 기술 권고안 14
6. 참고문헌 17

Guidelines? Recommendation?

첨부 3

급성 뇌졸중 영상촬영 프로토콜 표준화 및 팬텀 품질평가를 위한 기준안 (1차년도용)

2018.10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

목차

| | |
|--------------------------------|----|
| 1. 급성 뇌졸중 임상시험에서 영상검사 | 3 |
| 가. 활용되는 주요 영상의 종류 | 3 |
| 나. 영상의 역할 | 4 |
| 다. 영상 지표 | 5 |
| 2. 다기관 임상시험에서 영상촬영 표준화 | 11 |
| 가. 임상시험특화 표준화 | 11 |
| 나. 영상표준화를 위한 국제적 노력 | 11 |
| 다. 급성 뇌졸중 임상시험의 영상표준화 | 12 |
| 라. 비조영증강 CT 촬영프로토콜 | 12 |
| 마. 확산강조MRI 및 경사자장MRI 촬영프로토콜 | 13 |
| 바. CT 및 MR 혈관조영술 | 15 |
| 3. 팬텀을 이용한 영상표준화 및 품질평가 기준안 제시 | 16 |
| 가. 급성 뇌졸중 임상시험에서의 팬텀의 필요성 | 16 |
| 나. 기존 팬텀 | 16 |
| 다. 새로운 한국표준 팬텀 개발의 필요성 | 17 |
| 라. 한국형 뇌졸중 특이 MRI 팬텀 개발 | 18 |
| 마. 팬텀 시작품 사진 | 21 |
| 바. 팬텀을 이용한 영상표준화 및 품질평가 항목 | 21 |
| 사. 경사자장MRI 팬텀 평가 항목 | 22 |
| 4. 결론 | 23 |

Guidelines? Recommendation?

뇌졸중 영상 바이오마커 분석 프로그램

표준작업지침서

2018. 10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

국문표기: 본 보고서는 정부(식품의약품안전처, 18182임상평402)의 용역연구개발사업의 지원을 받아 수행된 연구임.

영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MEDS402).

목차

| | |
|---|---|
| I. 뇌경색의 정량적 평가를 위한 확산강조 MRI 영상분석 방법 | |
| 1. 목적 (Purpose) | 3 |
| 2. 범위 (Scope) | 3 |
| 3. 절차 (Procedures) | 3 |
| II. 뇌출혈 및 혈종 변화의 정량적 평가를 경사자장 영상 분석 방법 | |
| 1. 목적 (Purpose) | 8 |
| 2. 범위 (Scope) | 8 |
| 3. 절차 (Procedures) | 8 |

Guidelines? Recommendation?

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 301-827-1800 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 Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

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

Guidelines? Recommendation?

TABLE OF CONTENTS

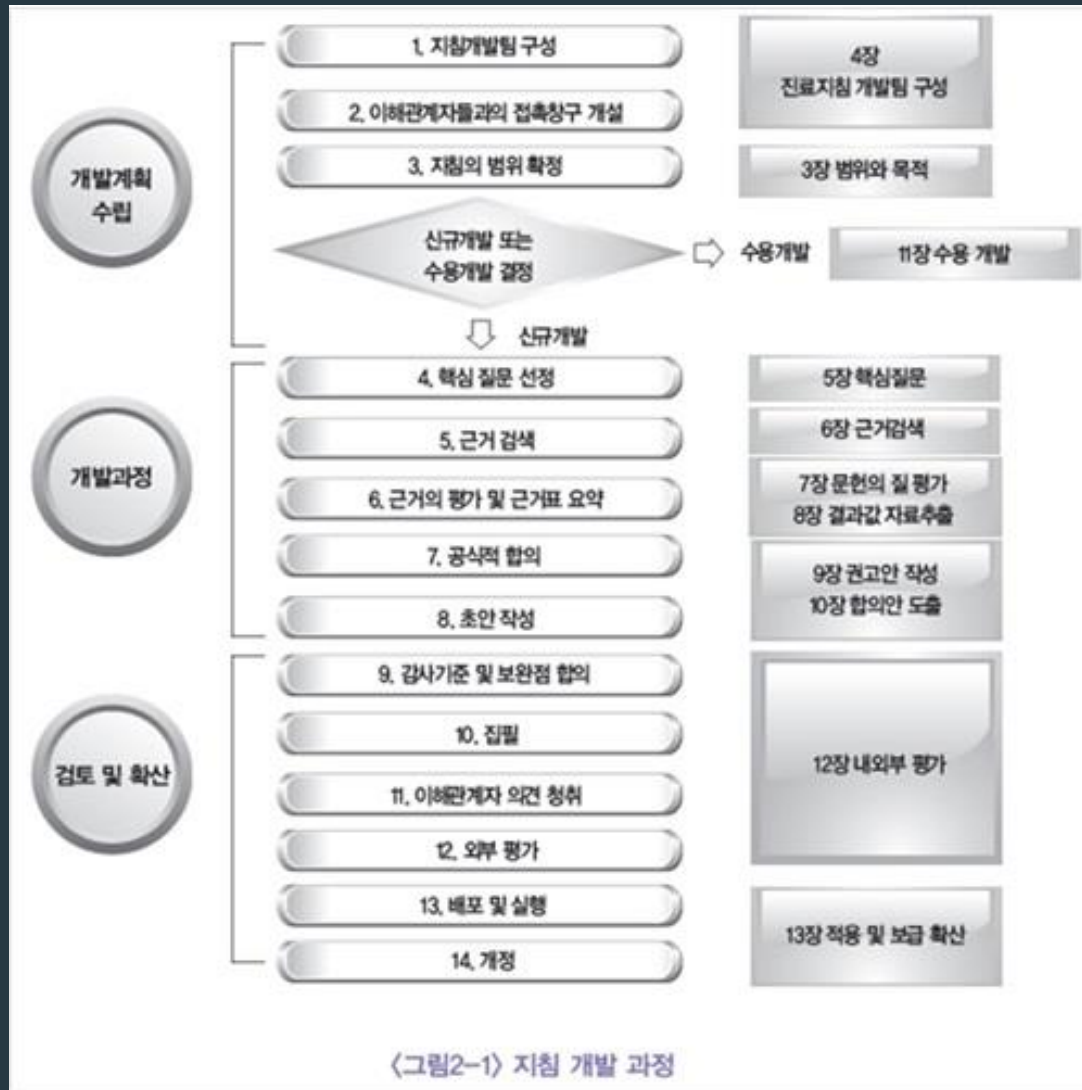
| | | |
|-------------|---|-----------|
| I. | INTRODUCTION..... | 1 |
| II. | BACKGROUND | 2 |
| III. | INITIAL CONSIDERATIONS | 4 |
| A. | Why Use Imaging in a Confirmatory Trial? | 4 |
| B. | Are Imaging Standards Important?..... | 4 |
| C. | Is Centralized Image Interpretation Important?..... | 4 |
| D. | Should Image Interpretation Be Blinded to Clinical Data?..... | 5 |
| E. | How Often Should Imaging Evaluations Be Performed?..... | 5 |
| F. | How Quickly Should Images Be Interpreted?..... | 6 |
| G. | What Procedures Should Be Standardized if Imaging Is an Important Aspect of a Clinical Trial Endpoint?..... | 6 |
| IV. | BEFORE IMAGING: DEVELOPING A CHARTER..... | 6 |
| A. | An Executive Summary of the Trial Design and the Role of Imaging in the Trial..... | 7 |
| B. | Image Acquisition Standards..... | 7 |
| | <i>1. Equipment Standardization and Operation</i> | <i>8</i> |
| | a. Vendor-specific equipment/platforms (e.g., injectors, scanners, software)..... | 8 |
| | b. Equipment technical settings to be used at each site | 9 |
| | c. The role of site imaging technicians in equipment operation, including identification of faulty or unacceptable images and the need to repeat imaging..... | 9 |
| | d. Phantoms to be used for site qualification and image quality monitoring..... | 9 |
| | e. Patient preparation, positioning, and comfort measures | 9 |
| | f. The date and time for imaging and alternatives | 10 |
| | g. Handling of off-protocol images | 10 |
| | h. Imaging risks | 10 |
| | i. Site qualification process..... | 10 |
| | j. Acquisition quality control monitoring process | 11 |
| | k. Data storage, transfer, and site display | 11 |
| | <i>2. Imaging Drug Standardization</i> | <i>11</i> |
| | a. Preparative drugs | 12 |
| | b. Contrast agents | 12 |
| | c. Radionuclide agents..... | 12 |
| C. | Clinical Trial Standards for Image Interpretation..... | 12 |
| | <i>1. Image Transfer, Receipt Documentation, and Initial Quality Assessment</i> | <i>13</i> |
| | <i>2. Image Display and Interpretation.....</i> | <i>13</i> |
| | a. Selection of images for interpretation, display sequence, and randomization..... | 14 |
| | b. Number of readers and their background qualifications..... | 14 |
| | c. Reader training and qualification..... | 15 |
| | d. Timing of image reads and the read process | 16 |
| | e. Imaging case report forms | 18 |
| | f. Imaging data lock process..... | 18 |
| | g. Quality control of the image display and interpretation process | 18 |

Guidelines? Recommendation?

TABLE OF CONTENTS

| | | |
|-------------|---|-----------|
| I. | INTRODUCTION..... | 1 |
| II. | BACKGROUND | 2 |
| III. | LOGISTICAL AND TECHNICAL CONSIDERATIONS..... | 3 |
| | A. Choice of Imaging Modality..... | 3 |
| | B. Is Centralized Image Interpretation Important for an Imaging-Based Primary Endpoint? .3 | |
| | C. Should Image Interpretation Be Blinded to Clinical Data? | 4 |
| | D. How Often Should Imaging Evaluations Be Performed?..... | 5 |
| | E. How Soon After Acquisition Should Images Be Interpreted? | 5 |
| | F. What Procedures Should Be Standardized for an Imaging-Based Clinical Trial Primary Endpoint? | 5 |
| IV. | THE EXTENT OF IMAGING PROCESS STANDARDS | 7 |
| | A. Are Existing Medical Practice Imaging Process Standards Sufficient for the Trial's Primary Endpoint? | 7 |
| | B. What Should Be Considered When Augmenting Existing Medical Practice Imaging Process Standards to Create Trial-Specific Imaging Process Standards? | 7 |
| | REFERENCES..... | 9 |
| | APPENDIX A: BEFORE IMAGING: CHARTER CONSIDERATIONS | 10 |
| | APPENDIX B: DURING IMAGING: MONITORING PLANS AND CHARTER MODIFICATIONS..... | 27 |
| | APPENDIX C: AFTER IMAGING: DATA TRANSFER, ARCHIVING, AND ANALYSIS OF IMAGING INFORMATION | 28 |

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Guidelines? Recommendation?

- 근거 (문헌) 검색 및 문헌의 질 평가
- 핵심 질문 선정
- Delphi 합의 도출
- 대한신경두경부영상의학회
- 대한신경중재치료의학회
- mfds.stroke.imaging@gmail.com

Guidelines? Recommendation?

- Infarct core를 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

Imaging protocols in acute ischemic stroke ?

- 전국 30개 병원
- Survey for Imaging protocols in acute ischemic stroke
- Review article

- 대한신경두경부영상의학회
- 대한신경중재치료의학회
- mfds.stroke.imaging@gmail.com

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.² 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

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

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

Standardization

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

- 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

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

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

Standardization

- National-wide Standardization: QIBA
- Trial-specific standardization: Study-specific with reference to QIBA

Standardization

➤ 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

The screenshot shows the RSNA website with the following content:

- Header:** RSNA logo, navigation links (Membership, Annual Meeting, Journals, Education, Research, Practice Tools), and utility links (Search, About, Donate, Login).
- Left Sidebar:** Research section with links for Funding opportunities, Research development guides, Imaging research tools, Research awards, and Quantitative Imaging Biomarkers Alliance (with sub-links for Metrology papers, Process, Profiles and protocols, QIBA Conformance Certificate Services, QIBA meetings, and Quantitative Imaging Data Warehouse (QIDW)).
- Main Content:**
 - Section Header:** Quantitative Imaging Data Warehouse (QIDW)
 - Text:** RSNA supports the Quantitative Imaging Data Warehouse (QIDW) to promote the development and adoption of quantitative imaging by the imaging research and clinical radiology communities.
 - Text:** The open image archive meets the operational needs for basic research into quantitative imaging as well as secondary analysis of archived images metadata. The project is a joint effort between RSNA's Quantitative Imaging Biomarkers Alliance Informatics Committee (RIC).
 - Text:** Funding for the project is provided in part by the National Institute of Biomedical Imaging and Bio Health, Department of Health and Human Services.
 - Text:** Archived data includes images from QIBA-created (phantoms), digital/synthetic reference objects (with associated metadata). This data is available to assist scanners, display stations, and imaging protocol performance evaluation of image analysis software.
 - Text:** The QIDW allows for bulk loading of files, storage related non-image data, such as covariates, clinical descriptions. It also provides for data mining of associated metadata.
 - Section Header:** Data inventory
 - Text:** View archived data include images from QIBA-created objects, digital reference objects and clinical images.
 - List-Group:**
 - COPD/Asthma Phantom
 - PET/CT Digital Reference Object
 - fMRI Digital Reference Object
 - US-SWS-Digital-Phantoms
 - DWI Phantom
 - QIBA DCE-MRI DRO
 - QIBA DCE-MRI WG
 - Text:** Explore the [QIDW data inventory](#).
 - Section Header:** Tools
 - Text:** Use our DSC MRI image simulation to create digital simulations of DSC perfusion acquisitions.
 - Text:** The user may select 1 of 3 models, and select values for the many different acquisition parameters and assumptions about the imaged tissue. The website will then create a 4D

The screenshot shows the QIDW website with the following content:

- Header:** QIDW logo, search bar (Quick search...), and utility links (Register or Log In).
- Section Header:** MR Modality Datasets
- Table:** A table listing MR Modality Datasets with columns for dataset name and access status (Public).
- Footer:** About, Contact, Web API, Report a bug, Privacy Notice, and © Kitware, Inc.

| MR Modality Datasets | Access |
|---|--------|
| Arterial Spin Labeling (ASL) MRI | Public |
| Diffusion Weighted MR Imaging (DWI) | Public |
| Dynamic Contrast Enhanced (DCE) MRI | Public |
| Dynamic Susceptibility Contrast (DSC) MRI | Public |
| Functional MRI (fMRI) | Public |
| MR Elastography (MRE) | Public |
| Musculoskeletal (MSK) MRI | Public |
| Proton Density Fat Fraction (PDFF) MRI | Public |

Standardization

REVIEW ARTICLE

Quantitative Imaging Biomarkers Alliance (QIBA) Recommendations for Improved Precision of DWI and DCE-MRI Derived Biomarkers in Multicenter Oncology Trials

Amita Shukla-Dave, PhD,^{1,2*} Nancy A. Obuchowski, PhD,³ Thomas L. Chenevert, PhD,⁴
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Harrison Kim, PhD, MBA,⁹ Catherine Coolens, PhD,¹⁰ Hendrik Laue, PhD,¹¹
Caroline Chung, MD,¹² Mark Rosen, MD, PhD,¹³ Michael Boss, PhD,¹⁴ and
Edward F. Jackson, PhD¹⁵

Physiological properties of tumors can be measured both in vivo and noninvasively by diffusion-weighted imaging and dynamic contrast-enhanced magnetic resonance imaging. Although these techniques have been used for more than two decades to study tumor diffusion, perfusion, and/or permeability, the methods and studies on how to reduce measurement error and bias in the derived imaging metrics is still lacking in the literature. This is of paramount importance because the objective is to translate these quantitative imaging biomarkers (QIBs) into clinical trials, and ultimately in clinical practice. Standardization of the image acquisition using appropriate phantoms is the first step from a technical performance standpoint. The next step is to assess whether the imaging metrics have clinical value and meet the requirements for being a QIB as defined by the Radiological Society of North America's Quantitative Imaging Biomarkers Alliance (QIBA). The goal and mission of QIBA and the National Cancer Institute Quantitative Imaging Network (QIN) initiatives are to provide technical performance standards (QIBA profiles) and QIN tools for producing reliable QIBs for use in the clinical imaging community. Some of QIBA's development of quantitative diffusion-weighted imaging and dynamic contrast-enhanced QIB profiles has been hampered by the lack of literature for repeatability and reproducibility of the derived QIBs. The available research on this topic is scant and is not in sync with improvements or upgrades in MRI technology over the years. This review focuses on the need for QIBs in oncology applications and emphasizes the importance of the assessment of their reproducibility and repeatability.

Level of Evidence: 5

Technical Efficacy Stage: 1

Standardization

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
doi:10.1093/neuonc/nov095
Advance Access date 6 August 2015

Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Benjamin M. Ellingson, Martin Bendszus, Jerrold Boxerman, Daniel Barboriak, Bradley J. Erickson, Marion Smits, Sarah J. Nelson, Elizabeth Gerstner, Brian Alexander, Gregory Goldmacher, Wolfgang Wick, Michael Vogelbaum, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Whitney B. Pope, Dewen Yang, Caroline Chung, Michael V. Knopp, Soonme Cha, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

A recent joint meeting was held on January 30, 2014, with the US Food and Drug Administration (FDA), National Cancer Institute (NCI), clinical scientists, imaging experts, pharmaceutical and biotech companies, clinical trials cooperative groups, and patient advocate groups to discuss imaging endpoints for clinical trials in glioblastoma. This workshop developed a set of priorities and action items including the creation of a standardized MRI protocol for multicenter studies. The current document outlines consensus recommendations for a standardized Brain Tumor Imaging Protocol (BTIP), along with the scientific and practical justifications for these recommendations, resulting from a series of discussions between various experts involved in aspects of neuro-oncology neuroimaging for clinical trials. The minimum recommended sequences include: (i) parameter-matched precontrast and postcontrast inversion recovery-prepared, isotropic 3D T1-weighted gradient-recalled echo; (ii) axial 2D T2-weighted turbo spin-echo acquired after contrast injection and before postcontrast 3D T1-weighted images to control timing of images after contrast administration; (iii) precontrast, axial 2D T2-weighted fluid-attenuated inversion recovery; and (iv) precontrast, axial 2D, 3-directional diffusion-weighted images. Recommended ranges of sequence parameters are provided for both 1.5 T and 3 T MR systems.

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See the editorial by Sul and Krainak, on pages 1179–1180.

Standardization

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
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Advance Access date 6 August 2015

Consensus recommendations for a standardized Brain Tumor Imaging

Table 1. Minimum standard 1.5 T & 3 T MRI protocol

| | 3D T1w Pre ^b | Ax 2D FLAIR ^l | Ax 2D DWI | Ax 2D T2w ^{h,i} | 3D T1w Post ^b |
|--|------------------------------------|-----------------------------|---|--------------------------------------|------------------------------------|
| Sequence | IR-GRE ^{e,f} | TSE ^c | SS-EPI ^g | TSE ^c | IR-GRE ^{e,f} |
| Plane | Sagittal/axial | Axial | Axial | Axial | Sagittal/axial |
| Mode | 3D | 2D | 2D | 2D | 3D |
| TR [ms] | 2100 ^m | >6000 | >5000 | >2500 | 2100 ^m |
| TE [ms] | Min | 100–140 | Min | 80–120 | Min |
| TI [ms] | 1100 ⁿ | 2000–2500 ^k | | | 1100 ⁿ |
| Flip angle | 10°–15° | 90°/≥160° | 90°/180° | 90°/≥160° | 10°–15° |
| Frequency | ≥172 | ≥256 | ≥128 | ≥256 | ≥172 |
| Phase | ≥172 | ≥256 | ≥128 | ≥256 | ≥172 |
| NEX | ≥1 | ≥1 | ≥1 | ≥1 | ≥1 |
| FOV | 256 mm | 240 mm | 240 mm | 240 mm | 256 mm |
| Slice thickness | ≤1.5 mm | ≤4 mm ^l | ≤4 mm ^l | ≤4 mm ^l | ≤1.5 mm |
| Gap/spacing | 0 | 0 | 0 | 0 | 0 |
| Diffusion options ^p | | | $b = 0, 500, 1000 \text{ s/mm}^2 \geq 3 \text{ directions}$ | | |
| Parallel imaging | Up to 2x | Up to 2x | Up to 2x | Up to 2x | Up to 2x |
| Scan time (approx) [benchmarked on 3 T Skyra] | 5–10 min [5:49 for 1 mm isotropic] | 4–8 min [3:22 for 2D FLAIR] | 2–4 min [1:22 for 3 direction DWI and 3 b-values] | 4–8 min [5:10 for 2D T2w equal echo] | 5–10 min [5:49 for 1 mm isotropic] |

National Cancer Institute (NCI), Bethesda, Maryland (M.K.G.); Adult Brain Tumor Consortium (ABTC) (B.M.E., E.G., P.Y.W.); IVY Consortium for Early Phase Clinical Trials (B.M.E., S.J.N.); American College of Radiology Imaging Network (ACRIN) (B.M.E., J.B., D.B.); European Organisation for Research and Treatment of Cancer (EORTC) (M.B., M.S., W.W., M.J.v.d.B.); Alliance for Clinical Trials in Oncology (B.J.E., E.G.); RSNA Quantitative Imaging Biomarker Alliance (QIBA) (B.M.E., D.B., G.G., B.J.E., M.V.K.); American Society of Neuroradiology (ASNR) (B.M.E., J.B., D.B., B.J.E., W.B.P.); American Society of Functional Neuroradiology (ASFNR) (J.B.); Radiation Therapy Oncology Group (RTOG) (M.V., M.R.G.)

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See the editorial by Sul and Krainak, on pages 1179–1180.

neuro-oncology/article-abstract/17/9/1188/1360348 by Univ of

Standardization

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
doi:10.1093/neuonc/nov095
Advance Access date 6 August 2015

Consensus recommendations for a standard

Table 1. Minimum standard 1.5 T & 3 T MRI protocols

| | 3D T1w Pre ^b |
|--|------------------------------|
| Sequence | IR-GRE ^{a,f} |
| Plane | Sagittal/axial |
| Mode | 3D |
| TR [ms] | 2100 ^m |
| TE [ms] | Min |
| TI [ms] | 1100 ⁿ |
| Flip angle | 10°–15° |
| Frequency | ≥172 |
| Phase | ≥172 |
| NEX | ≥1 |
| FOV | 256 mm |
| Slice thickness | ≤1.5 mm |
| Gap/spacing | 0 |
| Diffusion options ^p | |
| Parallel imaging | Up to 2x |
| Scan time (approx) [benchmarked on 3 T Skyra] | 5–10 min [5:49 isotropic] |

^aNational Cancer Institute (NCI), Bethesda, Maryland (M.K.G.); Adult Consortium for Early Phase Clinical Trials (B.M.E., S.J.N.); American European Organisation for Research and Treatment of Cancer (EO) Oncology (B.J.E., E.G.); RSNA Quantitative Imaging Biomarker Alliance Neuroimaging (ASNR) (B.M.E., J.B., D.B., B.J.E., W.B.P.); American Society Therapy Oncology Group (RTOG) (M.V., M.R.G.)

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See the editorial by Sul and Krainak, on pages 1179–1180.

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Supported by Bayer Healthcare.

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Brain Gliomas: Multicenter Standardized Assessment of Dynamic Contrast-enhanced and Dynamic Susceptibility Contrast MR Images¹

Purpose: To evaluate the feasibility of a standardized protocol for acquisition and analysis of dynamic contrast material-enhanced (DCE) and dynamic susceptibility contrast (DSC) magnetic resonance (MR) imaging in a multicenter clinical setting and to verify its accuracy in predicting glioma grade according to the new World Health Organization 2016 classification.

Materials and Methods: The local research ethics committees of all centers approved the study, and informed consent was obtained from patients. One hundred patients with glioma were prospectively examined at 3.0 T in seven centers that performed the same preoperative MR imaging protocol, including DCE and DSC sequences. Two independent readers identified the perfusion hotspots on maps of volume transfer constant (K^{trans}), plasma (v_p) and extravascular-extracellular space (v_e) volumes, initial area under the concentration curve, and relative cerebral blood volume (rCBV). Differences in parameters between grades and molecular subtypes were assessed by using Kruskal-Wallis and Mann-Whitney *U* tests. Diagnostic accuracy was evaluated by using receiver operating characteristic curve analysis.

Results: The whole protocol was tolerated in all patients. Perfusion maps were successfully obtained in 94 patients. An excellent interreader reproducibility of DSC- and DCE-derived measures was found. Among DCE-derived parameters, v_p and v_e had the highest accuracy (are under the receiver operating characteristic curve [A_c] = 0.847 and 0.853) for glioma grading. DSC-derived rCBV had the highest accuracy (A_c = 0.894), but the difference was not statistically significant ($P > .05$). Among lower-grade gliomas, a moderate increase in both v_p and rCBV was evident in isocitrate dehydrogenase wild-type tumors, although this was not significant ($P > .05$).

Conclusion: A standardized multicenter acquisition and analysis protocol of DCE and DSC MR imaging is feasible and highly reproducible. Both techniques showed a comparable, high diagnostic accuracy for grading gliomas.

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Online supplemental material is available for this article.

| x 2D T2w ^{h,i} | 3D T1w Post ^b |
|-----------------------------|------------------------------------|
| SE ^c | IR-GRE ^{a,f} |
| axial | Sagittal/axial |
| D | 3D |
| 2500 | 2100 ^m |
| 0–120 | Min |
| 0°/≥160° | 1100 ⁿ |
| 256 | ≥172 |
| 256 | ≥172 |
| 1 | ≥1 |
| 40 mm | 256 mm |
| 4 mm ^l | ≤1.5 mm |
| | 0 |
| p to 2x | Up to 2x |
| –8 min [5:10 for dual echo] | 5–10 min [5:49 for 1 mm isotropic] |

Standardization in Acute Ischemic Stroke

- QIBA (Quantitative Imaging Biomarkers Alliance)
- Oncology imaging

- Urgent circumstance in acute ischemic stroke
- Balancing between standardization and critical pathway

Standardization in Acute Ischemic Stroke

- Stroke Imaging Research (STIR) group in Stroke Treatment Academy Industry Roundtable (STAIR)의 Acute Stroke Imaging Research Roadmap II & III (2013, 2016)
- 뇌졸중 임상시험에 있어서 영상 획득과 해석에 대한 Consensus 및 권고안 제시
- 뇌졸중 임상시험의 영상 조건: Speed, Standardization, Quality control, Reproducibility, Centralization

Standardization 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

Standardization in Acute Ischemic Stroke

Special Report

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.

Summary

- Clinical Trial Imaging → Imaging study in Acute ischemic stroke
- Main authors & Consultant
- Recommendation & Guidelines & Survey → KSNR & KSIN
- Standardization → Only Radiologist

Acknowledgement

➤ Asan Image Metrics

➤ Kyung Won Kim, M.D., PhD.

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Medical Center

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