Clinical trial imaging in Acute ischemic stroke and Standardization

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Overview

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

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	

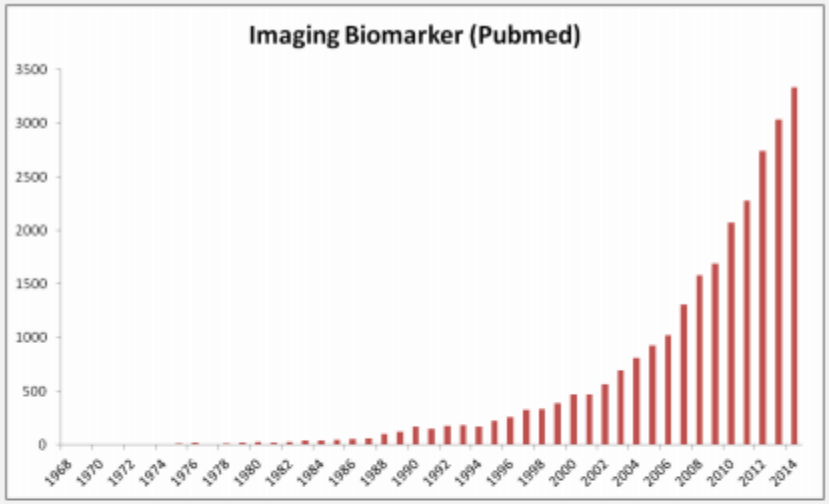
Biomarkers (Imaging, -Omics)

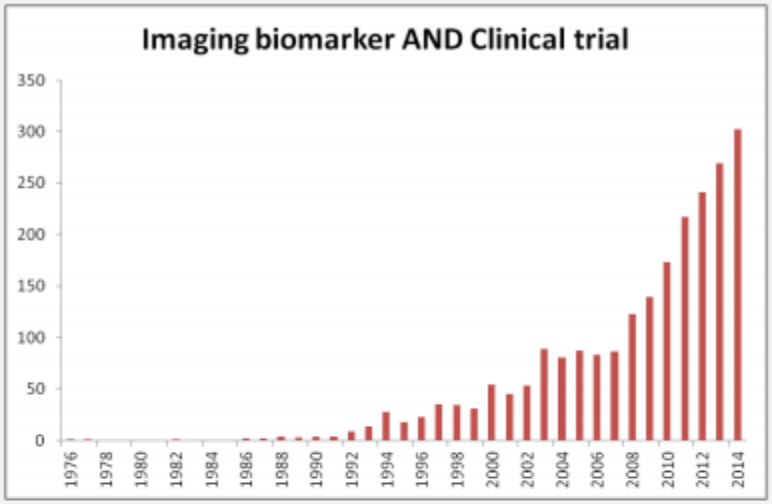
Advanced Clinical Trial

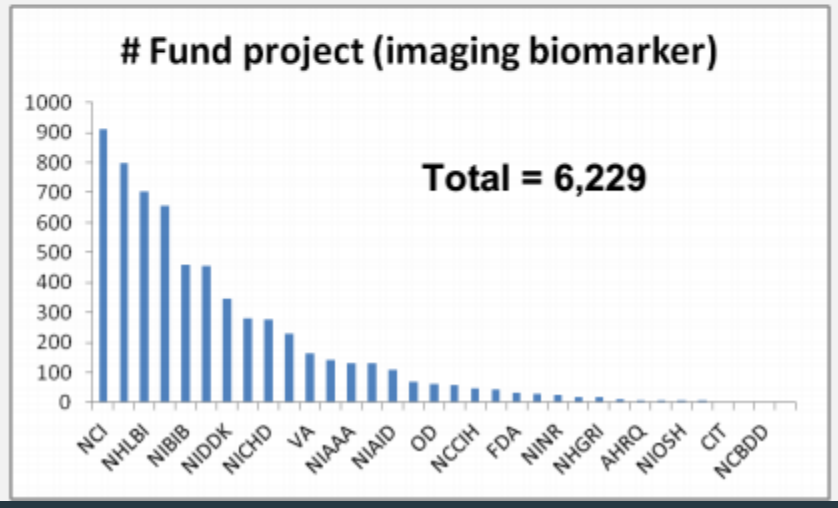
Animal Model | **Toxicology**

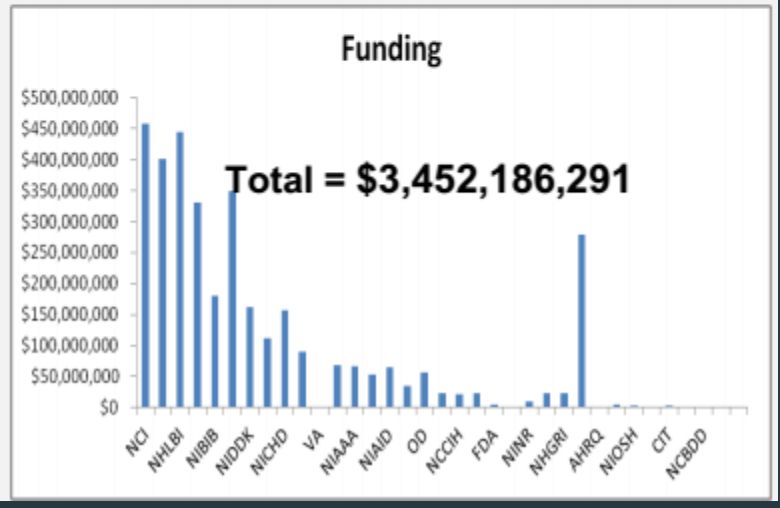
NICHE MARKET

Imaging biomarker









Imaging biomarker

역할

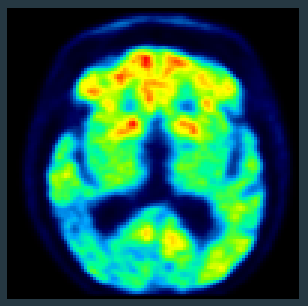
- Predictive biomarker
- 약력학/약동학 평가
- 약리 메커니즘
- 유효성/독성 평가

장점

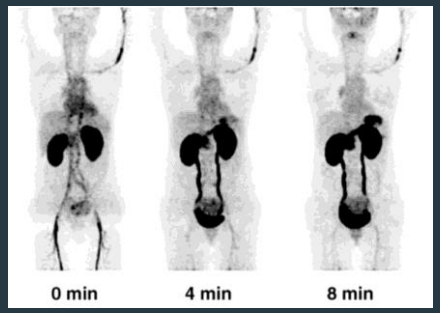
- 비침습적, 생체 내 현상
- 시간에 따라 반복적 관찰
- 개체수/피험자수 최소화
- 전임상–임상 연계

효과

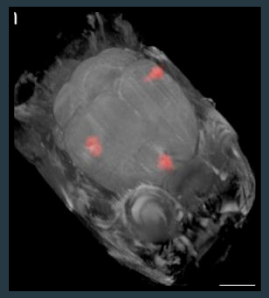
피험자수 ↓
시험기간 ↓
개발비용 ↓



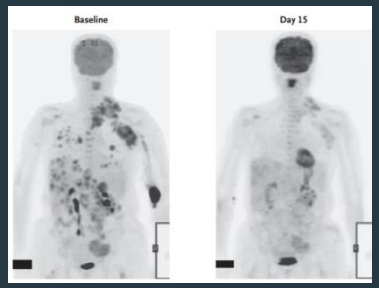
환자선별
:아밀로이드 PET으로
알츠하이머병 선별



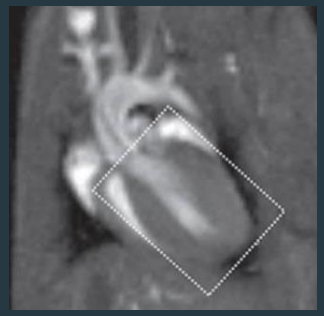
약물 약동학 평가
: Dynamic PET



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 CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 noncontrast CT는 Safety parameters로서 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 parameters로서 noncontrast CT를 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 outcome으로서 low-molecular-weight Heparin의 합병증 (예: 뇌경색 후 뇌출혈)을 밝히고자 하였으며 noncontrast CT를 이용하여 뇌경색 후 뇌출혈을 객관적으로 평가하고자 하였고 Independent image review system을 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 CT를 Safety parameters와 환자 배제 기준으로서 사용함. Independent image review system을 도입하여 noncontrast CT상 뇌경색과 뇌출혈을 평가하였음.

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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 CT**는 **Safety parameters**로서 사용됨. **Noncontrast CT가 환자 선정의 전면에 나온 연구이며** 뇌경색, 뇌출혈의 **검출 뿐 아니라 뇌경색의 부피를 정량적으로 분석**하였음.
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): Prevastatin의 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 **PWI**의 **정량적 감소**와 **MRA**의 **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.

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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 전송**하여 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**을 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 endpoint**로서 **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.

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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 MR을 사용**하였음. 환자 선정을 위해 **DWI과 PWI을 이용한 회생가능한 반음영의 정량적 분석을** 시행하였고 **Secondary outcome**을 위하여 **DWI과 noncontrast CT를 이용한 뇌경색 부피 분석**을 하였음. 치료에 의한 혈관의 재개통여부를 위해 MR 혹은 CT angiography를 이용하였으며 Safety outcome으로서 Noncontrast상의 뇌출혈 발생을 사용하였음. Imaging core lab과 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 outcome으로서 **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 lab과 Independent image review system을 통한 정성적·정량적 분석을 시행하였으며 정량적 영상 분석을 위해서 Commercial software를 사용하였음.

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Review

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

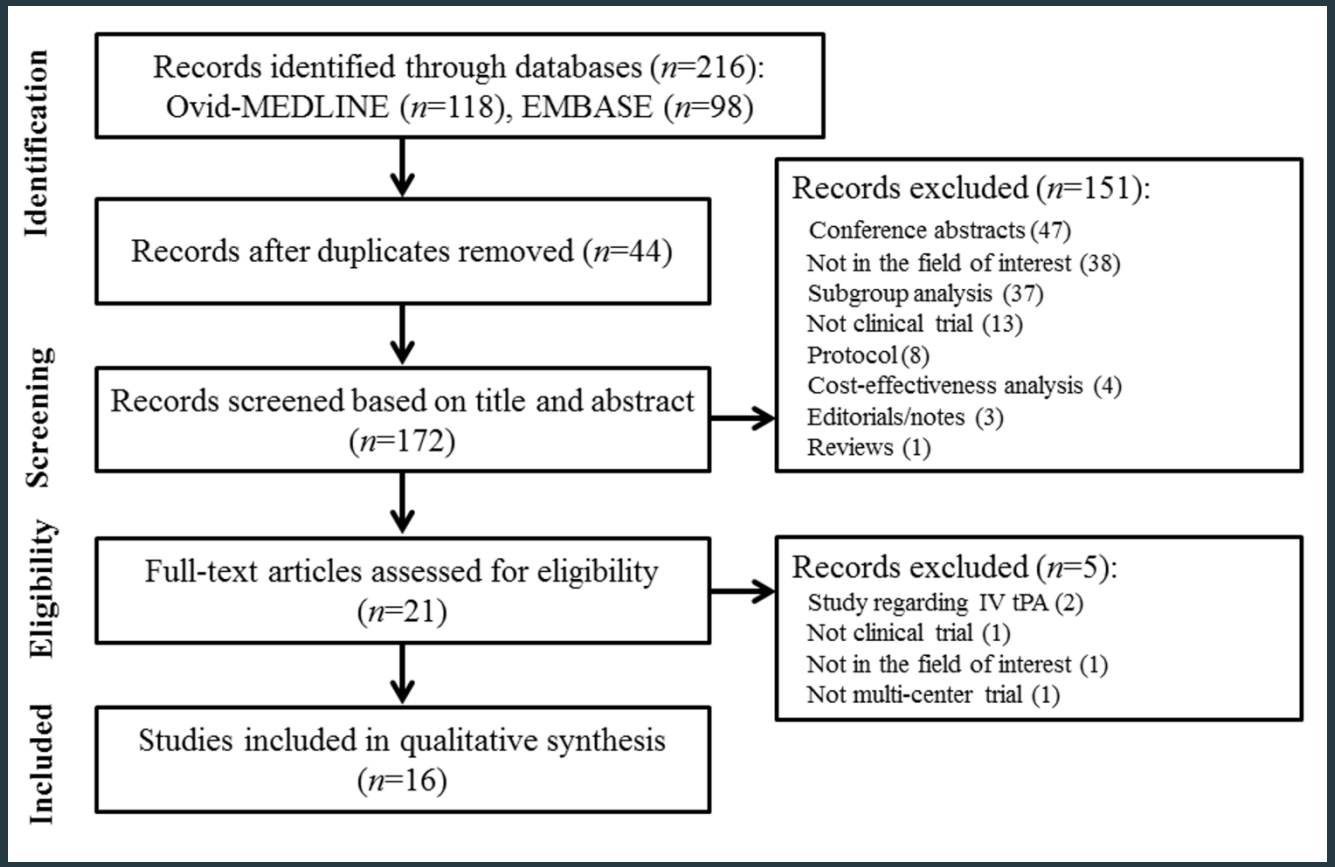
Introduction

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, noncontrast 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 efficacy[6-8] 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≤ 60 min after NECT and CT-to-recanalization time ≤ 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 ≥ 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)
Ciccone 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 ≥ 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) Preexsting 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, [b]2) > 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 [g]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 ≥ 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 (≥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-IA				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 (≥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.

Zaidat OO et al. Neurology 2012 and Stroke 2013

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			

Imaging CRO

Imaging support for multicenter clinical trials

- Imaging protocol / charter
- Global standards

Quantitative Imaging Biomarkers Alliance RSNA

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

- Site training
- Site monitoring

SAMSUNG 삼성의료원

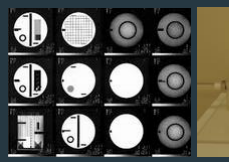
서울아산병원 Asan Medical Center

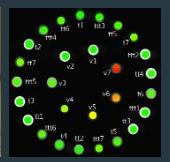
서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

- Imaging acquisition



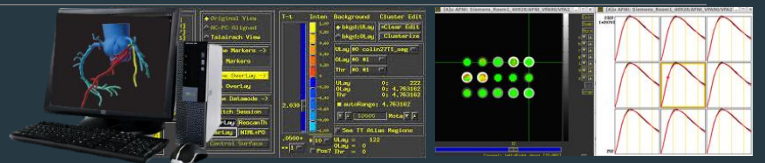
- QA/QC
- Data management





High Quality Imaging Service

- Post-processing
- Image analysis
- Central reading



Central Imaging Core Lab in clinical trials

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)

Experience

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. 비판독성 심방세동에 의한 급성 허혈성 뇌졸중 환자에서 조기 에독사반 투여의 효과 및 안전성 평가를 위한 무작위배정, 평행대조, 다기관 예비 임상시험 (Early adminstration 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

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 Quantiative
    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 Scale[8]

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

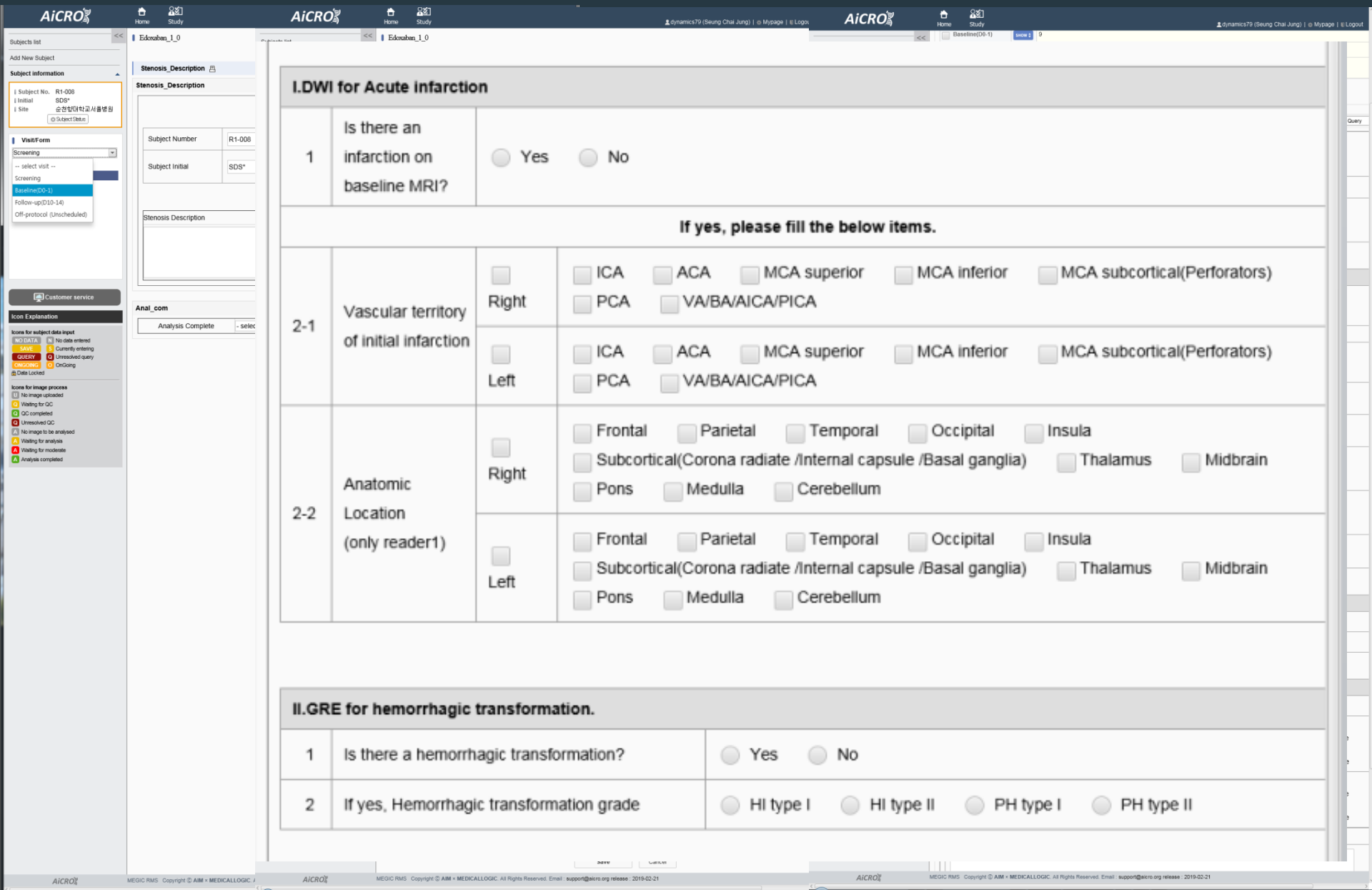
Table S4. Thrombolysis in Cerebral Infarction (TICI) Rating Scale[3]

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 Scale[7]

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

eCRF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Study
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Subjects list
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Subject information
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Initial SDS*
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Subject Status
Visit/Form
Screening
-- select visit --
Screening
Baseline(D0-1)
Follow-up(D10-14)
Off-protocol (Unscheduled)
Customer service
Icon Explanation
Stenosis_Description
Subject Number R1-008
Subject Initial SDS*
Stenosis Description
Anal_com
Analysis Complete
I.DWI for Acute infarction
1 Is there an infarction on baseline MRI? Yes No
If yes, please fill the below items.
2-1 Vascular territory of initial infarction
Right
ICA ACA MCA superior MCA inferior MCA subcortical(Perforators)
PCA VA/BA/AICA/PICA
Left
ICA ACA MCA superior MCA inferior MCA subcortical(Perforators)
PCA VA/BA/AICA/PICA
2-2 Anatomic Location (only reader1)
Right
Frontal Parietal Temporal Occipital Insula
Subcortical(Corona radiate /Internal capsule /Basal ganglia) Thalamus Midbrain
Pons Medulla Cerebellum
Left
Frontal Parietal Temporal Occipital Insula
Subcortical(Corona radiate /Internal capsule /Basal ganglia) Thalamus Midbrain
Pons Medulla Cerebellum
II.GRE for hemorrhagic transformation.
1 Is there a hemorrhagic transformation? Yes No
2 If yes, Hemorrhagic transformation grade HI type I HI type II PH type I PH type II

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)

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

Trial & Imaging

NCCN National Comprehensive Cancer Network®

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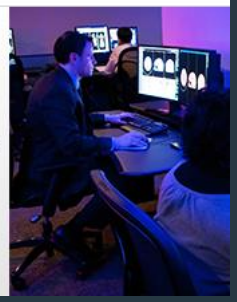
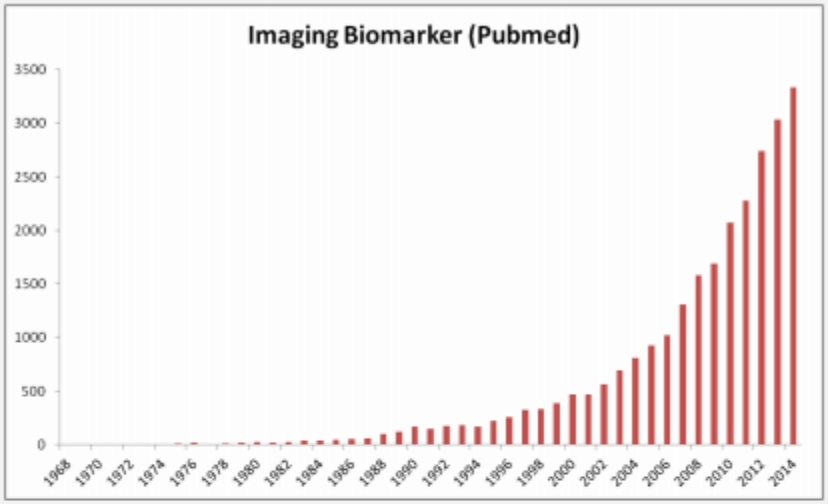


Trial Imaging은 종합학문
- Whole body
- Whole imaging process
- Business & development
- Regulation
- Science
- IT platform

임상시험 영상활용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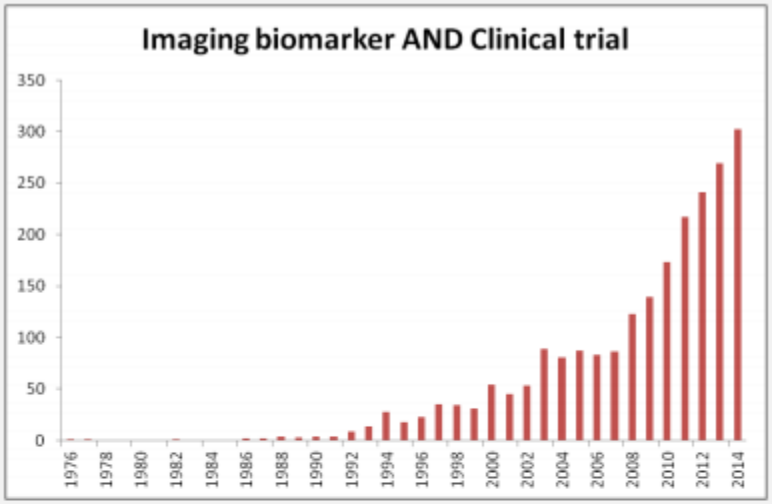
2500
2000
1500
1000
500
0
1968 1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014


Imaging biomarker AND Clinical trial
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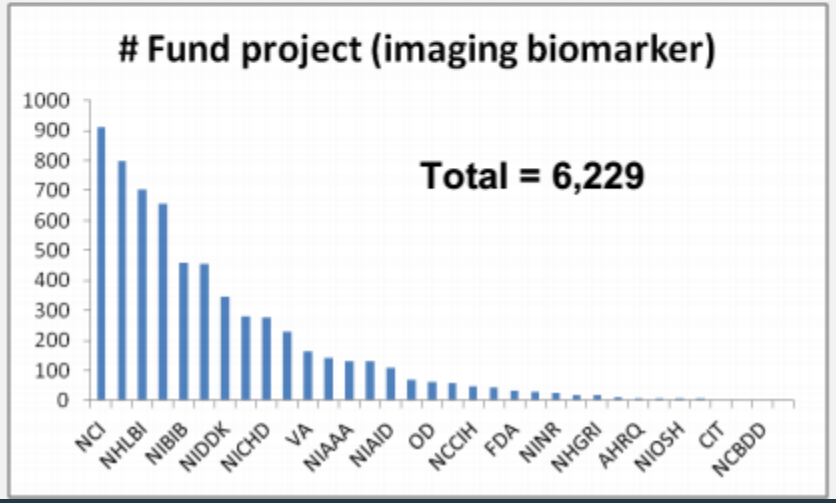
300
250
200
150
100
50
0
1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014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Total = 6,229
1000
900
800
700
600
500
400
300
200
100
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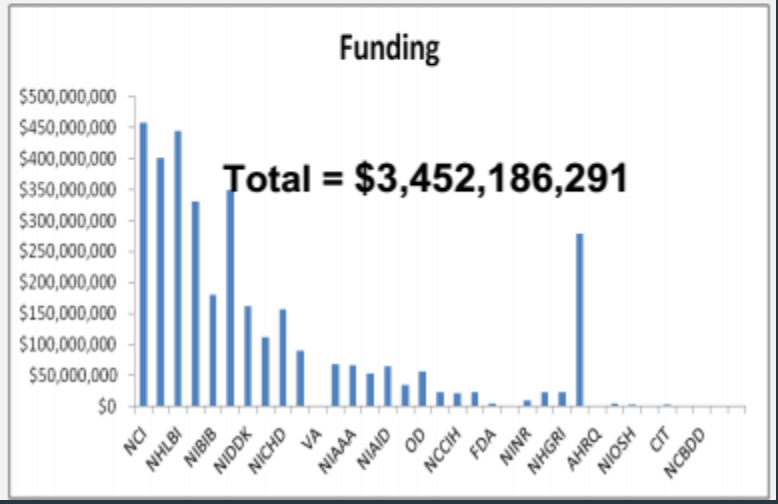
Funding
Total = $3,452,186,291
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$450,000,000
$400,000,000
$350,000,000
$300,000,000
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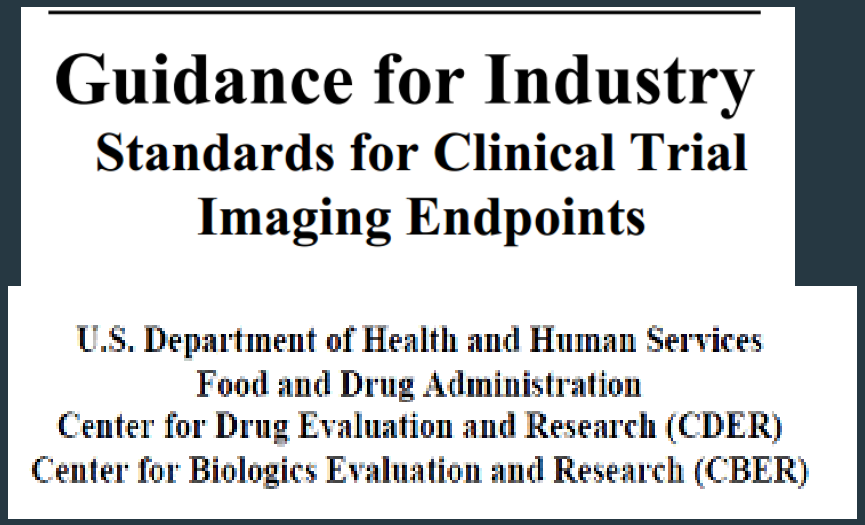
NCI NHLBI NIBIB NIDDK NICHD VA NIAAA NIAID OD NCCIH FDA NINR NHGRI AHRQ NIOSH CIT NCBDD

기준과 시스템 필요성

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



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 최소화는 것은 약효 평가를 위한 임상 시험의 신뢰성을 높이는 데 매우 중요한 요소이다.

기준과 시스템 필요성

국내 OO 제약회사

항암제 임상시험 완료

실태조사(Inspection)

식품의약품안전처

식약처 지적사항

- 영상 판독자의 적격성이 평가되었는가?
- 영상 판독이 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 활성도

- 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 지침와 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?

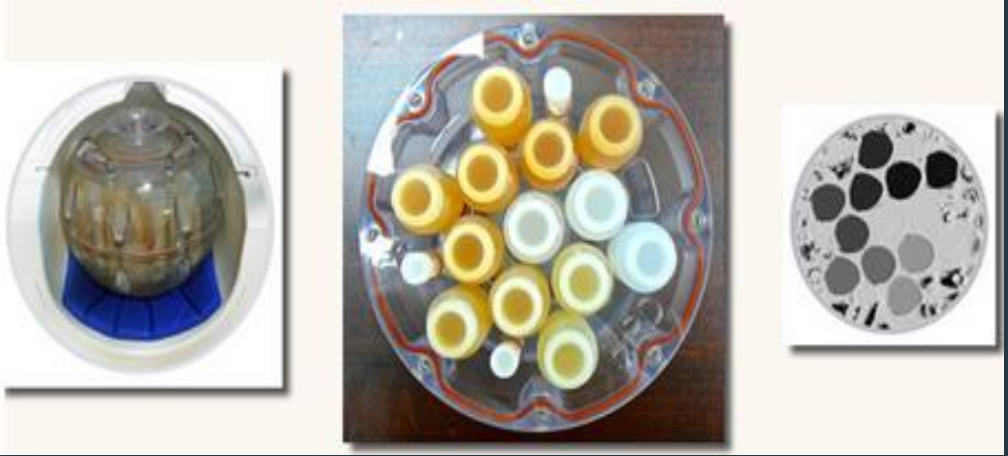
- 뇌졸중 치료 약물 임상시험에서의 영상 바이오마커의 기준안을 제시한다.

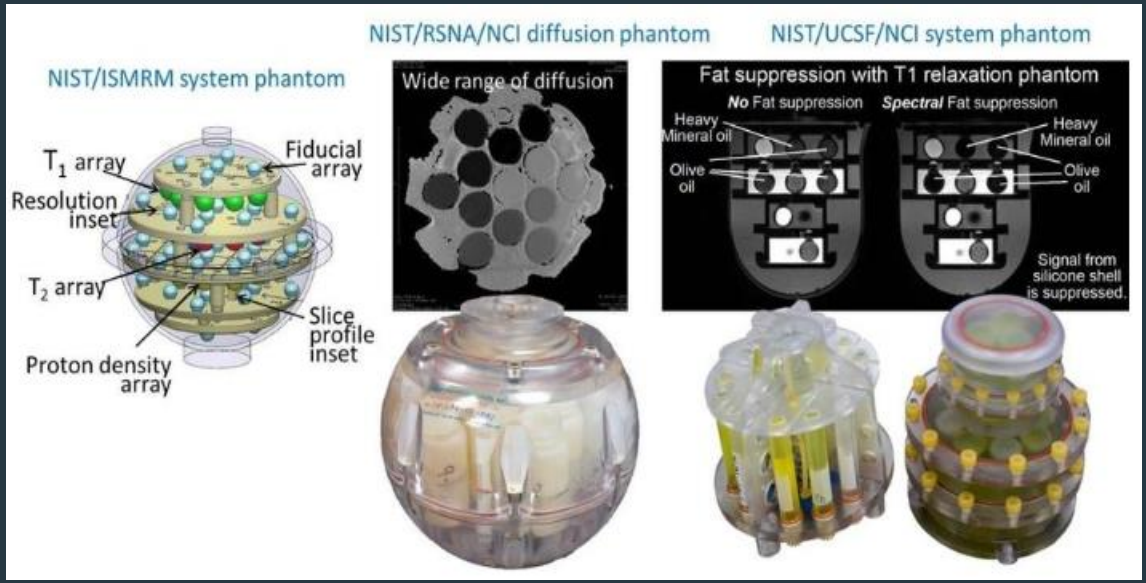
1. 뇌졸중 영상 바이오마커 표준화 팬텀
2. 뇌졸중 영상 바이오마커 분석 소프트웨어
3. 뇌졸중 영상 바이오마커의 촬영, 전송, 분석 등의 기준

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/RSNA/NCI diffusion phantom
NIST/UCSF/NCI system phantom
NIST/ISMRM system phantom
Wide range of diffusion
Fat suppression with T1 relaxation phantom
No Fat suppression
Spectral Fat suppression
Heavy Mineral oil
Olive oil
Signal from silicone shell is suppressed.
T1 array
Fiducial array
Resolution inset
T2 array
Slice profile inset
Proton density array

뇌졸중 영상 적합 팬텀

서울아산병원 Asan Medical Center

영상바이오마커 선정
내부 물질 협의
팬텀 디자인

KRISS 한국표준과학연구원

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 X 10^{-3} to 1.1 x 10^{-3} mm^2/s at 0°C
- Long-term stability > 15 months (Pierpaoli et al, 2009)

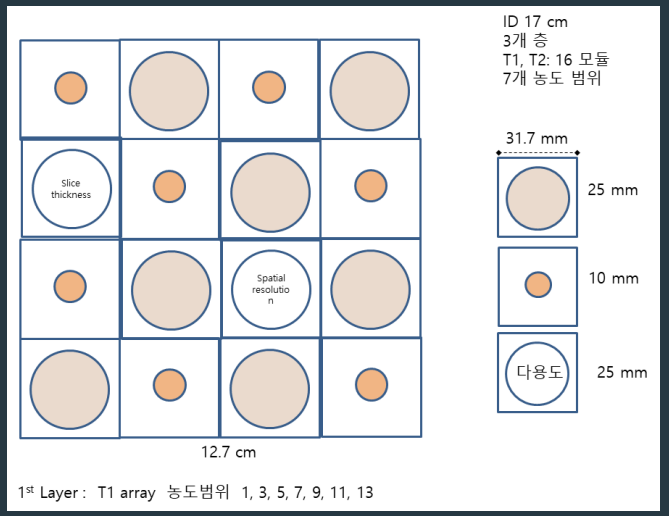
2) PEG (polyethylene glycol) with T1/T2 modifier

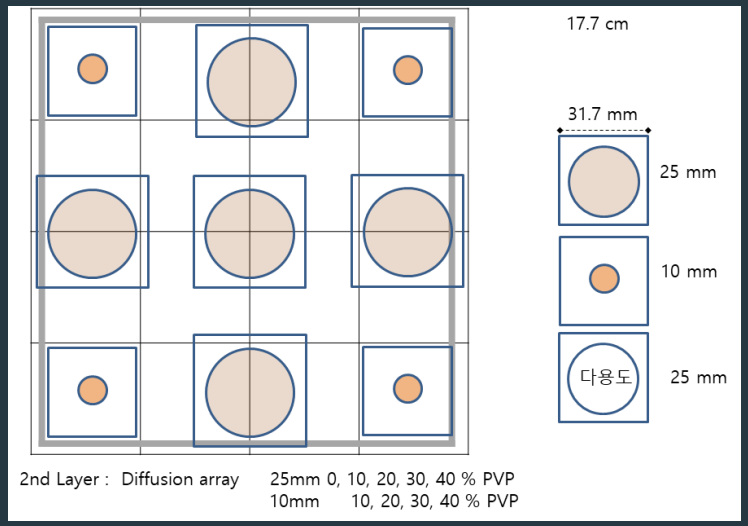
- PEG은 농도조절을 통해 diffusivity를 조절가능함
- T1/T2 modifier로 gadobutrol이 사용가능 (Gatidis et al, 2014).

뇌졸중 영상 적합 팬텀

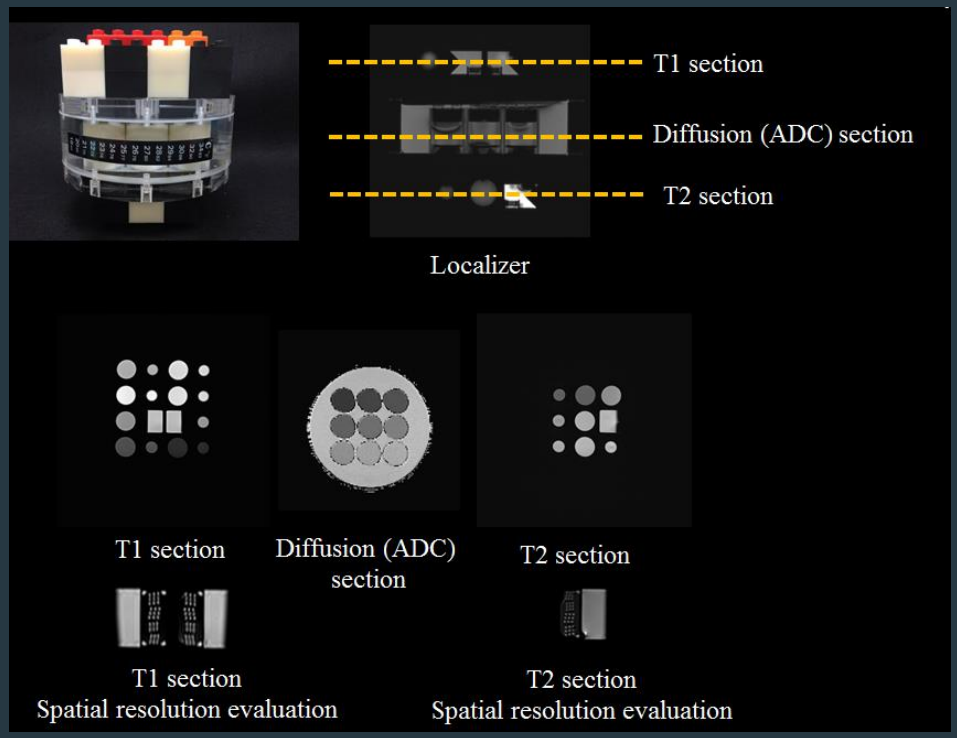
- 뇌졸중 표준화 팬텀을 위한 영상바이오마커 선정: DWI, GRE (T2*), T1
- K-Stroke-Block (KSB) 팬텀과 QIBA 및 NIST/ISMRM system 팬텀과의 차별점

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

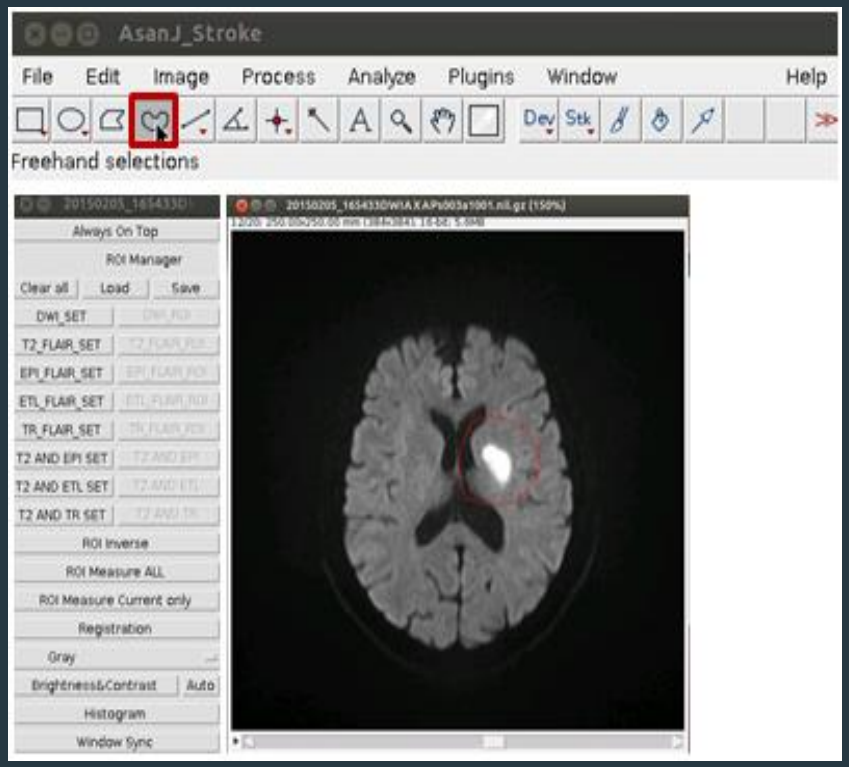
가격 경쟁력 (미국 제품의 반값)

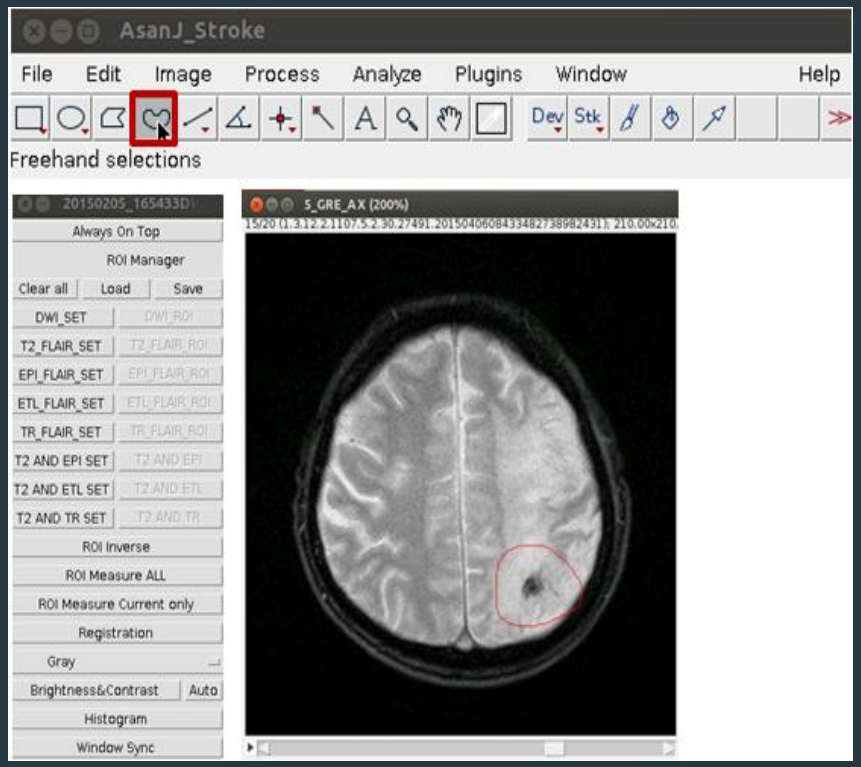
조립이 용이하고 맞춤형 디자인 가능

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

Datasharing.aim-aicro.com/strokevolumetry

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).

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Guidelines? Recommendation?

첨부 3

급성 뇌졸중 영상촬영 프로토콜 표준화 및 팬텀 품질평가를 위한 기준안

(1차년도용)

2018.10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

목차

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 (18182MFDS402).

목차

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

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08/08/11

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?

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Guidelines? Recommendation?

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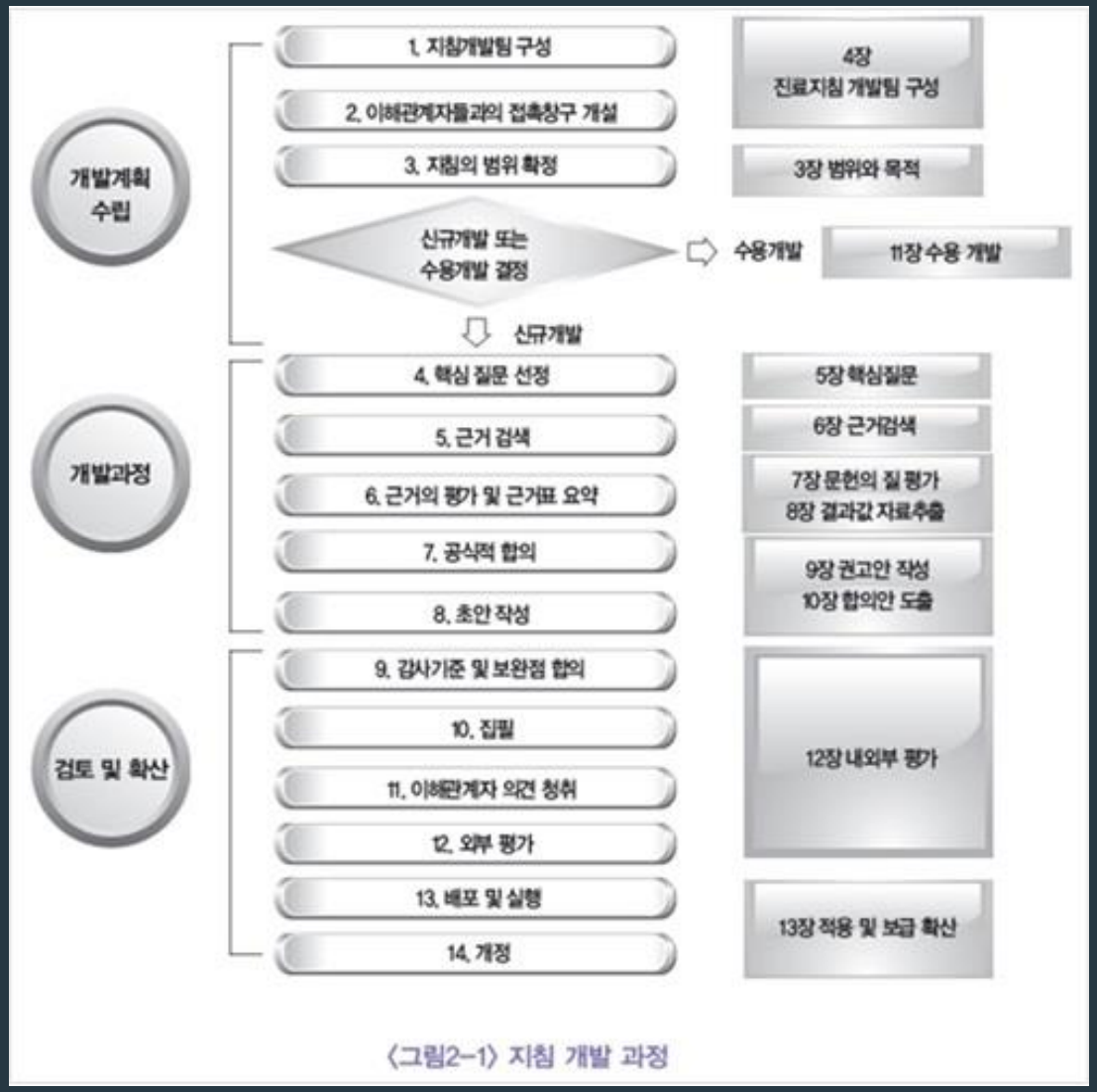
Guidelines? Recommendation?



〈그림2-1〉 지침 개발 과정

Guidelines? Recommendation?

- 근거 (문헌) 검색 및 문헌의 질 평가: NECA 최미영
- 핵심 질문 선정
- Delphi 합의 도출

- 대한신경두경부영상의학회
- 대한신경중재치료의학회

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

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

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

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- 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

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- 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

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

Standardization

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

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

Courtesy of 김인성 Ph.D.

Standardization

- National-wide Standardization: QIBA

- Trial-specific standardization: Study-specific with reference to QIBA

Courtesy of 김인성 Ph.D.

Standardization

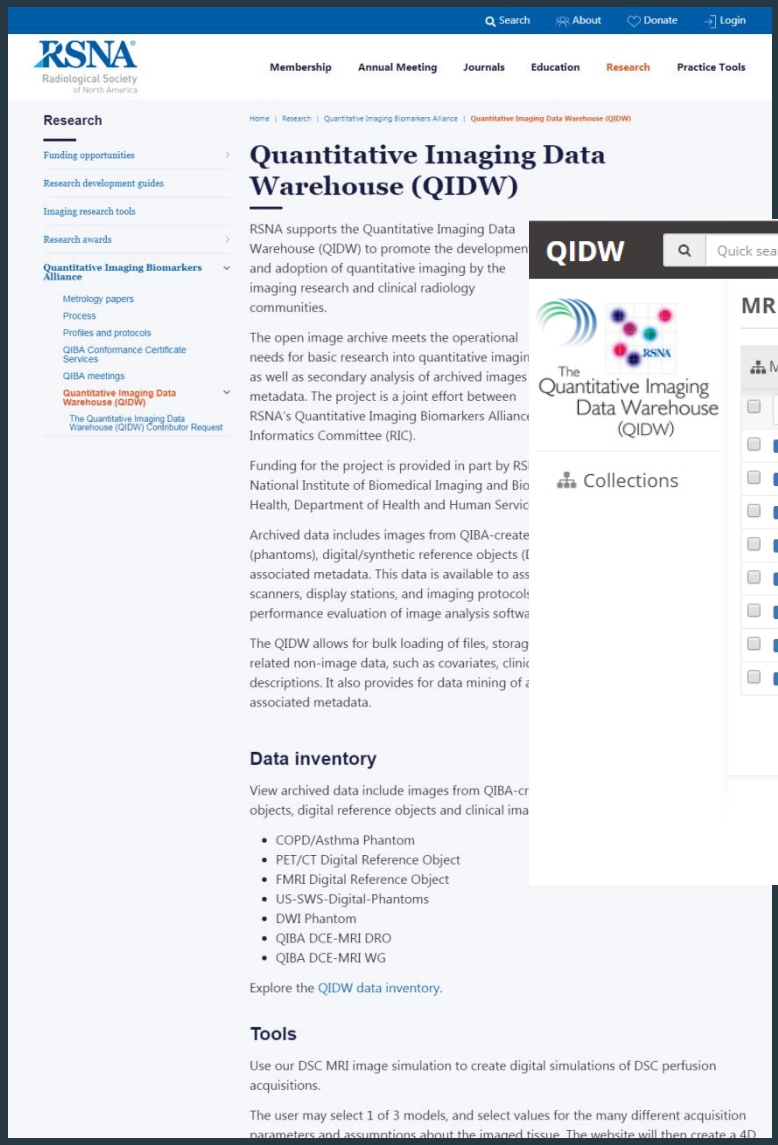
- QIBA (Quantitative Imaging Biomarkers Alliance)

  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



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] Sachin Jambawalikar, PhD,[5] Lawrence H. Schwartz, MD,[5] Dariya Malyarenko, PhD,[4] Wei Huang, PhD,[6] Susan M. Noworolski, PhD,[7] Robert J. Young, MD,[2] Mark S. Shiroishi, MD,[8] 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, PhD[15]

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

J. MAGN. RESON. IMAGING 2018.

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

UCLA Neuro-Oncology Program and UC California – Los Angeles, Los Angeles, Ca University of California – Los Angeles, L Hospital, Heidelberg, Germany (M.B.); D Providence, Rhode Island (J.B.); Departr Department of Radiology, Mayo Clinic, Netherlands (M.S.); Department of Radi California (S.J.N., S.C.); Department of N (E.G.); Center for Neuro-Oncology, Danc Massachusetts (B.A., P.Y.W.); Medical an of Neurooncology, National Center of Ti Neurological Surgery, Brain Tumor and University Hospital Zurich, Zurich, Switze Minnesota (E.G.); Martinos Center for Bi Massachusetts (J.K.-C.); Division of Canc Department of Radiation Oncology, Uni Center for Innovation in Biomedical Ima Ohio (M.V.K.); Department of Neuro-Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands (M.J.v.d.B.); Department of Neurological Surgery, University of California – San Francisco, San Francisco, California (S.C., S.C.); Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas (W.K.A.Y.); Department of Neurology, David Geffen School of Medicine, University of California – Los Angeles, Los Angeles, California (T.F.C.); Neuro-Oncology Branch, National Cancer Institute (NCI), Bethesda, Maryland (M.R.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.

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.

Standardization

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
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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[j]	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]			$b = 0, 500, 1000$ s/mm^2 ≥3 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 dual echo]	5–10 min [5:49 for 1 mm isotropic]

Contrast Injection[o]

National Cancer Institute (NCI), Bethesda, Maryland (M.R.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.

Standardization

Neuro-Oncology

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

Consensus recommendations for a s

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

	3D T1w Pre[b]
Sequence	IR-GRE[e,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]

National Cancer Institute (NCI), Bethesda, Maryland (M.R.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 Allia Neuroradiology (ASNR) (B.M.E., J.B., D.B., B.J.E., W.B.P.); American S Therapy Oncology Group (RTOG) (M.V., M.R.G.)

Corresponding Author: Benjamin M. Ellingson, PhD, Radiological Sciences, Los Angeles CA 90095 (bellingson@mednet.ucla.edu).

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

Radiology

Brain Gliomas: Multicenter Standardized Assessment of Dynamic Contrast-enhanced and Dynamic Susceptibility Contrast MR Images[1]

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Antonella Castellano, MD, PhD
Marcello Cadioli, MSc
Gian Marco Conte, MD
Valeria Cuccarini, MD
Alberto Bizzi, MD
Marco Grimaldi, MD
Antonella Costa, MD
Giovanni Grillea, MD
Paolo Vitali, MD, PhD
Domenico Aquino, MSc
Maria Rosa Terreni, MD
Valter Torri, MD
Bradley J. Erickson, MD, PhD
Massimo Caulo, MD, PhD

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_z] = 0.847 and 0.853) for glioma grading. DSC-derived rCBV had the highest accuracy (A_z = 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.

Online supplemental material is available for this article.

[1] From the Neuroradiology Unit and CERMAC, Vita-Salute San Raffaele University and IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milan, Italy (N.A., A. Castellano, M. Cadioli, G.M.C.); Neuroradiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy (V.C., A.B., D.A.); Department of Radiology, Humanitas Clinical and Research Hospital, Rozzano, Milan, Italy (M.G.); Department of Neuroradiology, Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico, Milan, Italy (A. Costa); IRCCS Neuromed, Pozzilli (Isernia), Italy (G.G.); Neuroradiology Unit, C. Mondino National Neurologic Institute, Pavia, Italy (P.V.); Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy (M.R.T.); Methodology for Clinical Research Laboratory, Department of Oncology, IRCCS Mario Negri, Milan, Italy (V.T.); Department of Radiology, Mayo Clinic, Rochester, Minn (B.J.E.); and Department of Neuroscience and Imaging and ITAB-Institute of Advanced Biomedical Technologies, University G. d'Annunzio, Chieti, Italy (M. Caulo). Received February 15, 2017; revision requested May 22; revision received September 13; accepted October 2; final version accepted October 27. **Address correspondence to** N.A. (e-mail: anzalone.nicoletta@hsr.it).

Supported by Bayer Healthcare.

x 2D T2w[h,i]	3D T1w Post[b]
SE[c]	IR-GRE[e,f]
xial	Sagittal/axial
D	3D
2500	2100[m]
0–120	Min
	1100[n]
0°/≥160°	10°–15°
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

STIR and VISTA Imaging Investigators. Stroke 2013

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.

STIR and VISTA Imaging Investigators. Stroke 2016

뇌졸중 임상시험 영상 기준안

- 근거 (문헌) 검색 및 문헌의 질 평가
- 핵심 질문 선정
- Delphi 합의 도출

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

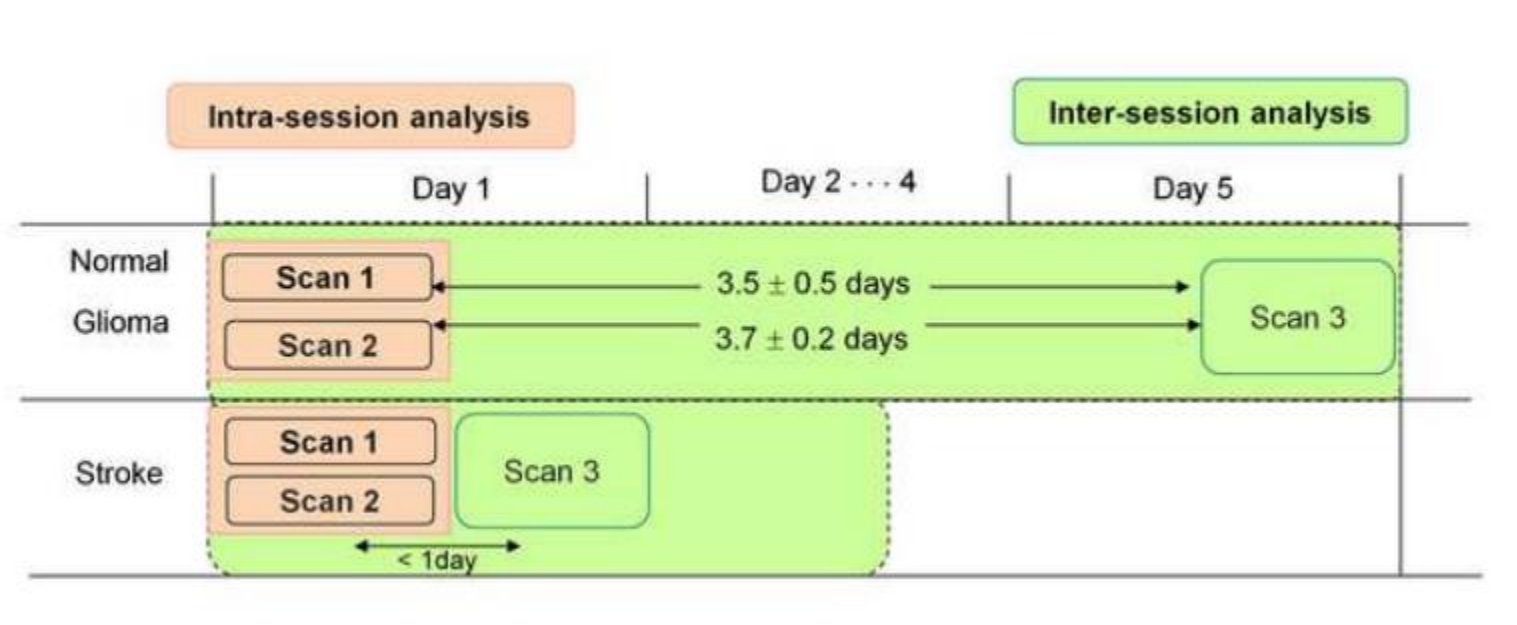
Standardization II

- Amide proton transfer weighted imaging
- Arterial spin labeling

- Repeatability and Reproducibility
- Multicenter comparison
- Longitudinal comparison

Standardization II

- **Amide proton transfer weighted imaging: Repeatability**



Standardization II

- **Amide proton transfer weighted imaging: Repeatability**

	Healthy subjects	Patients with glioma	Patients with stroke
Number of subjects	19	15	12
Number of male subjects	10	5	9
Age (years)	53.8 ± 13.4	53.6 ± 10.9	68.5 ± 8.7
Imaging interval (intersession, days)	3.5 ± 0.5	3.7 ± 0.2	Less than 1 day
Supratentorial locations	19	15	12
Infratentorial locations	19	0	0
Lesionsize (mL)	-	28.7	6.6
ROI size (mL)	0.2	28.7	6.6

Revision

Standardization II

- **Amide proton transfer weighted imaging: Repeatability**

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

Revision

Standardization II

- **Amide proton transfer weighted imaging: Repeatability**

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

Revision

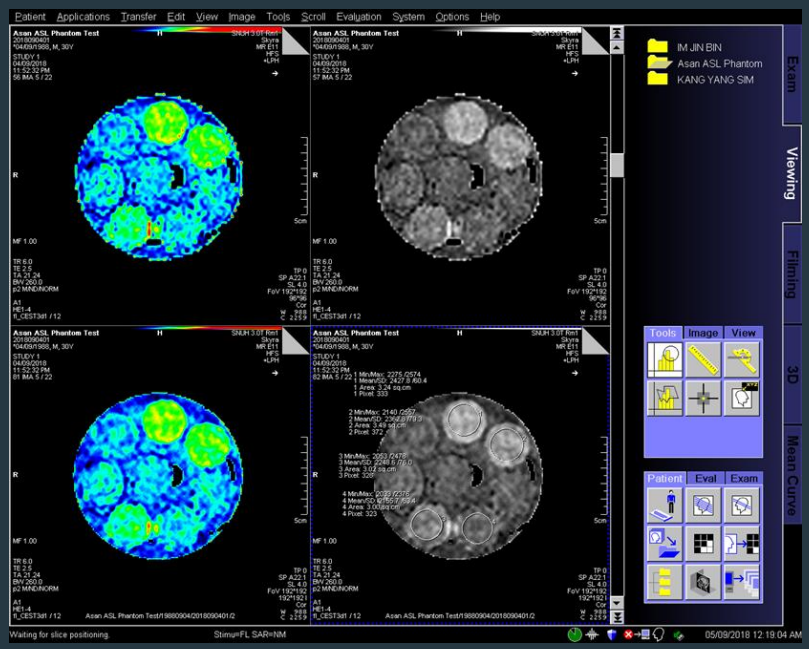
Standardization II

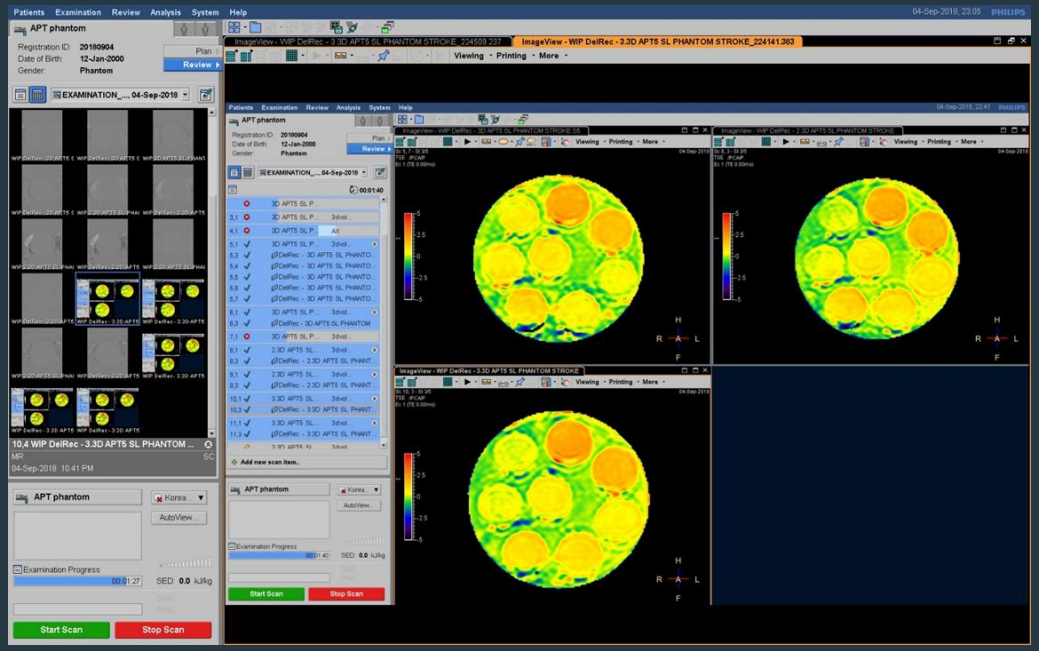
- Amide proton transfer weighted imaging: Repeatability

- The reproducibility of the APTw signal was excellent in supratentorial locations, irrespective of disease condition, while it was poor in infratentorial locations due to severe B0 inhomogeneity and susceptibility, which affects MTR asymmetry. Therefore, APTw signals measured in infratentorial locations may not be considered reproducible values.

Standardization II

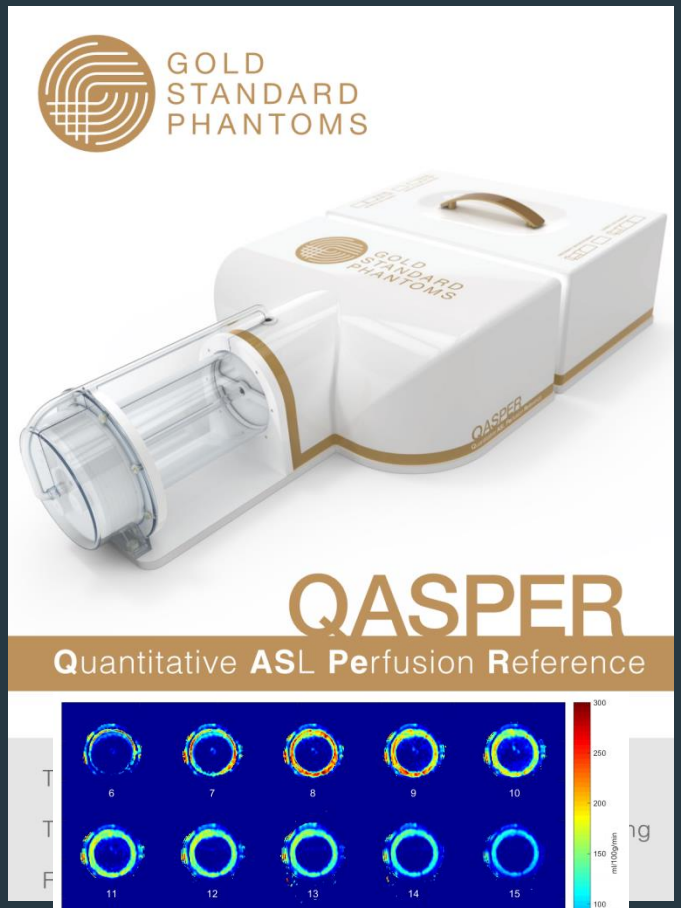
- **Amide proton transfer weighted imaging: Reproducibility**

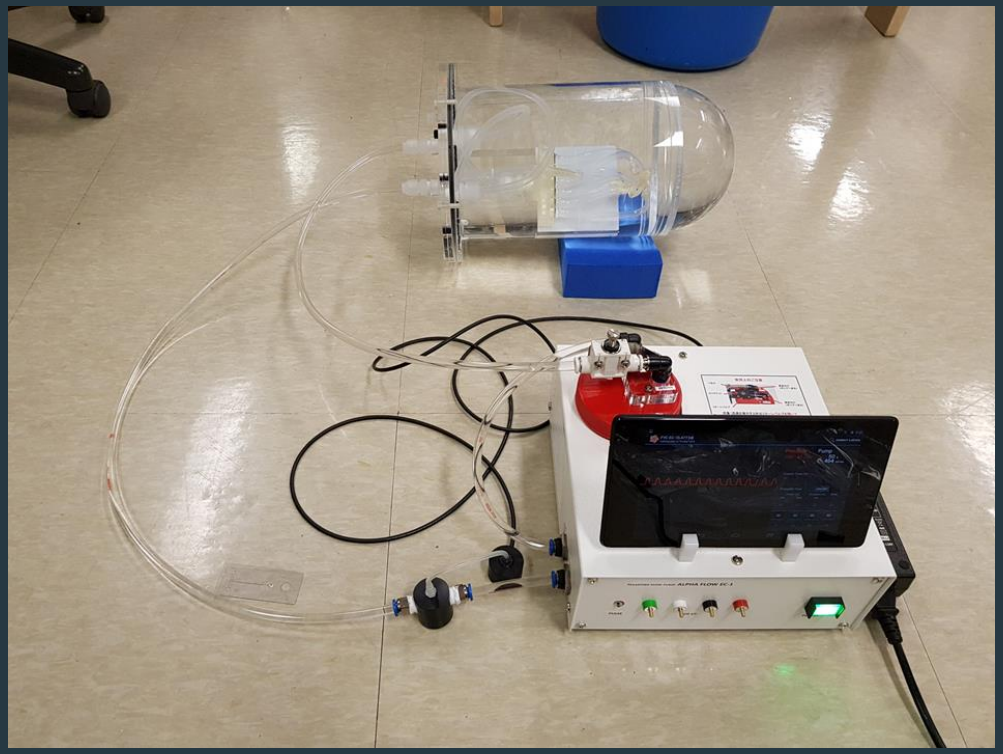




Standardization II

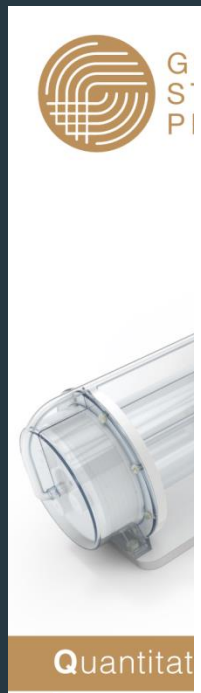
- **Arterial Spin Labeling: Repeatability & Reproducibility**





Standardization II

- **Arterial Spin Labeling: Repeatability & Reproducibility**



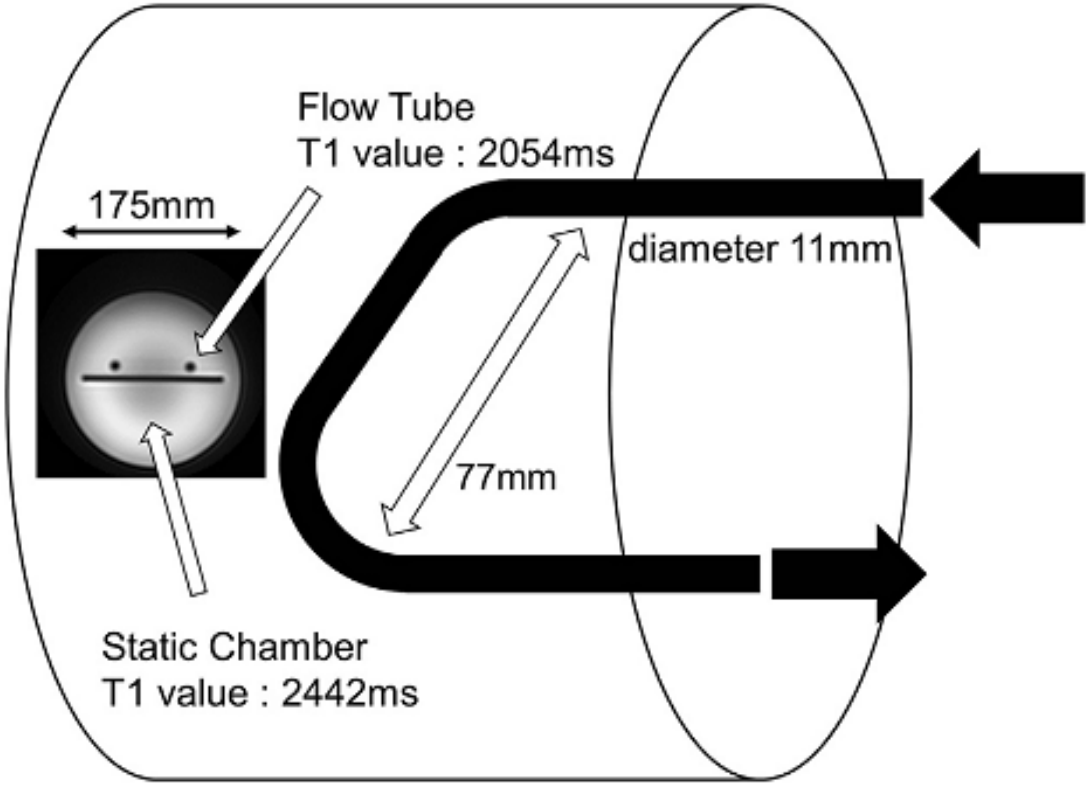
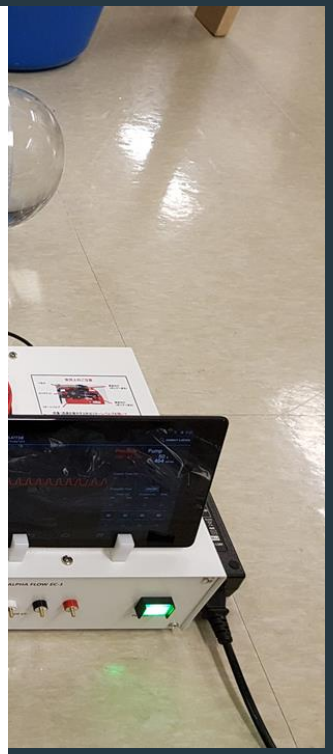


Fig. 3. External view of the flow phantom.
The speed of the flow tubes was 2.5 cm/s, the T1 value in the static chamber was set to 2442 ms, and the T1 value in the flow tubes to 2054 ms.



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Summary

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

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경청해 주셔서 감사합니다.