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Regulatory Challenges Associated with Endovascular Therapy Trials (EVT)

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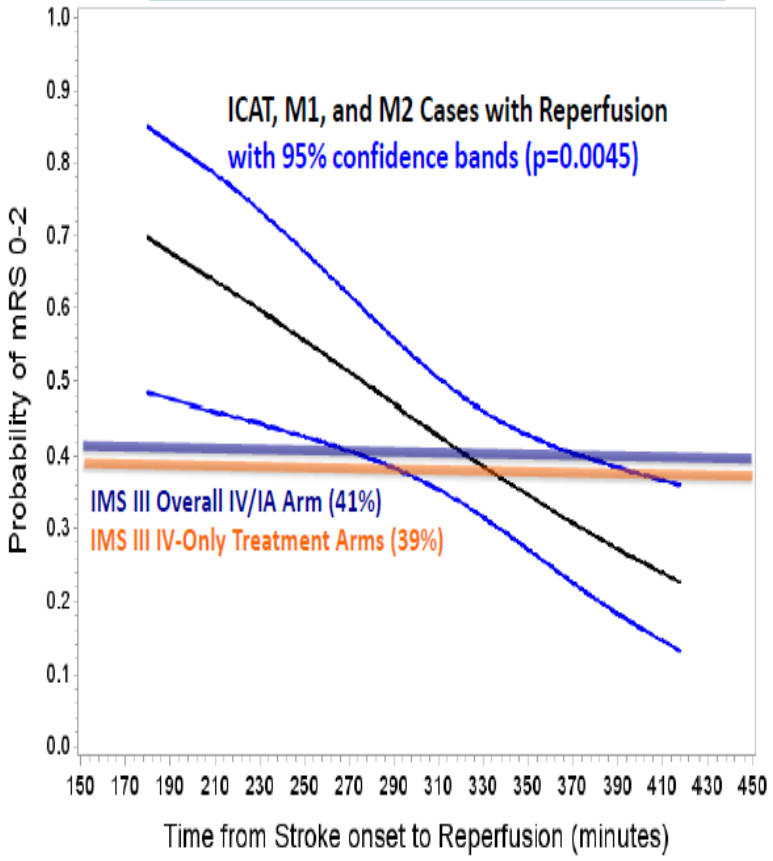
Time is the enemy!

IMS III Study



Would **faster transition from IV start to IA start** or **faster IA procedure times** have led to better outcome rates in the IV/IA arm of the IMS III?

Key Reasons for Delays in Treatment:

- Transfer to Comprehensive Facilities
- Imaging and Diagnosis
- Informed Consent

*presented at International Stroke Conference 2013

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Exemptions from informed consent requirements for emergency research: 21 CFR 50.24(a)

(1)
IRB approval w/ concurrence with a licensed physician,
Subject is in a life threatening situation,
Available treatments are unproven or unsatisfactory, and
Valid scientific evidence to determine S/E of an intervention

(2) Obtaining informed consent is not feasible:

I. Patient unable to consent due to medical condition
II. Intervention under investigation must be administered before from subjects' legal representative is feasible
III. No reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

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Exemptions from informed consent requirements for emergency research: 21 CFR 50.24(a)

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

I. Subjects are facing a life-threatening situation that necessitates intervention;
II. Animal and preclinical studies supports the potential direct benefit to the subject; and
III. Reasonable risk assessment associated with the investigational intervention, the subjects' medical condition, and risk / benefit of standard therapy

(4) Clinical investigations could not practicably be carried out without the waiver
(5) Investigation plan defines the length of the therapeutic and the investigator has committed to attempt to contact a legally authorized representative for each subject within the noted window; and this plan will be IRB approved.
(6) IRB approval for consenting procedures and the informed consent.

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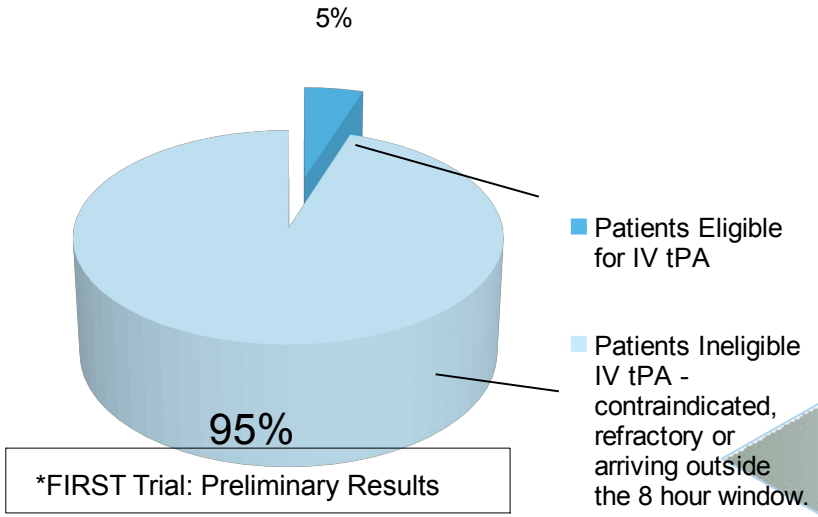
Study of “adjunctive” EVT benefit in tPA eligible/ treated patients



*FIRST Trial: Preliminary Results

Variation of tPA indication/ AHA recommendation

Limit “ labeling support” for an indication to only subjects treated with 3 hr time window

Request for demonstrable r-tPA failure (wait one hour) to assess “rapid neurological improvement” and create ‘equivalent populations’

Speed vs. Precision

“Please ensure subjects in both arms of the trial will complete the 1hr IV infusion of r-tPA and that the determination of ‘rapid neurological improvement’ will not occur prior to that point, and that randomization will follow that determination”

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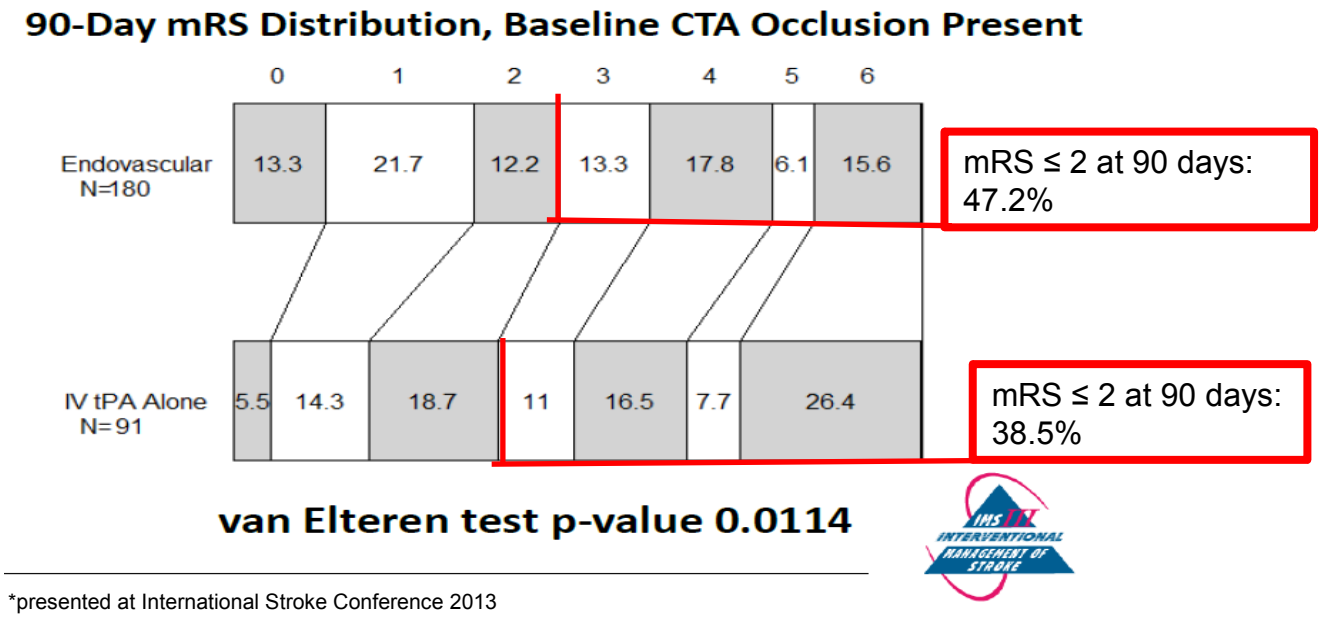
Patient Selection and Confirmation of Clot



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FDA Guidance for Neurothrombectomy Devices

- Enrollment of patients with evidence of a treatable occlusion, such as angiographic evidence of occlusion
- Exclude subjects with neurological signs that are rapidly improving at the time of randomization or treatment

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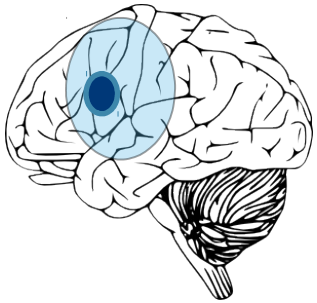
When does treatment begin in Stroke (tPA administration, best medical management, EVT)



Issue	FDA Comments	Guidance
Inability to clearly reconcile “time of treatment” between r-tPA and r-tPA +EVT	Time to measurement of 24-27 hour post treatment assessments will vary between treatment groups	Address the impact of this when comparing between the two groups

Need specific guidance on how the FDA wishes for key post-treatment assessments to be managed across varying types of treatments

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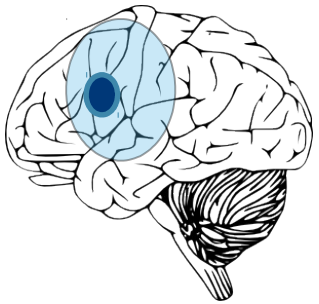
Imaging Selection and Triage of Stroke Patients



- In house vs. transfer (ship and drip)
  - NCCT vs. MRP vs. CTP
    - NCCT vs. MRP vs. CTP

Issue	FDA Comments	Guidance
SOC Imaging protocol is variable within centers	We cannot assume that subjects selected via different screening methodologies (CT vs. MR) will be equivalent at baseline	We recommend you incorporate poolability assessment for screening method (CT or MRI) into your safety design

Need specific guidance on how the FDA wishes for key imaging assessments conducted in the screening of subjects

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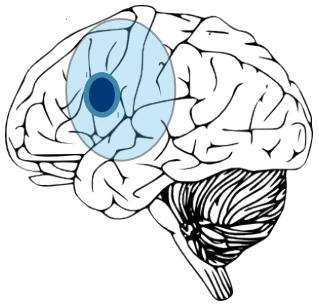
Imaging Selection and Triage of Stroke Patients



In house vs. transfer (ship and drip)

NCCT vs. MRP vs. CTP

NCCT vs. MRP vs. CTP

Issue	FDA Comments	Guidance
SOC Imaging protocol is variable within centers	Appears that timing of imaging to determine perfusion will differ between various types of centers	Plan to address the potential impact of this in your labeling application

Need specific guidance on how the FDA wishes for key imaging assessments conducted in the screening of subjects

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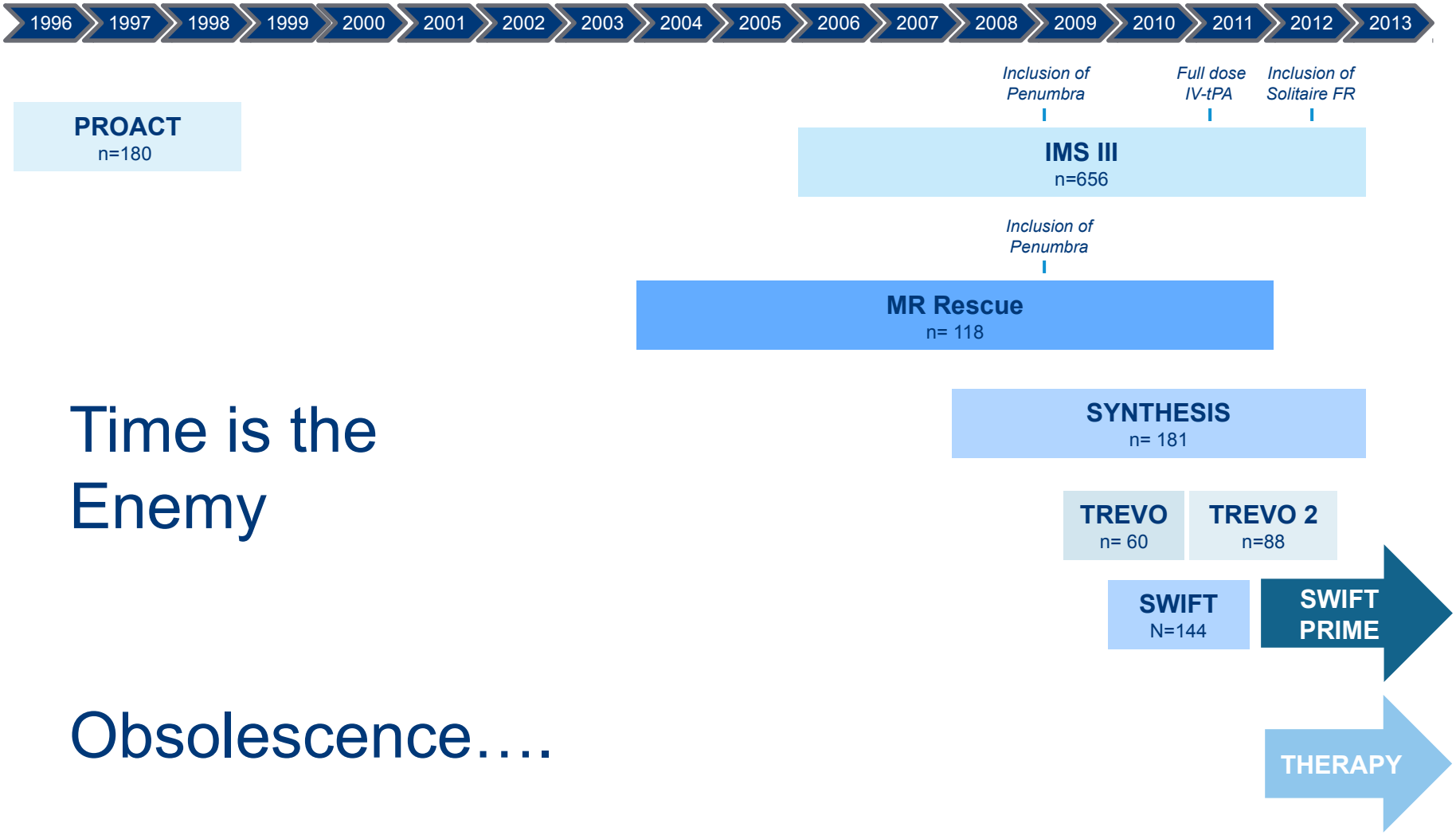
Key Intra-Arterial Stroke Studies



Time is the Enemy

Obsolescence….

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Thank You

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