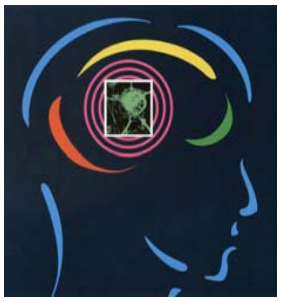
Stanford MEDICINE



defuse·3

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Funded by a Grant from the National Institutes of Health

DEFUSE and DEFUSE 2

- Patients with Target mismatch profile have a powerful association between reperfusion and favorable clinical outcomes following intravenous tPA:

Magnetic Resonance Imaging Profiles Predict Clinical Response to Early Reperfusion: The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study

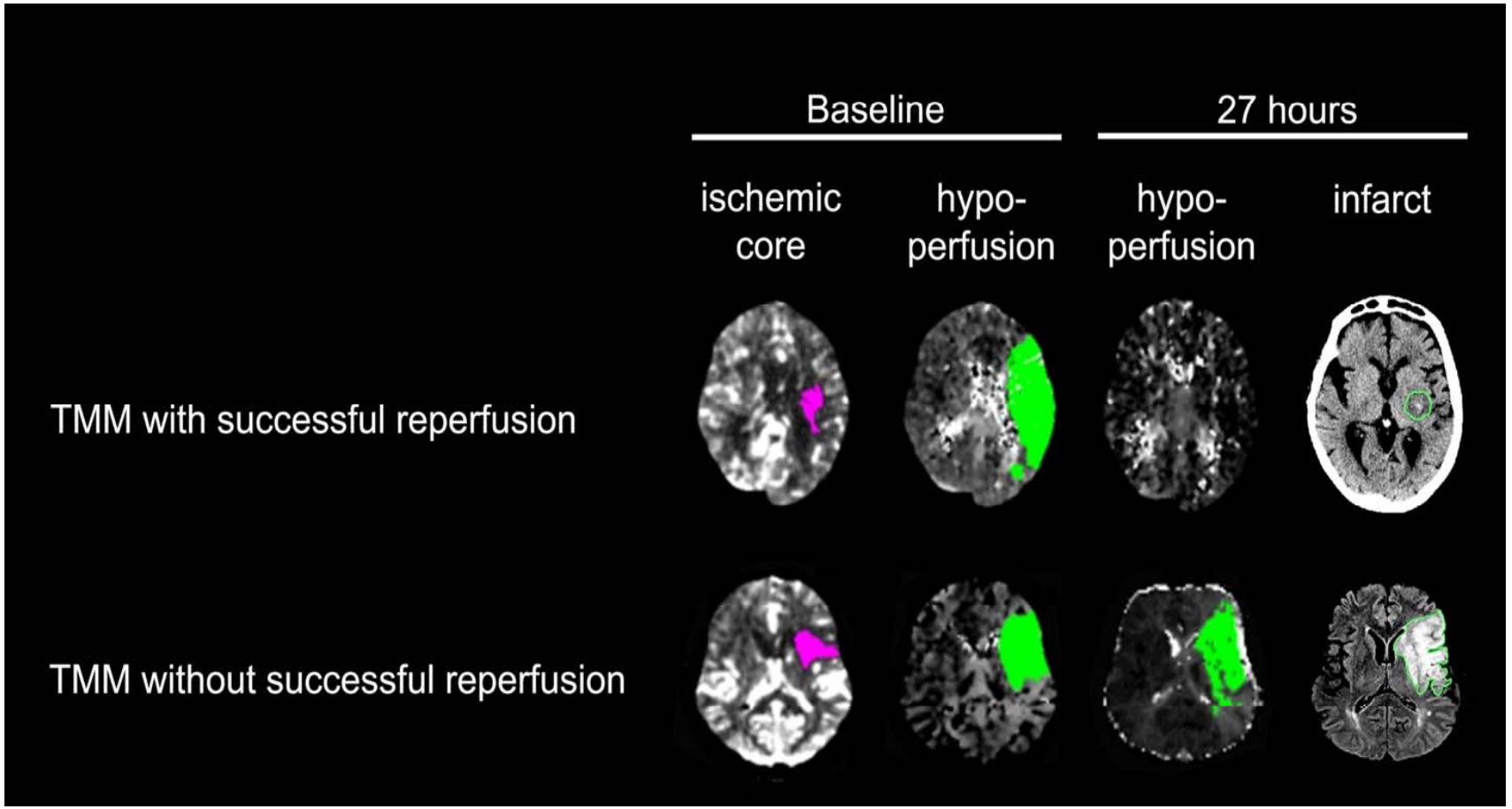
Annals of Neurology, 2006

- And following endovascular therapy:

MRI Profile and Response to Endovascular Reperfusion After Stroke (DEFUSE 2): A Prospective Cohort study

Lancet Neurology, 2013

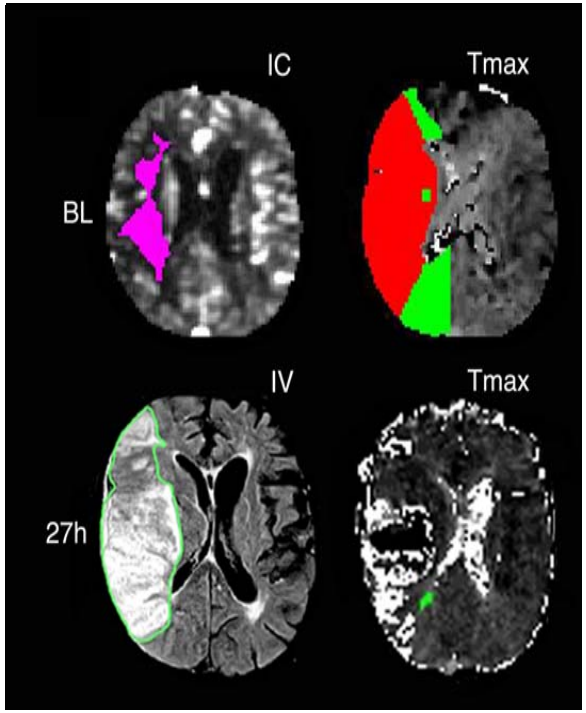
Target mismatch profile



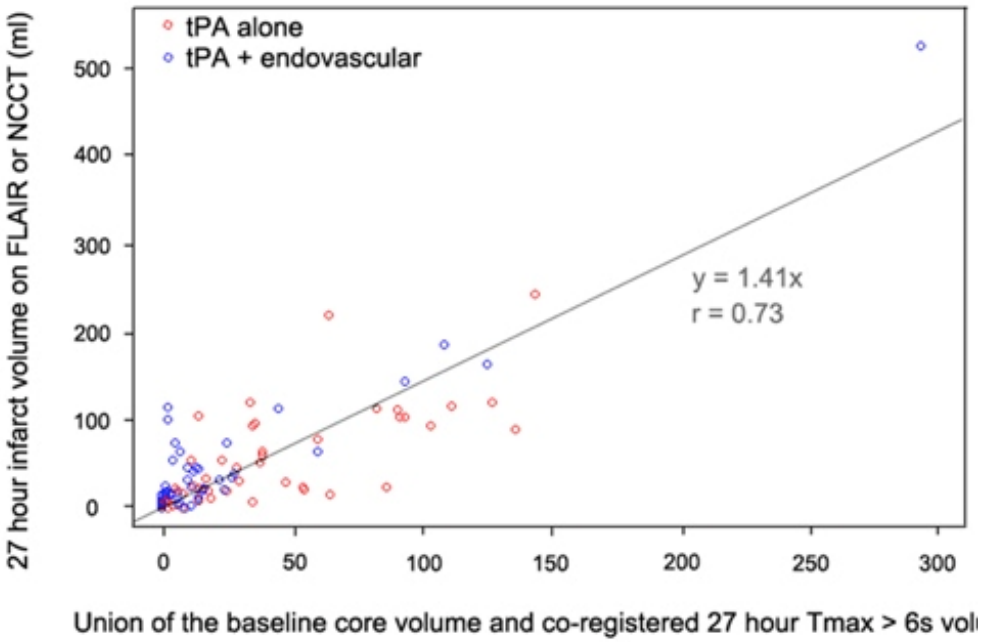
SWIFT PRIME: Infarct Prediction using RAPID

RAPID ischemic core and hypoperfusion volumes predicted infarct size

- Baseline core predicts infarct volume in reperfusers
- Baseline hypoperfusion predicts infarct in non-reperfusers
- Malignant profile predicts infarct growth despite reperfusion



Albers GW, et al. In press, Annals of Neurology



Albers GW, et al. Ann Neurol, in press

TMM Patients in SWIFT PRIME
(80% CT Perfusion, 20% MRI)

median absolute error

Core predicts infarct volume 9 ml
in pts with >90% reperfusion

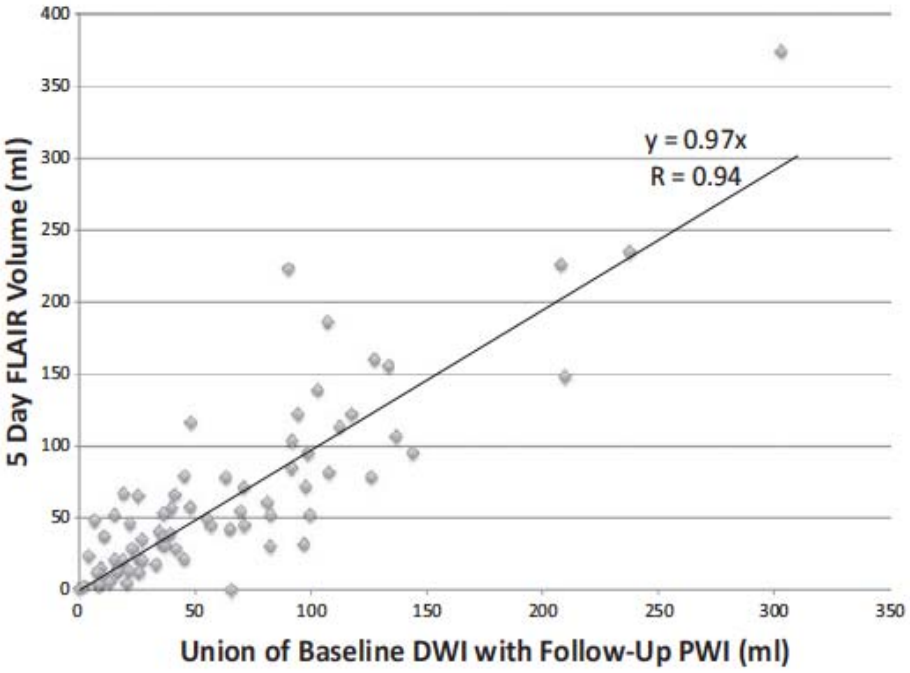
Union core + f/u Tmax>6s 13 ml
predicts infarct volume

TMM Patients in DEFUSE 2
(all MRI)

median absolute error

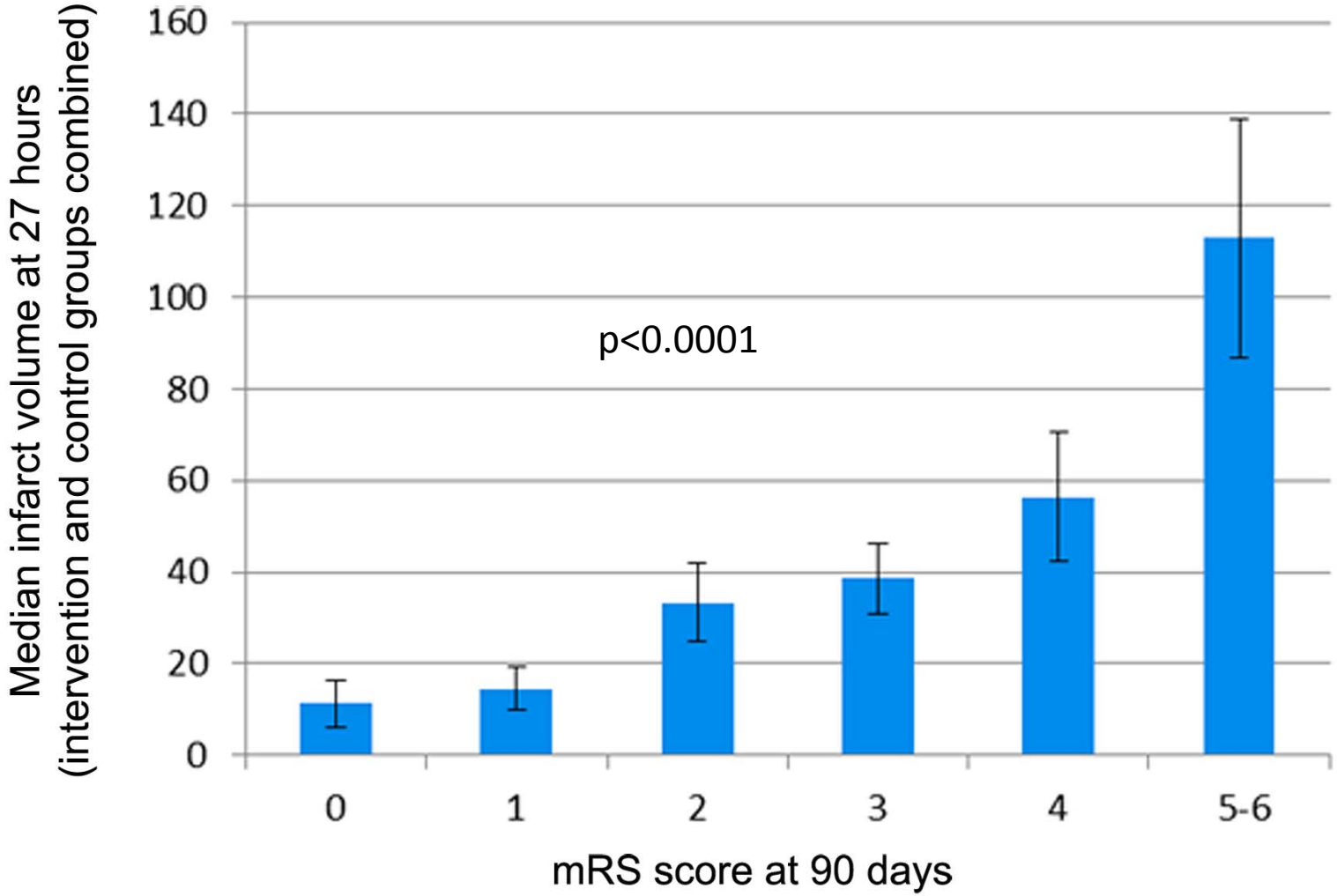
DWI predicts infarct volume 8 ml
in pts with >90% reperfusion

Union DWI + f/u Tmax>6s 15 ml
predicts infarct volume



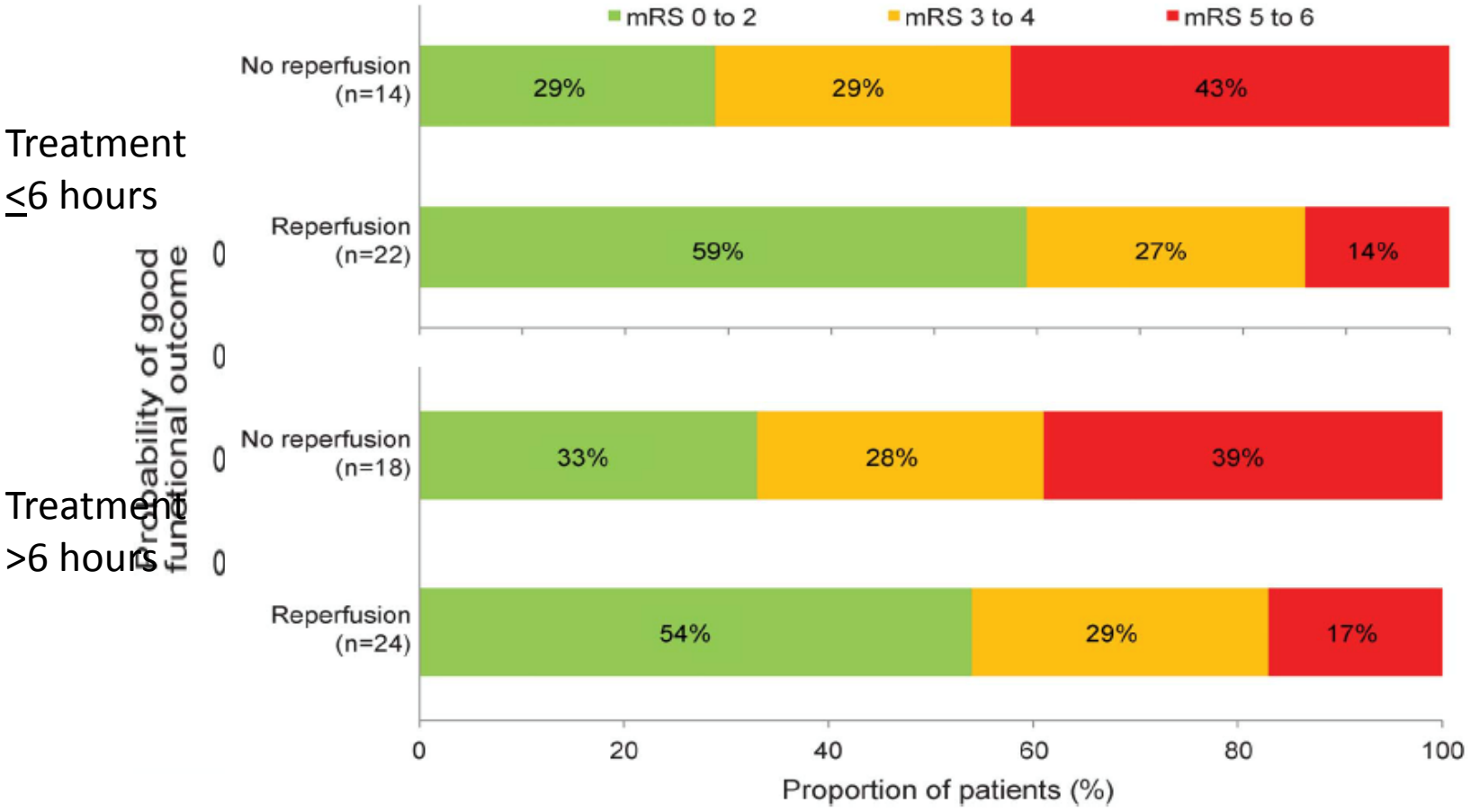
Wheeler HM, et al. Stroke, 2013

SWIFT PRIME: Infarct volume strongly correlates with clinical outcome



Albers GW, et al. Stroke, August 2015

DEFUSE 2:
Response to reperfusion is not time-dependent in patients with salvageable tissue



Lansberg and Cereda, et al. Neurology; Aug 2015

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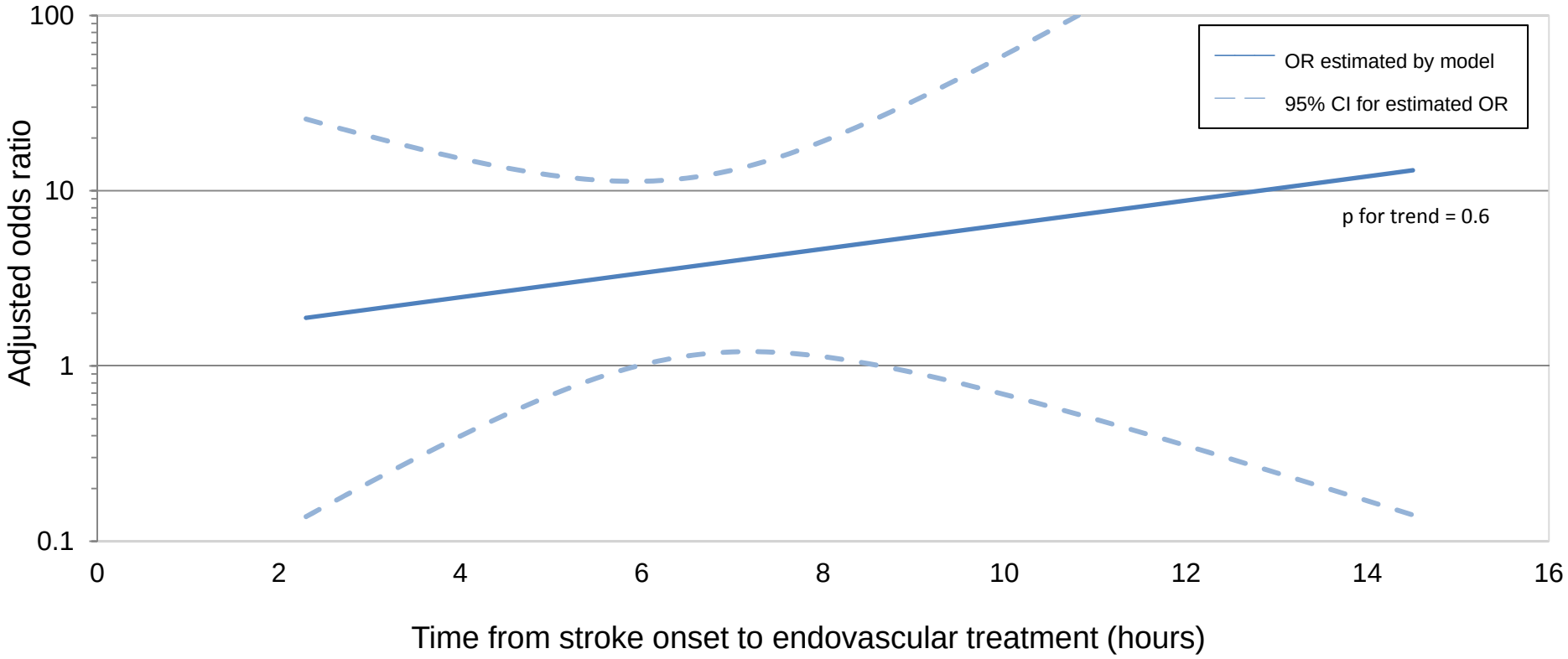

Lansberg and Cereda, et al. Neurology; Aug 2015

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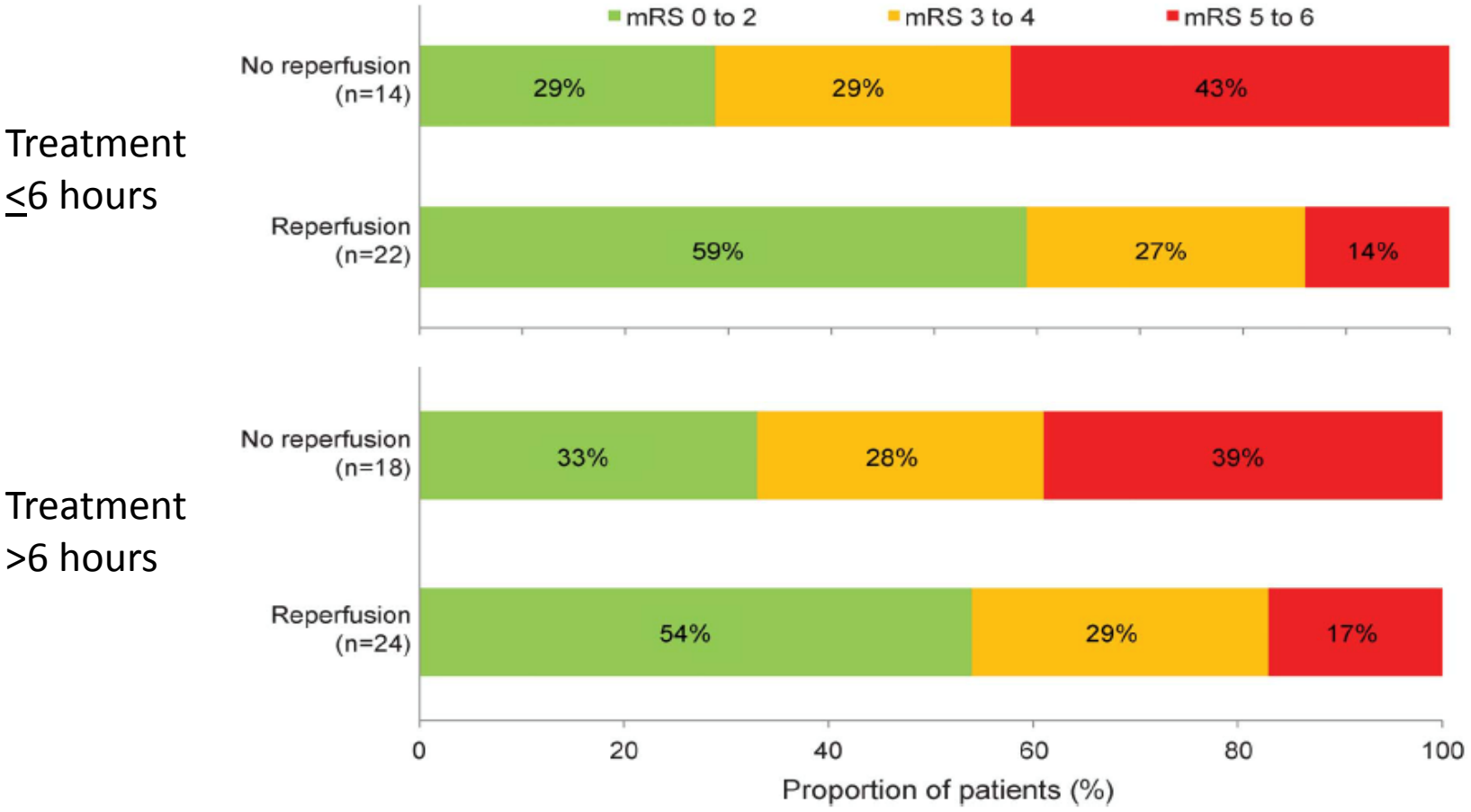
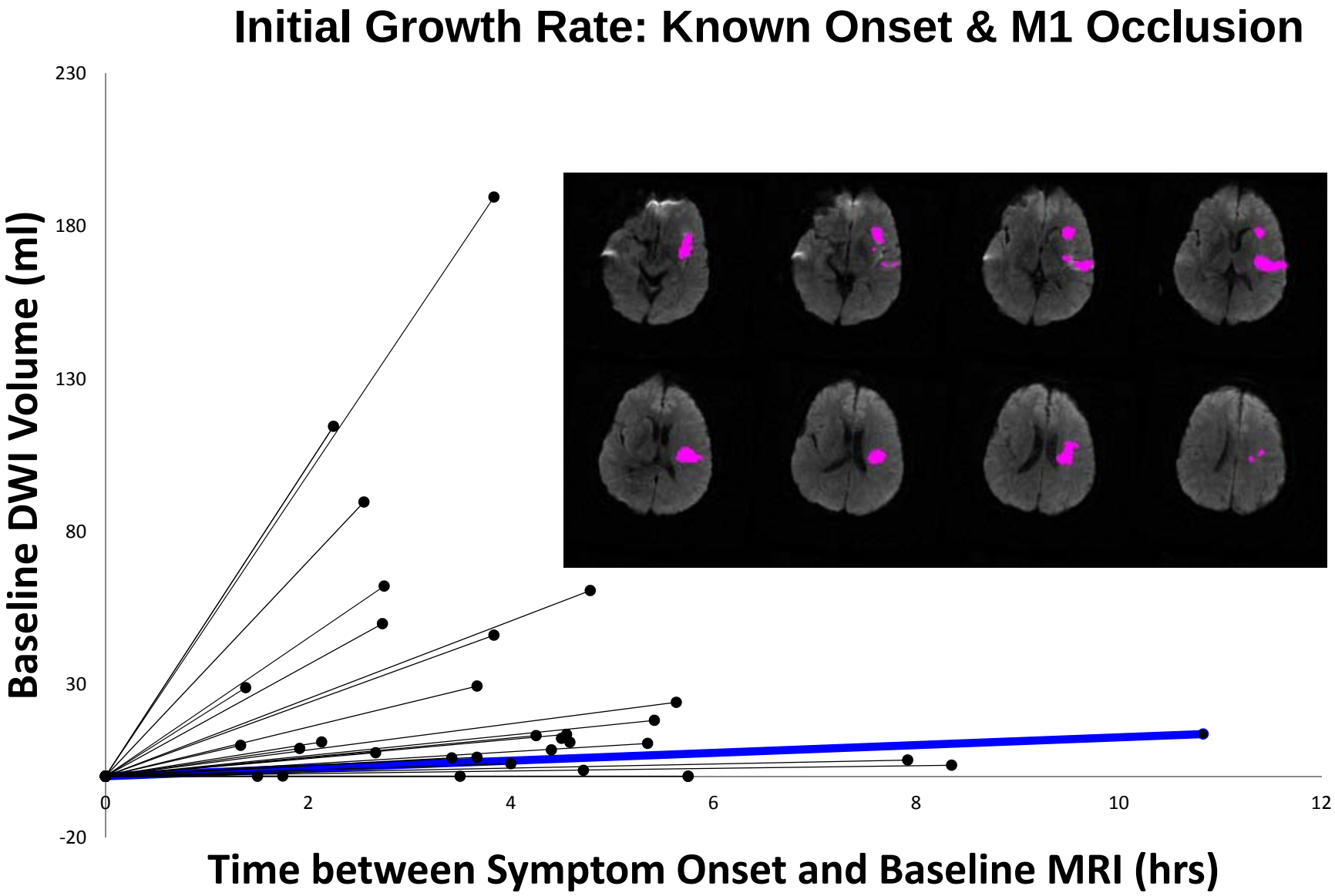


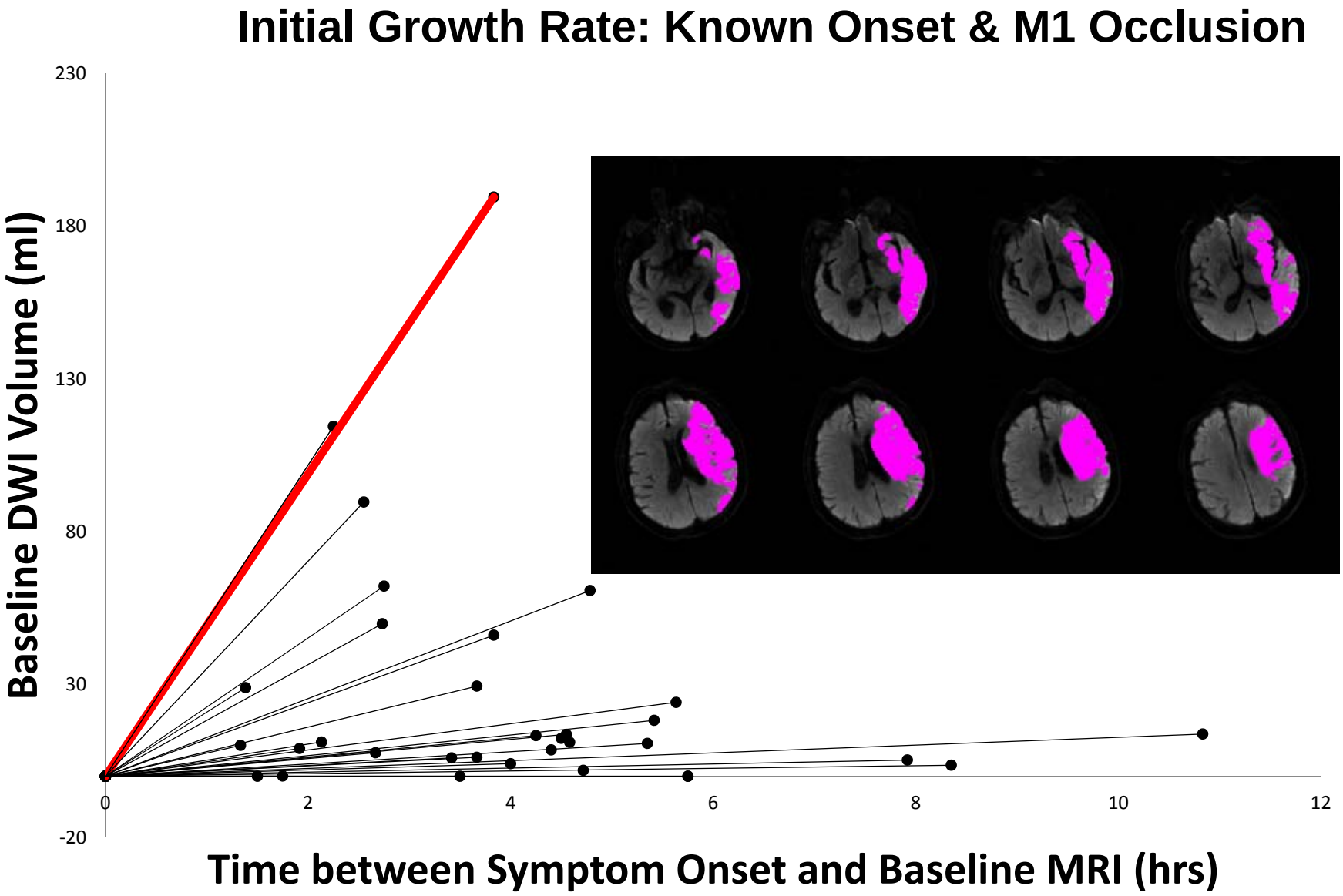
Lansberg and Cereda, et al. Neurology; Aug 2015

DEFUSE 2



Wheeler HM, et al. Int J Stroke. 2015

DEFUSE 2



Wheeler HM, et al. Int J Stroke. 2015

DEFUSE 3: Premise

Infarct growth is highly variable

Many patients have salvageable tissue beyond 6 hours

Advanced CT/MR imaging can identify these patients

These patients will benefit from modern endovascular therapies

DEFUSE 3: NIH-funded, prospective, randomized, multi-center, adaptive, blinded endpoint trial

- Paradigm shift
  - From time-based selection to imaging-based selection
- Target population
  - Anterior circulation ischemic stroke; ICA or M1 occlusions (CTA/MRA)
  - Salvageable tissue on CT perfusion or MR diffusion / perfusion
  - Endovascular therapy within 6-16 hours of last known well
- Design
  - 1:1 randomization; standard medical therapy vs. endovascular
  - 45 sites

DEFUSE 3 Protocol

Maarten Lansberg, MD PhD

DEFUSE 3 Protocol Director

Schedule of Events

Evaluation	Baseline	24 hours after randomization	5 days or discharge	30 days	90 days
Informed Consent	✓				
History & Physical	✓			✓	✓
NIHSS Score	✓	✓	✓	✓	✓
Modified Rankin Scale	✓			✓	✓
TOAST subtype			✓		
NeuroQol				✓	✓
MRI or CTP scan	✓	✓			
EKG / Laboratory Evaluation*	✓	✓			
Adverse Event Assessment		✓	✓	✓	✓

Inclusion Criteria

1. Signs and symptoms consistent with an acute anterior circulation stroke
2. Age 18-85 years
3. Baseline NIHSSS ≥ 6
   - Remains ≥ 6 immediately prior to randomization
4. Endovascular treatment (femoral puncture) between 6-16 hours of stroke onset*
5. Pre-stroke baseline mRS score 0-2
6. Anticipated life expectancy of ≥ 6 months
7. Patient or Legally Authorized Representative has signed Informed Consent

*Stroke onset: Time of last known at neurologic baseline, including wake-up strokes

Exclusion Criteria

1. Other serious, advanced, or terminal illness
2. Pre-existing neurological or psychiatric disease that would confound the evaluations
3. Participation in another drug or device study
4. Pregnancy
5. Contraindication to MRI/CTP contrast (incl. iodine allergy refractory to pretreatment meds)
6. Treated with tPA >4.5 hrs after time last known well
7. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; oral anticoagulant with INR > 3 (recent use of new oral anticoagulants ok if eGFR > 30 ml/min)
8. Seizures at stroke onset if precludes obtaining an accurate baseline NIHSS assessment
9. Baseline blood glucose of <50mg/dL (2.78 mmol) or >400mg/dL (22.20 mmol)
10. Baseline platelet count < 50,000/uL
11. Untreateable sustained hypertension (SBP >185 mmHg or DBP >110 mmHg)
12. Presumed septic embolus; suspicion of bacterial endocarditis or cerebral vasculitis
13. Mechanical clot retrieval attempted prior to 6 hrs from symptom onset

Neuroimaging Inclusion Criteria

MRA / CTA reveals

- M1 segment MCA occlusion, or
- ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)

AND

Target Mismatch Profile on CT perfusion or MRI (RAPID)

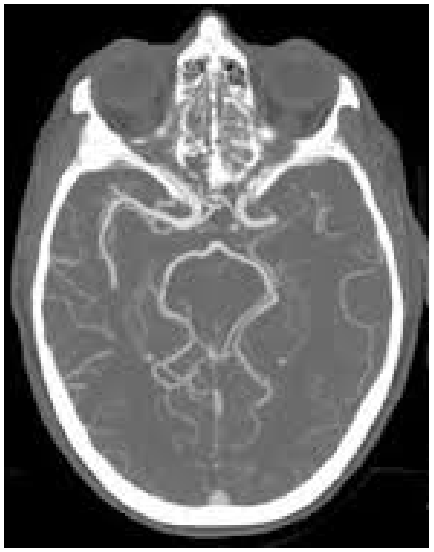
- Ischemic core volume < 70 mL

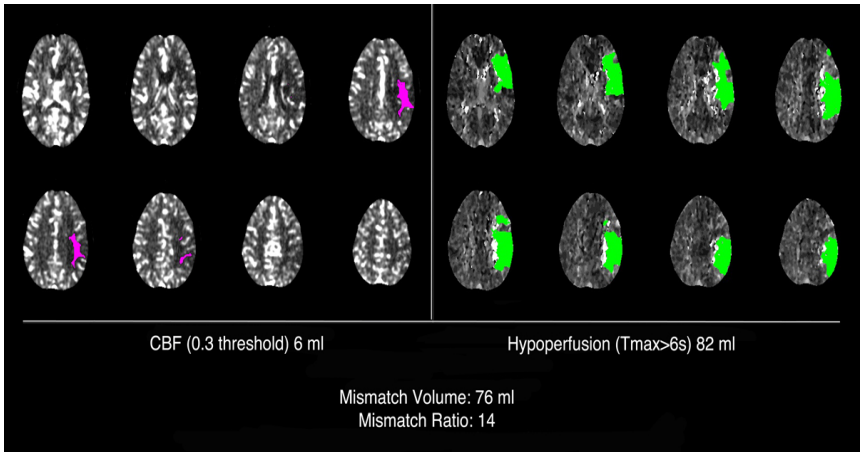
  and

- Mismatch ratio > 1.8

  and

- Mismatch volume ≥ 15 mL





Alternative Neuroimaging Criteria

If MR perfusion is technically inadequate:

- DWI lesion volume < 25 mL, and
- ICA or MCA-M1 occlusion on MRA or CTA (within 60 minutes)

If CTA/MRA technically inadequate:

- Tmax >6s perfusion deficit consistent with MCA occlusion, and
- Target Mismatch criteria are met

If CT Perfusion technically inadequate: obtain MRI

Neuroimaging Exclusion Criteria

- ASPECTS < 6 on non-contrast CT
- Evidence of
  - Intracranial tumor (except small meningioma)
  - Acute intracranial hemorrhage
  - Neoplasm
  - Arteriovenous malformation
- Significant mass effect with midline shift
- Evidence of ICA flow-limiting dissection or aortic dissection
- Intracranial stent implanted in the same vascular territory that would preclude safe deployment / removal of neurothrombectomy device
- Intracranial occlusions in multiple vascular territories

Novel Adaptive Design Developed for DEFUSE 3

Adaptive design*

- Based on 2 biological assumptions that outcomes with endovascular therapy are better
  - In patients with smaller ischemic core volumes
  - In patients with faster time-to-treatment
- Accrual shift to subgroup with maximal response at one of two interim analyses (N=200 and 340), maximum sample size = 476

*Lai TL, Lavori PW, Liao OY. *Contemp Clin Trials*. 2014;39:191-200

Michael Marks

DEFUSE 3 Endovascular PI

Endovascular Devices

FDA cleared thrombectomy devices will be included:

- Solitaire Device
- TREVO Retriever
- Penumbra system
  - Penumbra Aspiration Pump 115V
  - Penumbra System Separator Flex [026, 032, 041 and 054]
  - Penumbra System MAX
  - Penumbra Pump MAX

Endovascular Protocol

- The use of thrombectomy devices will be accompanied by the use of cervical balloon guide catheter to achieve flow arrest and aspiration or a distal suction thrombectomy catheter.
- If there is a severe stenosis of the common carotid artery or the proximal internal carotid artery, investigators may also use other FDA devices approved for angioplasty or FDA devices approved for stenting of the carotid artery as deemed appropriate.
- The use of adjuvant intra-arterial (IA) thrombolytic medication is prohibited.

Endovascular Protocol

- Based on recently presented data demonstrating that endovascular therapy is substantially less effective in patients treated under general anesthesia conscious sedation will be strongly recommended.
- General anesthesia will be allowed if the patient has a clear contraindication to conscious sedation and the indication for general anesthesia will be recorded in the CRF.

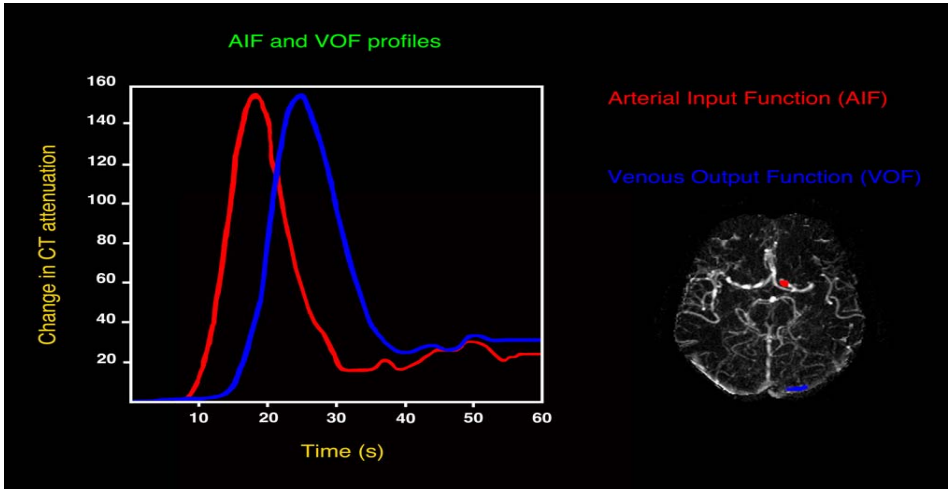
Additional Topics

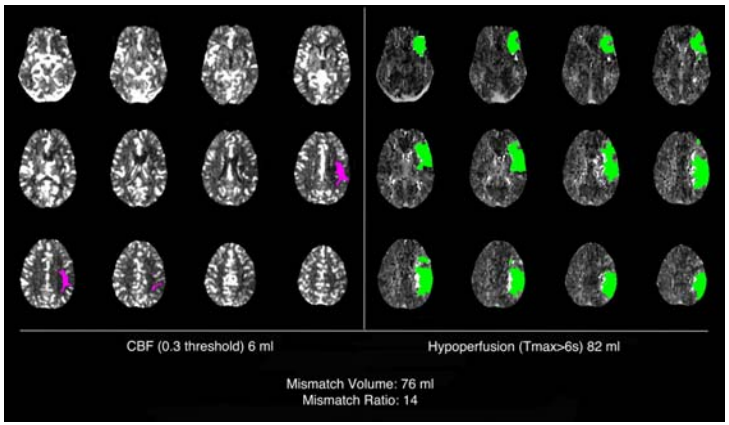
- RAPID in DEFUSE 3
- Site Selection
- Timeline
- Workflow examples

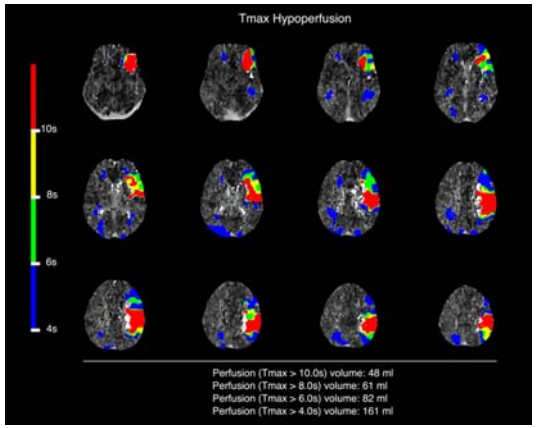
RAPID in DEFUSE 3

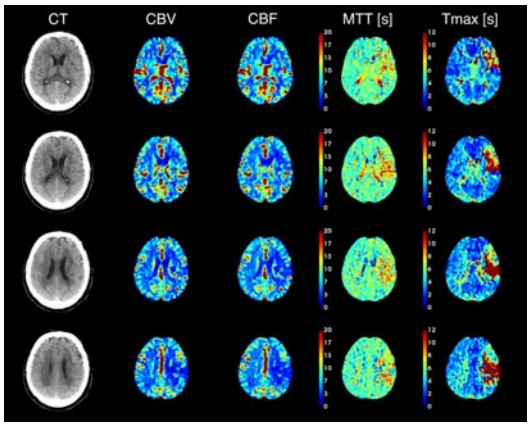
FDA cleared research version of RAPID, (courtesy of iSchemaView) installed at each site to ensure uniformity in:

- Image acquisition
- Processing time
- Image quality
- Physician interpretation



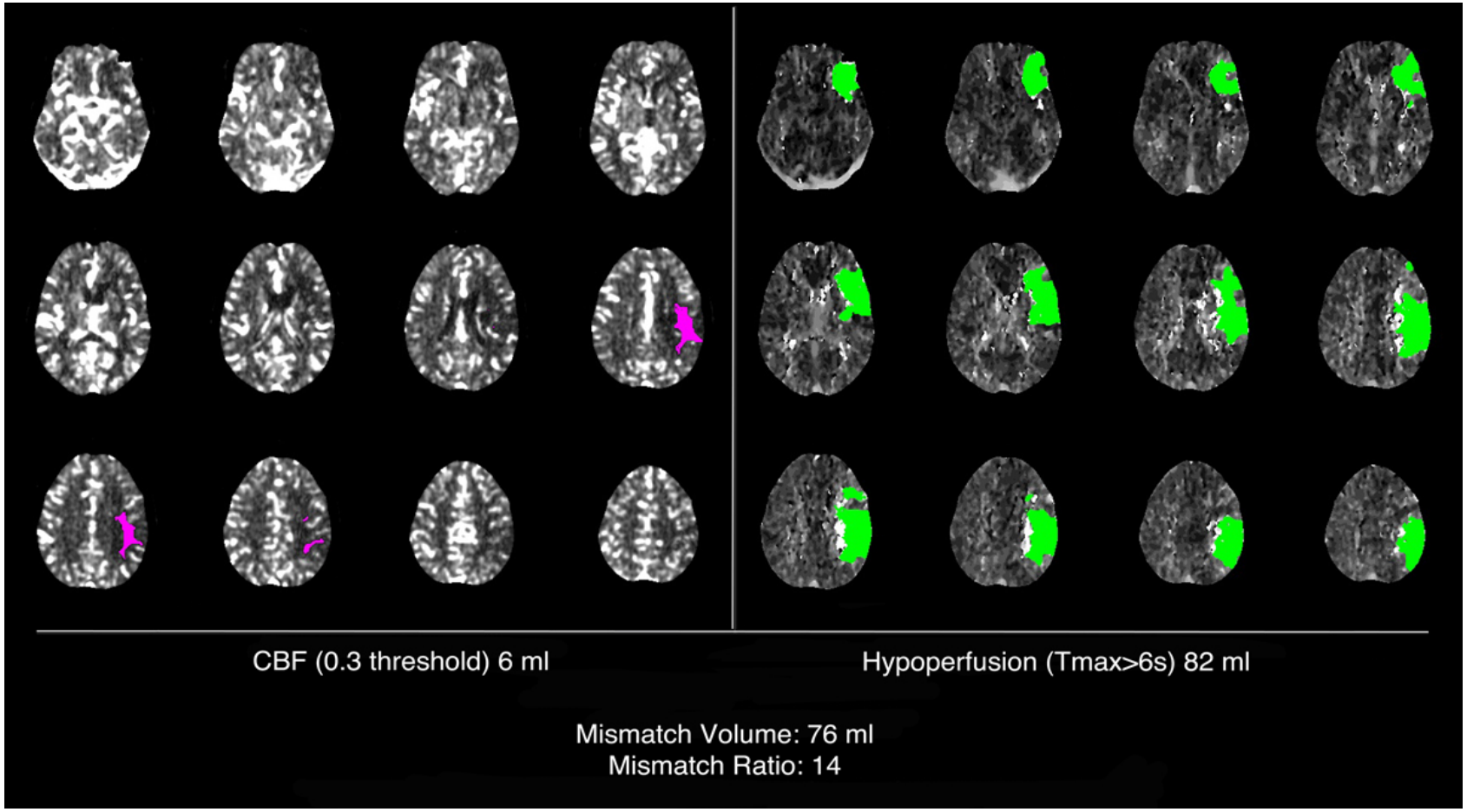






RAPID Software (Stanford / iSchemaViewRAPID)

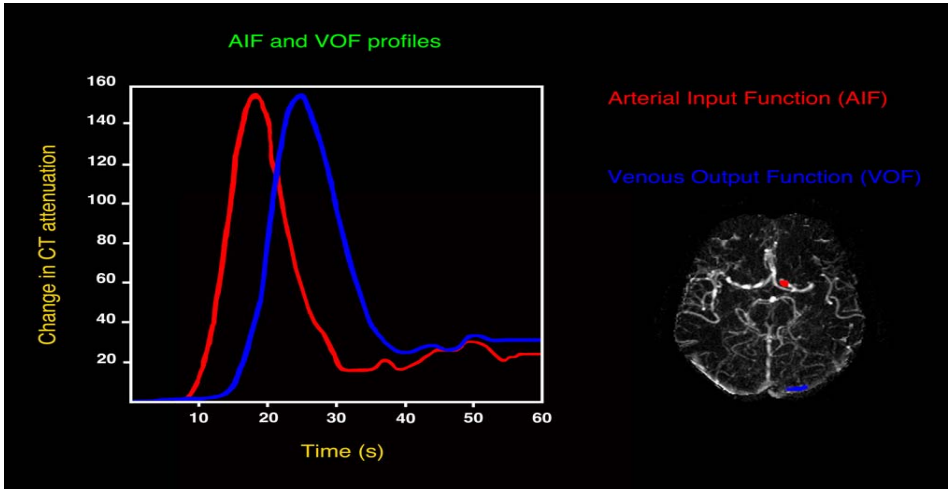
Research License from iSchemaView

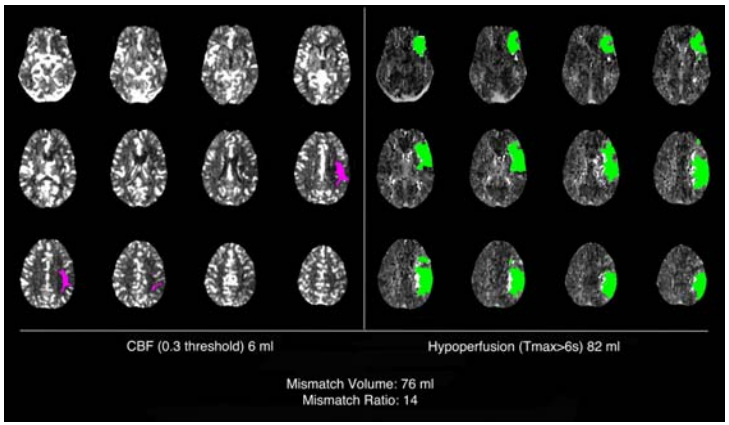


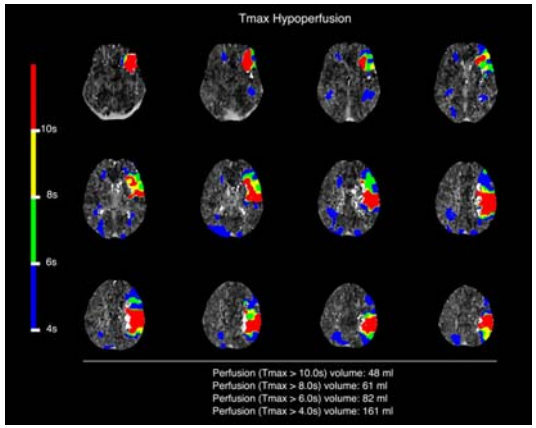
RAPID in DEFUSE 3

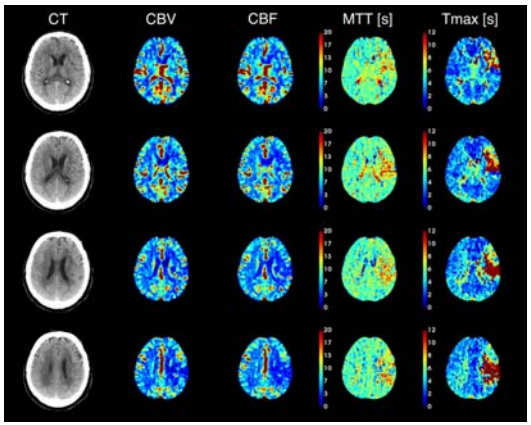
FDA cleared research version of RAPID, (courtesy of iSchemaView) installed at each site to ensure uniformity in:

- Installation
- Research only use
- Images not read by radiology
- Routine processing of standard of care perfusion









DEFUSE 3 Imaging Protocols

Sequence	Scan Parameters (3T)	Time
MRI		**6 min**
Localizer	128X256; 28 FOV;5/5mm, GRE	24 sec
Calibration		5 sec
DWI	128x128, 24 FOV, 5/0mm, 30 slices, 1 NEX, R=2; b=0 and 1000 s/mm^2 over 3 axes, TE/TR=min/7000ms.	25 sec
GRE	256x192; 24 FOV; 5/0 mm, 30 slices, TE/TR= 25/800ms, flip 20, interleaved EPI, 16 shots	27 sec
MRA intracranial	256x192, 1 mm; 4 slabs, 26 phase-encodes; 6 overlap, 22 FOV, 0.8 rFOV, fractional echo, ZIPx2, ZIPx512, minTE, flowcomp, TR=18ms, flip=18, inferior->superior ramppulse, R=2; 19 MIPS	143 sec
PWI	128x128; 24 FOV; 5/0 mm, 17 slices, TE/TR=35ms/1800ms, R=2 using 0.1mmol/kg Gadolinium @ 4ml/sec.	108 sec
CT (example below for GE VCT; comparable protocols will be used for other scanner models)		**5-6 min**
Non-con head	2.5 – 5mm, 40 slices, 120-140kV, 265-290mA	120-180 sec
CTA	0.625mm, 0.984:1/39.37cm, 120kV, 550mA , inject and observe for 15 sec until contrast concentration in ascending aorta reaches 80HU (smart prep) then the CT gantry moves along with the bolus of the contrast material from the aortic arch up to the apex of the brain in 5sec.	90 sec
CTP	22 FOV, 40mm, 8x5mm, 1.8sec time interval, 45 cycles, 80kV, 125mA; 2 runs	90 sec

Site Selection

Objective criteria for site selection:

- Level of interest
- Equipoise
- # of potentially eligible patients
- Availability of CT perfusion or MR perfusion
- Recommendation from RCC
- Competing trials

CRITERIA	YES/NO	POINT ALLOCATION	TOTAL/CRIT.	JUSTIFICATION
Patient Volume				
<20		0		1st Quartile = 20
20-70		+1		Q1-Q3 captures most centers
>70		+2		3rd Quartile = 70
RCC status				
RCC		+5		Based on pre-selection as RCC by StrokeNET
Alternative or first site recommended by RCC		+4		Based on RCC report on team's prior experience
Additional sites recommended by RCC		+2		Based on RCC report on team's prior experience
Imaging				
Routine perfusion imaging		+2		Experience and funding
MRI 24-hour access		+1		Ensure 24/7 screening
CTP 24-hour access		+1		Ensure 24/7 screen; (AND argument, not OR, vs MRI: ensures access)
Imaging access 7 days per week		+1		Ensure 24/7 screening
Equipoise				
Equipoise 6-8 hours		+1		Confirmed with sites, prerequisite for trial
Participation in other trials				
DAWN		-5		Protocol similarity major
POSITIVE		-3		Protocol similarity moderate
MR WITNESS		-2		Protocol similarity mild

Additional Topics

- Timeline
  - Central IRB
  - Central Contracting
  - RAPID installation
  - Web DCU
  - Investigator training
- Workflow examples

Workflow in DEFUSE 3

69 yo male transferred to DEFUSE 3 site 7 hours after onset; NIHSS 16; CT negative at outside hospital

- No clinical exclusions for DEFUSE 3
- Consent form signed - enroll patient in WebDCU
- Stroke MRI performed

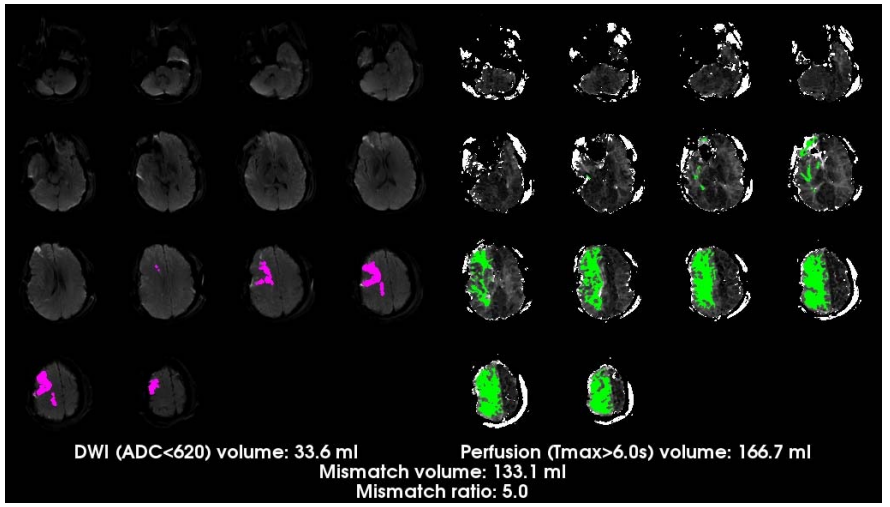
  DWI ASPECTS 7

  MRA R ICA occlusion

  MR perfusion performed (sent to RAPID; site does not do clinical perfusion imaging)

Review RAPID results

Randomize patient in WebDCU



Workflow in DEFUSE 3

79 yo female arrive to ER at 8 am; last seen well 10 pm last night

NIHSS 17

- Stroke CT performed immediately upon ER arrival

  Non con CT- ASPECTS 8

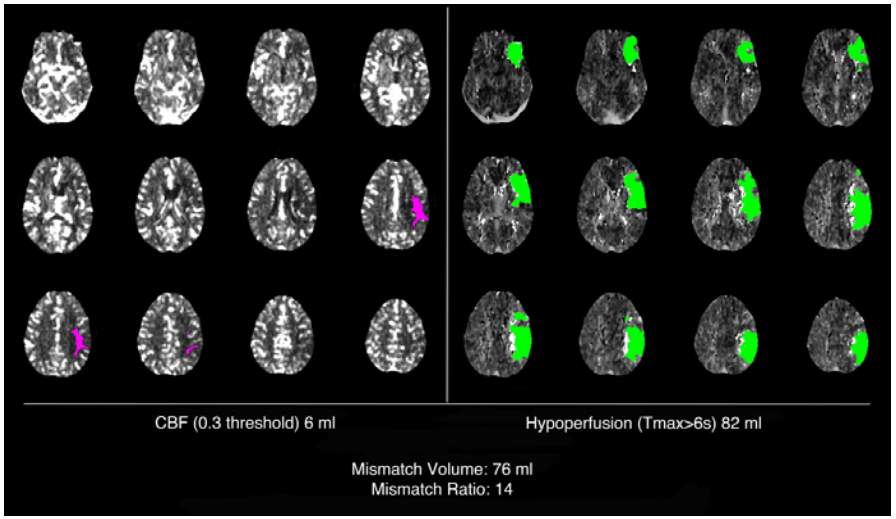
  CTA L MCA occlusion

  CTP performed (images autosent to RAPID + routine clinical CTP processing)
- Patient meets DEFUSE 3 clinical inclusion criteria
- Consent form signed
- Enroll patient in WebDCU

Review RAPID results to confirm

Target mismatch profile

Randomize patient in WebDCU



Workflow in DEFUSE 3

63 yo male transferred to DEFUSE 3 site 12 hours after onset; NIHSS 21

- No clinical exclusions for DEFUSE 3
- Consent form signed - enroll patient in WebDCU
- Stroke MRI performed

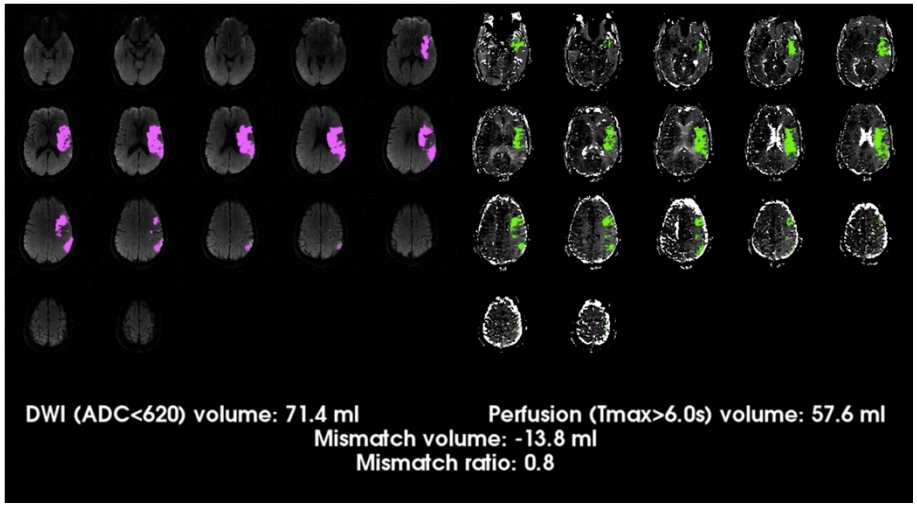
  DWI ASPECTS 6

  L MRA MCA occlusion

  MR perfusion performed (sent to RAPID; routine clinical perfusion processing)

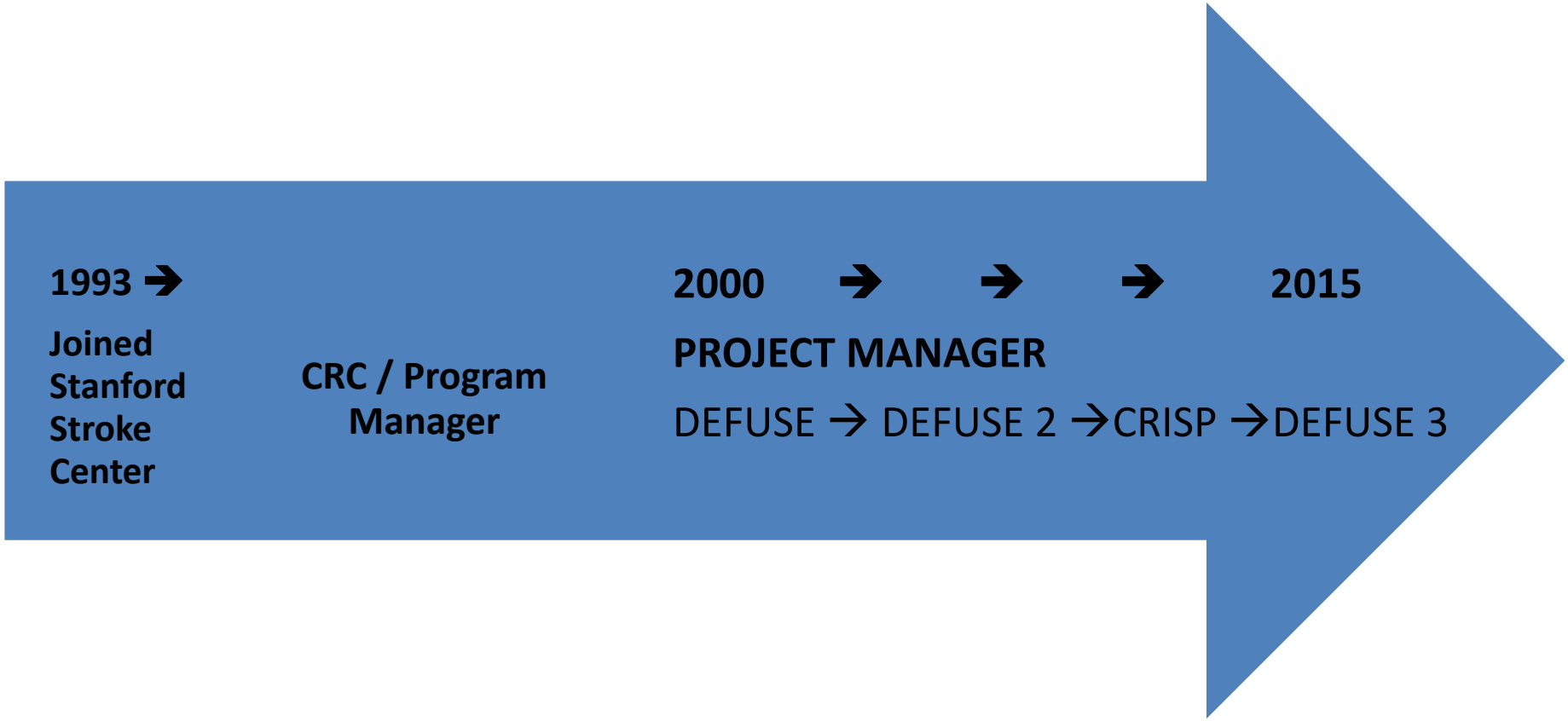
Review RAPID results

DO NOT randomize patient in WebDCU



Stephanie Kemp

DEFUSE 3 Project Manager


1993 →
Joined Stanford Stroke Center
CRC / Program Manager
2000 → → → 2015
PROJECT MANAGER
DEFUSE → DEFUSE 2 →CRISP →DEFUSE 3

What will I do for DEFUSE 3?

- Assist with the execution of Rapid License Agreements at Clinical Performing Sites
- Develop and provide the training for the clinical trial nurses/coordinators at the clinical sites.
- Perform site Initiation visits (on-site study orientation and training)
- Be available throughout the duration of the study, for nursing/coordinator questions related to the study

Judith Spilker

Project Manager (NCC)

NCC Project Manager Responsibilities

- trial-wide communication
- orchestration of required training activities with Stanford PM
- coordination of and assistance with site assessment and/or initiation visits with Stanford PM
- collection and review of trial related regulatory documents
- recruitment performance tracking and site performance analysis
- primary contact for sites for non-data entry issues
- Collaborates with **Contracts Manager at the NCC** to develop and execute a DEFUSE 3 Protocol Trial Agreement (PTA) for both network and non-network performance sites
- **The NCC financial analyst** to track and issue payments to all sites.

Documents to have in place prior to enrollment

- RAPID License agreement between iSchemaView and the Clinical Performance Site (October 2015 onward)

- Subaward from Stanford Univ. to the Univ. of Cincinnati to enable Protocol Trial Agreements (October – November 2015)

- Protocol Trial Agreements (PTAs) between the Univ. of Cincinnati (NCC) and the DEFUSE 3 Clinical Performance Sites or other institutions as defined in the MTA. (November – January for initial roll out)

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Regarding Per Patient Budgets

- This is a fixed fee per patient clinical trial.
  - Endovascular arm-$6307.40
  - Medical Management Arm $6,023.40

(Allocation of funds for specific trial tasks /costs can be used at the sites discretion)

- The budgets were set and approved by NINDS when the proposal went in and was awarded. **There is no extra money for additional overhead in the award**.

- The NIH StrokeNet used the 25 Regional Coordinating Center on-campus and off-campus rates. We calculated an average of both and averaged those two numbers to get the 42%.

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

Use of RAPID software in DEFUSE 3

- Each clinical performance site will run the perfusion data on their standard CT imaging software from manufacturer. These data are what is processed and read by their radiologist "**as standard of care**." Clinical performance sites can (*but are not required)* purchase the RAPID software which is an added software that further processes the perfusion data from their machine.

- In DEFUSE 3, the CTP data from the Clinical performance site imaging machine is separately routed through a research version of RAPID and then centrally to Stanford. Radiology physician staff at the site *never sees or reads* the RAPID CTP data. They can't use it clinically. No RAPID data goes back to the PACS system. RAPID data comes back to investigator only to make the enrollment decision.

- Thus, Clinical performance sites can not have CT perfusion be their **standard of care** using the research version of RAPID since they use/read their own clinical imaging perfusion data. There is no incentive or need to buy RAPID software to be used in DEFUSE 3 as standard of care.

CIRB Approvals –Parent and Children

Required Child site Documents Checklist
Local Site Context Sheet (study specific)-will be provided to sites and needs IRB review and input.
Site information sheet – as available in WebDCU™
FWA- verify most current version at NCC
Reliance Agreement
ePAS Assurance Statement - signed by site PI
Informed consent document - (complete unlocked sections of template)
HIPAA authorization language (in consent or provide if standalone)
Study Team Listing (key personnel) (Delegation of Authority Log) in WebDCU™
CIRB fCOI forms for study team- sites to enter into WebDCU
HSP training certification for study team-sites to enter into WebDCU
CV 's–Site PI / Site Co-PI
HIPAA training study team- sites to enter into WebDCU
Recruitment Materials-must be CIRB approved if site developed

1.Readiness Review-(2 week turn around) local review of Protocol and ICF template , insertion of local language into ICF(COI, injury compensation, contact information) and initiate local site ancillary reviews. Local site context form needs to be returned to CIRB.

2.Child site CIRB review and approval- may require contingencies to be addressed rapidly at the site. All approvals and ICFs stored on WebDCU.

3.Annual continuing review requiring site participation. CIRB minutes posted on WebDCU.

Clinical Performance Site startup… and Enrollment

- PPI site approval- resources (machines and people) to do the work are available
- Site PTAs and Licensing agreements are completed
- Child site readiness review , child submissions and approval
- Complete Regulatory document collection in WebDCU™
- The tools to train designated personnel are finalized and site training has taken place
- Electronic CRFs and database is ready to randomize and enroll
- RAPID technology is in place and operational

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

Avoid walking in a straight line and begin to process in Parallel.

- Know your institutional contracting requirements and contacts -find the road blocks and plan for them.
- Know your local IRB review requirements, work closely with them to meet turn around times. Written documentation of this review is required.
- Be open and ready for “site visits” and site training. Anticipate late 2015 or early 2016.

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Yuko Palesch

Principal Investigator: Data Management Center

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

National Data Management Center (NDMC)

MUSC Health

Medical University of South Carolina

Changing What's Possible

UNIVERSITY OF Cincinnati

NDMC Location

Medical University of South Carolina (MUSC)

↓

College of Medicine (COM)

Department of Public Health Sciences (DPHS)

Data Coordination Unit (DCU)

StrokeNet National Data Management Center (NDMC)

NDMC DEFUSE 3 Study Team

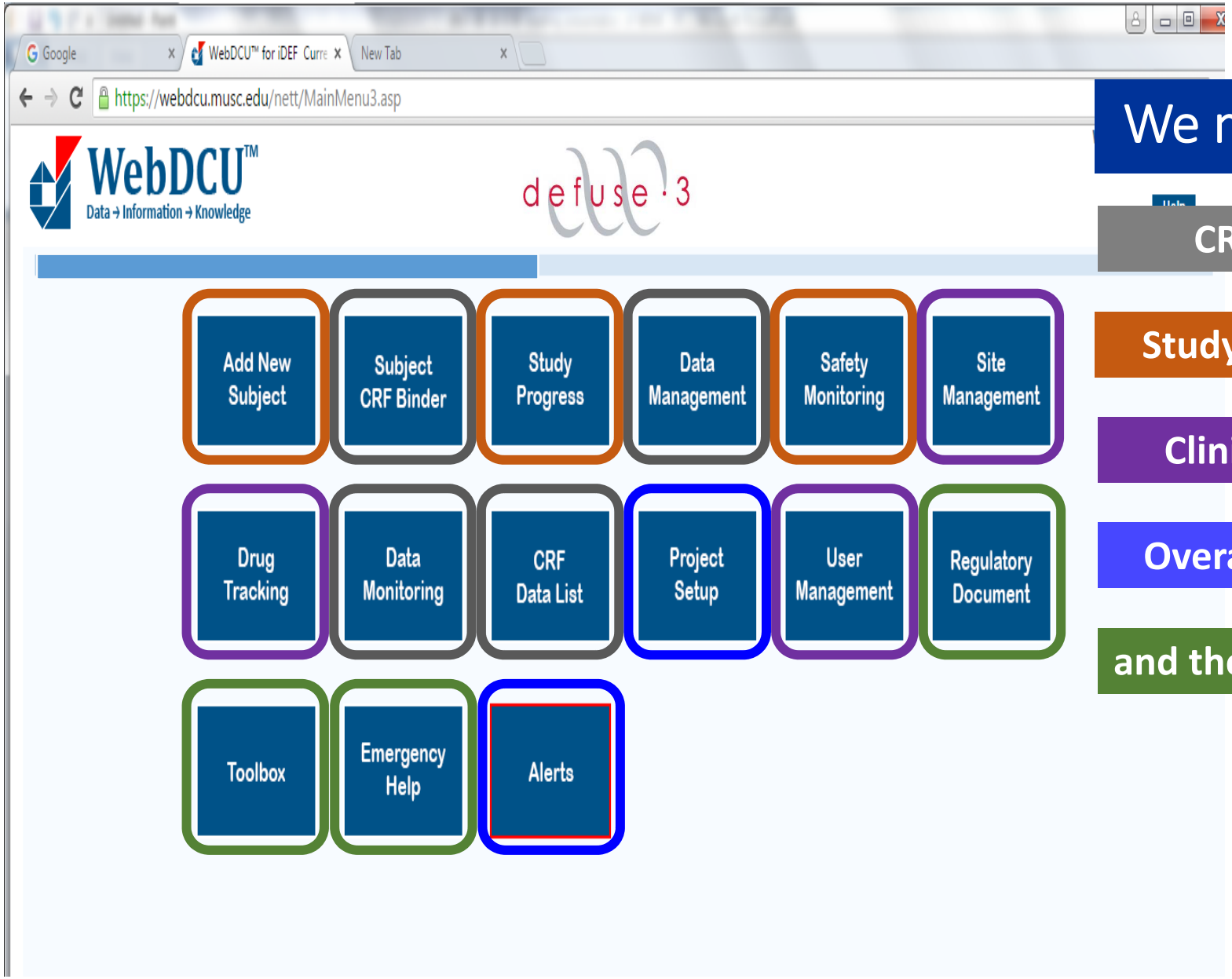
Sara Williams, Data Manager

TBD, Statistical Programmer

NDMC DEFUSE 3 Work Scope

- Pre-Implementation
  - Protocol, CRF, and SAP development
  - Study database setup in WebDCU™
  - Integration of randomization into WebDCU™
- Implementation
  - Data management and QA
  - Site Monitoring
  - Interim reports and analyses
  - Interaction with DSMB as unblinded statis
  - Represent NDMC on the DEFUSE-3 Exec Committee
- Post-Implementation
  - Database lock
  - Analyses and publications/presentations
  - Submission of Public Use Data Sets (PUDS)

WebDCU™ - A One-Stop Shop



We manage:

CRF Data

Study Subjects

Clinical Sites

Overall Project

and the StrokeNet

DEFUSE 3 Leadership

Stanford

Principal Investigator	Greg Albers
Co-Principal Investigator	Michael Marks
Protocol Director	Maarten Lansberg
Project manager	Stephanie Kemp
Blinded Statistician	Phil Lavori
Perfusion Imaging	Soren Christensen
Imaging Core Lab	Max Wintermark

National Coordinating Center

Principal Investigator	Joe Broderick
Project manager	Judy Spilker

Data Management Center

Principal Investigator	Yuko Palesch
Unblinded Statistician	Sharon Yeatts

Executive Committee / Endovascular Committee*

Greg Albers

Joe Broderick

Colin Derdyn*

Scott Hamilton

Stephanie Kemp

Maarten Lansberg

Helmi Lutsep

Michael Marks*

Claudia Moy

Yuko Palesch

Peter Rasmussen*

Wade Smith

Judy Spilker

Tom Tomsick*

Max Wintermark

Sharon Yeatts

Sam Zaidat*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