



MISTIE – ICES Trial

Site Initiation


January 6, 2010
Supported by a grant from the
NIH/NINDS
Assisted by a donation of Cathflo® from
Genentech, Inc.
And a donation of surgical equipment from
Codman, Inc.
UCLA Surgical Center Supported by the
NINDS SPOTRIAS Program

Sites



<p>USA</p> <p>Bayview Medical Center University of Maryland Johns Hopkins University Loyola University Medical Center Medical University of South Carolina Montreal Neurological Institute at McGill University Mt. Sinai Medical Center New Jersey Neuroscience Institute at JFK Medical Center NorthShore University Health System St. Louis University Stanford University Mt. Sinai Medical Center Virginia Commonwealth University University of Cincinnati University of Maryland</p> <p>EUROPE</p> <p>Erlangen, DE Göttingen, DE Newcastle General Hospital, UK Technical University of Aachen, DE University of Cambridge, UK University of Heidelberg, DE</p>	<p>Baylor College of Medicine Bronson Hospital Duke University Medical Center Georgetown University Mayo Clinic, Jacksonville Rush University Sutter Neuroscience Medical Group St. Luke's Hospital Temple University University of Alabama at Birmingham University of Texas, San Antonio</p> <p>ICES</p> <p>Case Western Reserve Columbia Medical Center Fairfax INOVA, VA Massachusetts General Hospital University of Pittsburgh Thomas Jefferson University University of California, LA University of California, SF</p>
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Administrative Centers



- Surgical Review Center: Cincinnati
- CC and DMC: JHU
- Central Pharmacy: JHU Pharmacist
- Monitoring: Steve Mayo, Emissary, Inc
- EDC: Vision® Prelude Dynamics

Overview

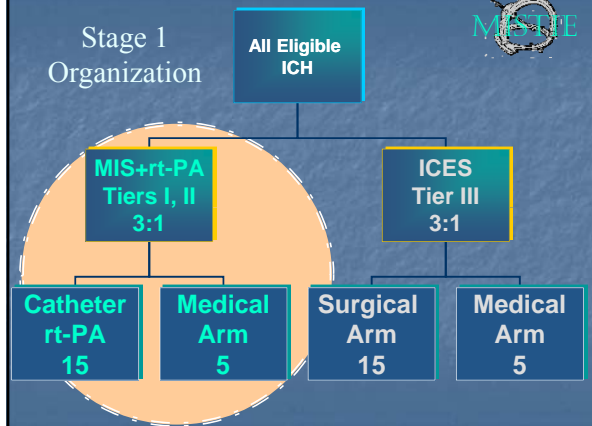


Phase IIa: safety and PK trial




- Version 6.1 (14 Oct 2008)
- Randomized
- Minimally Invasive Surgery plus rt-PA for ICH Evacuation vs. Best Medical Care

Stage 1 Organization




Stage 1



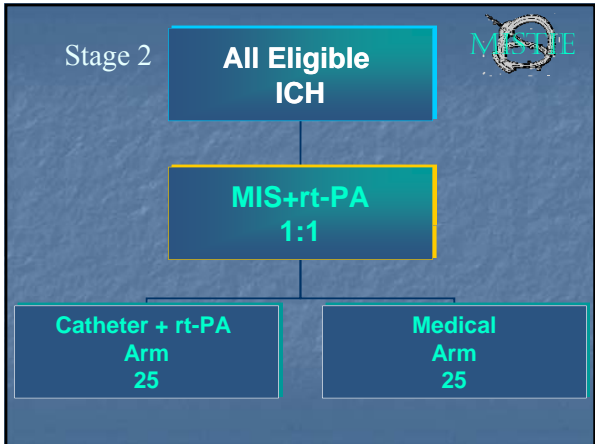
MISTIE: Tier I, II Dose Finding

- n=40
- 0.3 mg q 8 hrs completed May, 2008
- 1.0 mg q 8 hrs (8/20 enrolled)
- 3:1 randomization
- 30 surgical : 10 medical

Stage 2: Safety



- Safety (n=50)
 - 1:1 randomization
 - 25 MIS=rt-PA vs. 25 medical





Objective

- Use image-guided surgery (MRI or CT)
- One-time clot aspiration
- With tPA over 72 hours*
 - Test the safety of intervention
 - Assess ability to remove clot from brain tissue
 - Assess procedure as feasible and safe

*Cases include endpoint with aspiration only



Primary Endpoints

- Safety
 - 30-day mortality
 - Procedure-related mortality
 - Incidence of cerebritis, meningitis
 - Rate of rebleeding



Secondary Endpoints

- Preliminary Efficacy
 - Rate clot reduction at days 4-5, determined by CT scans, absolute clot size reduction at days 4-5
 - 90- & 180-day outcomes
 - Glasgow Outcome Scale (GOS)
 - Extended GOS (eGOS)
 - Modified Rankin Scale (mRS)
 - Stroke Impact Scale (SIS)
 - Post-operative size reduction



Inclusion/Exclusion Criteria



6.1 Inclusion Criteria

- Age 18-80
- GCS \leq 14 or NIHSS \geq 6
 - Including 12: distal hand movements
- Spontaneous supratentorial ICH \geq 20 cc
- Dx CT within 12 hrs of bleed (unknown time is exclusionary)
- Intention to initiate surgery 48° from Dx CT
- 1st dose w/in 54 hrs of Dx CT (maximum: hr 66 from bleed)



6.1 Inclusion Criteria

- SBP < 200 mmHg sustained for 6 hours closest to randomization
- Historical Rankin score of 0 or 1
- Negative pregnancy test

CT Inclusion Criteria


- Stability scan at least 6-hr post Dx CT; can be more
- ≤ 5 cc $(A*B*C)/2$ difference compared to Dx
- No new ICH
- No obstructive IVH requiring placement of an EVD to **manage** mass effect/hydro)

6.1 Exclusion Criteria


- Irreversible clotting disorders
- Platelet count $\leq 100,000$
- INR ≥ 1.7 , nonreversible
- Abnormal PT or aPTT
- Suspected internal bleeding

6.1 Exclusion Criteria


- Irreversible impaired brainstem function
 - Bilateral, fixed dilated pupils
 - Bilateral extensor motor posturing
 - GCS ≤ 4
- Unstable cranial mass or compartment syndrome

6.1 Exclusion Criteria 

- Infratentorial hemorrhage (i.e., brain stem, midbrain, cerebellar hematomas)
 - Radiographic
 - Complete third nerve palsy
- Suspected/untreated aneurysm or AVM (unless ruled out by angiogram or MRI/MRA)
- Internal bleeding, any system
- Lactating women

6.1 Exclusion Criteria 

- Uncontrolled bleeding
 - Puncture/access sites
 - venous cutdown
 - arterial puncture
 - recent surgical site

6.1 Exclusion Criteria 

- Mechanical valve
- Known risk for embolization
 - Left heart thrombus
 - Mitral stenosis with A-fib
 - Acute pericarditis
 - SBE

6.1 Exclusion Criteria



- Concurrent illness that would interfere with safety assessments/outcome follow-up
- Participation in another interventional trial
- Previous MISTIE patient
- Requiring specific surgical intervention other than the trial elements

Temporary Exclusion Screening



- Small clot: check again in 12-24 hrs
- No stability: check again in 12-24 hrs
- Abnormal laboratory values
- Uncontrolled BP
- INR: Reversal of coumadin permitted
 - Patient must not require coumadin during the acute hospitalization
- Coagulopathy
 - Patient must have a sustained INR < 1.7 using short- and long-acting pro-coagulants (NovoSeven, FFP, and/or vitamin K)

Randomization





Randomization

- Stratification 1st by clot size
 - Small: 20-40 cc ICH
 - Large: > 40 cc ICH
- Randomized to surgery or medical in blocks of 4
- Vision Database interactive
 - Enter size of ICH, I/E, whether a run-in or not
 - Assigns subject number, tier and randomization to surgery or medical treatment
- Day 1 = the date of Randomization (medical & surgical)



Protocol



Baseline Activities

	Screening	Pre Surgery
Diagnostic CT (SOC)	X	
Stability CT (6 hours after diagnostic CT)	X	
Blood pressure control sustained over a minimum of 6 hours prior to randomization	X	
Pregnancy test	X	
NIHSS	X	
Medical History/Review of Systems		X
Barthel Index		X
Modified Rankin		X

Visits, Dosing and Scans



	Day 1*	Day 2	Day 3
MRI /MRA (or CTA)	X		
MIS (Surgical Group Only)	X		
Place protocol catheter (Surgical Group Only)	X		
Post OP Review of Systems (Surgical Group Only)	X		
Post OP catheter placement CT scan (Surgical Group Only)	X		
Drug Administration 1* dose 3 hrs post op, then Q8H (Surgical Group Only)	X	X	X
Daily CT Scan		X	X

*Day 1 = date of randomization

Days 1 - 6



	Days 1-6
Daily Lab Assessments Days 1 – 6 Catheter Tip Culture Post Removal	X
Vital Signs Days 1-4: Hourly Days 5 & 6: Q4H	X
Hourly Neurochecks, TILS Days 1-4: Hourly Days 5 & 6: Q4H	X

Follow Up



	Day 4	Days 5 - 6	Day 7	Day 30	Day 90	Day 180
MRI/MRA (or CTA)			X			
Daily CT Scan	X			X		X
CT Post Catheter Removal or Surgery Done on Day 2		X				
Continue VS, Neurochecks, TIL	Hourly	Q4Hr	Q4Hr			

Therapy Intensity Level (TIL) key



0	None
S/P	Sedation/Paralysis
VD	Ventricular Drainage
M	Osmotherapy (Mannitol, etc.)
BP ↑	Blood Pressure Supportive Agent (pressors)
BP ↓	Anti-hypertensive agent
H	Aggressive Hyperventilation (PCO2 <30)
B	Barbiturate/Other Agents for Inducing Coma
SD	Surgical Decompression
F	Ventricular Catheter Flush

Run-In and Surgical Enrollment



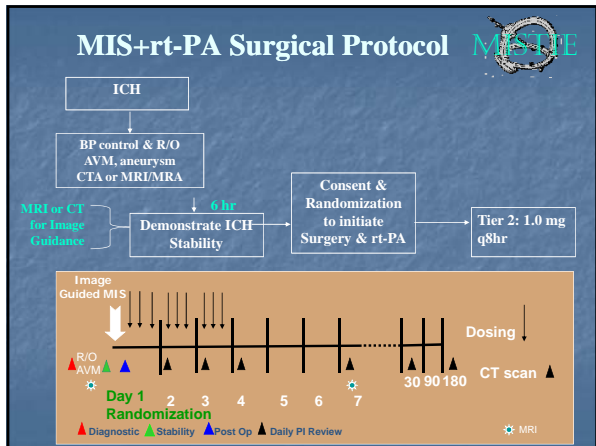
Blank area for notes related to Run-In and Surgical Enrollment.

Randomized to Surgery



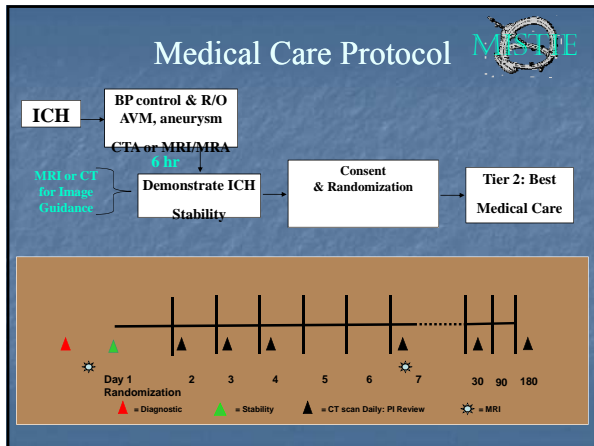
- Performed by certified neurosurgeon
- Performed in operating room preferred
- Use protocol-specified introducer and catheter
- Single aspiration with 10 ml syringe
- Antibiotic coverage

Blank area for notes related to Randomized to Surgery.



Medical Enrollment


- ## Medical Management
- Use standard ICU protocols, including
 - ICP management
 - Neurological status assessment
 - Cardiovascular management, goal BP \leq 160/90
 - Respiratory care
 - Nutritional support
 - Deep venous thrombophlebitis / pulmonary embolus prophylaxis
 - Withdrawal of care



- ### Medical Group Protocol MISTIE
- Parallels surgical group
 - CT scans daily, day 30, day 90
 - MRI baseline and Day 7
 - VS through Day 6
 - Lab assessments through Day 6
 - Hemocult Day 3
 - NIHSS Day 7
 - No PK


- ### Imaging Goals MISTIE
- Surgical goal:
 - Evaluate for clot stability
 - Primary aim of the trial: safety
 - Medical/surgical goal:
 - Quantitatively measure clot resolution
 - Secondary aims of the trial: efficacy
 - Imperative all subjects scanned Q24^o
 - Through day 4-5 depending on surgery on day 1 or day 2
 - Want 4 days of CTs

Drug Administration
Tier II




Pharmacy

- Janet Mighty, Study Pharmacist
 - Conducts one-on-one in-service with site pharmacist
- Prefer sterile hood in pharmacy



Training

- Pre-shipment
- Pharmacy Training includes
 - Shelf storage-reconstitution-syringe storage
 - Flush
 - Frozen or used within 8 hours at 41°
- Upon site activation, overnight to Rx



Packaging



- CathFlo® 2 mg vials (boxes of 6)
- Reconstituted with 2 ml sterile water
- 1 Vial = 2 injections
 - 1st syringe sent to floor with flush syringe
 - 2nd drug and flush refrigerated in pharmacy and delivered 7 hours later
 - Good for 8 hours unless frozen

Aseptic Technique




- Administered with sterile field and gown
- Administer port closest to head
- Most sites needle-less

Administration




- 1.0 ml CathFlo® (1.0mg/1ml) syringe
- 3.0 ml NS flush syringe
- = 4 ml total instilled
- Q 8 hrs x 72 hours
- Total daily dose = 3.0 mg
- Catheter closed to drainage 1 hour




Stopping Study Drug

- Surgical endpoints
 - Compared to stability CT scan
 - The ICH volume 10 cc
 - Or, 80% reduction
 - 9 doses of rt-PA unless ports not clot
- Treatment failure
 - Clinically significant rebleeding
 - Withdrawal from the trial would be in the patient's best interest
- The patient withdraws consent.



Catheters and Drainage



Catheter Management

- Avoid aspiration and irrigation
 - Exceptions:
 - PK sampling
 - Culture for suspected infection
 - Irrigation for catheter blockage
- Remove 24-36 hrs post last dose
- Get CT scan after removal

Study Specific Catheter



- Codman external drainage: Ventricular Catheter Set (Ref 82-1705)
- Drainage catheter close 1 hr after each dose
- Remove 24 and 36 hours post last dose
- Send catheter tip for culture
- Obtain CT post removal

Hourly ICH Catheter Data



- Intake
 - Total
 - Cumulative
- Output in the drainage bag
 - Total
 - Cumulative
- Catheter Maintenance
 - Catheter placed
 - Catheter open or closed
 - Catheter was removed.

Concomitant Medications



MISTIE

Permitted Medications

- For reversal of anticoagulation.
 - NovoSeven
 - DDAVP
 - FFP
 - Plasma concentrate
 - Vitamin K

MISTIE


Concomitant Drugs

- Not all medications collected
- Classifications
 - Antihypertensives – all classes
 - Anesthetics, sedatives, neuromuscular blockers
 - Anticoagulants, antiplatelets
 - Antihistamines
 - Mannitol
 - Barbiturates, benzodiazepines
 - Blood products
 - Antibiotics

MISTIE


Held Medications

- Until 72 Hrs
- Antithrombotics and antiplatelets
 - Antiplatelet agents
 - Low molecular weight (fractionated) heparin
 - Regular low dose heparin, 5,000 U SC BID (or sooner if medically necessary to treat a clinical symptom)




Held Medications

- Until Day 7
 - Urokinase
 - Retiplase
 - Desmetoplas
 - Systemic rt-PA



Held Medications

- Until Day 30
 - Anticoagulants used in stroke and pulmonary embolus prophylaxis
 - Warfarin
 - Heparin (full dose)
 - Thrombolytics



Prohibited for 12 Months

- Enoxaparin at HIGH therapeutic doses ≥ 1.0 mg/kg sc q12 h
- Subsequent DVT prophylaxis in the ICU at usual dose permitted
 - 30 mg sc q12 h
 - 40 mg sc QD



Laboratory Samples



Screening

- Toxicology (Urine and Serum)
- Pregnancy test



Local Daily Labs x 6 Days

- 2 light blue tubes
 - PT, PTT, INR, d-Dimer
 - Plasminogen, Fibrinogen
- 1 lavender tube
 - Hematology: WBC, HCT, platelet count
- Hemocult: Day 3 only

PK Samples



- Dose 1
 - Baseline = OR aspirate
 - 3 samples post dose (1hr, 3hrs, 7 hrs 50 min)
- Dose 4 (may perform at dose 3)
 - Prior to dose
 - 3 samples post dose (1hr, 3hrs, 7 hrs 50 min)
- Each sampling: fill 1 black and 1 blue vacutube
 - Prefer 2 cc per tube, 1 cc min
- Deliver within 10 min on ice for processing

Form number: 1.0000.07.000008 **MISTIE PK SAMPLING** Subject ID: _____

Date: _____ Time of Dose 1: _____

Aspirate Sample Schedule	Time (24 HR)	Total Aspirate Volume Collected (mL)	% PK Ingested (mL)	Flush Ingested (mL)	Length of Ingesting (from port to reach)	ICP (weight) or volume	Initials or Signature
Prior to Dose 1 (OR)							
Open Caliber 1 hr p.dose							
1 hour after Dose 1							
3 hours after Dose 1							
7 hours 50 minutes after Dose 1							

Date: _____ Time of Dose 4: _____

Aspirate Sample Schedule	Time (24 HR)	Aspirate Volume Collected (mL)	% PK Ingested (mL)	Flush Ingested (mL)	Length of Ingesting (from port to reach)	ICP (weight) or volume	Initials or Signature
Prior to Dose 4							
Open Caliber 1 hr p.dose							
1 hour after Dose 4							
3 hours after Dose 4							
7 hours 50 minutes after Dose 4							


COMMENTS: _____

PK Samples




- Prepared kits
 - 8 labeled packets per dose
 - Vacutubes (4 black, 4 blue)
 - Cryovials (4 for black, 4 for blue)
 - Lab requisition needed for in-house processing
- Batch ship Denise Rhoney, PharmD, WSU
- Include completed PK paper requisition (photocopy for your records)

Daily Monitoring




- Vital Signs, Neurochecks, and TILs

Vital Signs



- SBP, DBP
- HR
- T
- RR
- GCS (E,V,M)
- ICP if applicable
- Intubation if applicable

Therapy Intensity Level



<ul style="list-style-type: none"> ■ 0=None ■ S/P=Sedation/Paralysis ■ VD=Ventricular Drainage ■ M=Osmotherapy (Mannitol, etc.) ■ BP↑=Blood Pressure Supportive Agent (pressors) ■ BP↓=Anti-hypertensive agent 	<ul style="list-style-type: none"> ■ H=Aggressive Hyperventilation (PCO2 <30) ■ B=Barbiturate/Other Agents for Inducing Coma ■ SD=Surgical Decompression ■ F=Ventricular Catheter Flush
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Follow-Up



30 & 180 Days

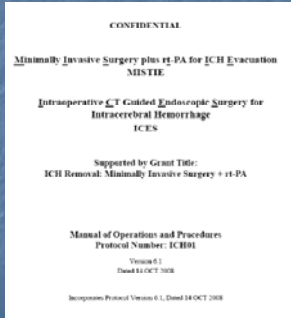
- NIHSS (certification required)
- mRankin (certification required)
- BI
- GOS
- eGOS
- Stroke Impact Scale



90 Day Phone Interview

- Modified Rankin Scale
- Barthel Index
- Glasgow Outcome Scale
- Extended GOS
- Stroke Impact Scale

Manual of Operations and Procedures



TOC



- Chapter 1.0: General Information
- Chapter 2.0: Organizational Structure and Personnel
- Chapter 3.0: Regulatory Documentation
- Chapter 4.0: Personnel Required, Duties, and Certification Requirements
- Chapter 5.0: Funding
- Chapter 6.0: **Logistics and Operations EVENT TABLE**
- Chapter 7.0 Screening, Enrollment, and Randomization
- Chapter 8.0: Clinical Trial Procedures
- Chapter 9.0: Pharmacokinetic Samples (Tiers 1 and 2 only)
- Chapter 10.0: Reporting and Data Submission

TOC



- Chapter 11.0 Special Reporting Procedures
- Chapter 12.0 Special Instructions
- Chapter 13.0 Detailed Protocol (version 6.1; dated 14 OCT 08)
- Chapter 14.0 Data Forms/Completion Instructions **VISION USER'S MANUAL**
- Chapter 15.0 Participating Centers Contact Information
- Chapter 16.0: **MISTIE Surgical Center**
- Chapter 17.0: MISTIE-ICES Surgical Center
- Chapter 18: Training
- Chapter 19: Test Article Shipping, Accountability, and Administration
- **PROTOCOL SUMMARY – 2 page summary for distribution**



Safety Reporting



Adverse Event

- Untoward medical occurrence that occurs during the protocol reporting period, regardless of whether it is considered related to the procedure



Reporting

- AE Coding Guide numerical codes
- Collect AEs through Day 6
- After Day 6
 - Neurological AEs
 - SAEs
 - Deaths
 - Reported directly into the Vision database



Outcome

- Resolved
- Ongoing
- Died



Causality

- Not related
- Possibly related
- Probably related
- Related



Additional SAEs

- Event (serious or not) resulting from a protocol deviation
- AE Coding Guide **yellow highlight**

AE Coding
Guide
TOC

AE Category	AE Description	AE Category	AE Description	AE Category	AE Description
1. Death	Death	11. Sudden Cardiac Death	Sudden Cardiac Death	21. Sudden Death	Sudden Death
2. Life-Threatening	Life-Threatening	12. Myocardial Infarction	Myocardial Infarction	22. Myocardial Infarction	Myocardial Infarction
3. Hospitalization	Hospitalization	13. Stroke	Stroke	23. Stroke	Stroke
4. Disability	Disability	14. Seizure	Seizure	24. Seizure	Seizure
5. Significant Change in Laboratory Values	Significant Change in Laboratory Values	15. Anaphylaxis	Anaphylaxis	25. Anaphylaxis	Anaphylaxis
6. Significant Change in Vital Signs	Significant Change in Vital Signs	16. Hypertension	Hypertension	26. Hypertension	Hypertension
7. Significant Change in ECG	Significant Change in ECG	17. Hypotension	Hypotension	27. Hypotension	Hypotension
8. Significant Change in Blood Chemistry	Significant Change in Blood Chemistry	18. Arrhythmia	Arrhythmia	28. Arrhythmia	Arrhythmia
9. Significant Change in Hematology	Significant Change in Hematology	19. Bradycardia	Bradycardia	29. Bradycardia	Bradycardia
10. Significant Change in Coagulation	Significant Change in Coagulation	20. Tachycardia	Tachycardia	30. Tachycardia	Tachycardia



Reporting


- Must complete db SAE screen within 24 hours of discovery
- Email sent to CC automatically
- Safety Monitor reviews case by case
- Reviewed by Medical Monitors, Endpoint Committees, DSMB and shared with sites as an annual report



Protocol Deviations



Protocol Deviations




- Major: Material departure from the protocol, particularly anything that affects the rights, safety, or welfare of the subject or the integrity of the data being collected
- Minor: Non-significant missing fields
 - Enter “not done”
 - Use comments fields to explain why not done

Enrollment and Consent



- Study-specific procedures performed before consent obtained
- Informed consent not obtained
- Consent process not documented
- Ineligible subject is enrolled
- Pregnancy test not done (women of child-bearing potential)

Surgery



- Performed by non-study surgeon
- Trajectory not matching ICH long axis
- Aspiration procedure not within protocol parameters
- No prophylactic antibiotics



Dosing

- First dose not within 54 hrs of diagnostic CT
- Missed doses of study medication (not delay per protocol/safety)
- Catheter manipulations too close to dosing
 - Manipulate then wait at least 3 hours before dose
 - Just gave a dose? Wait 12 hours to manipulate




ICU Care and Follow-up

- Phlebitis prophylaxis not utilized
- NIHSS performed by non-certified person



Documentation

 MISTIE

Source Documents

- Medical records
 - Hospital, laboratory, outpatient, radiology, OR, ED
- Worksheets required by coordinating center
- Print-outs
 - ECG, ICP, vital signs, electronic reports
- Pharmacy dispensing records

 MISTIE

Regulatory Documents

- Signed informed consent for each subject
- Signed agreement, protocol and amendments
- IRB approvals and stamped consent form
- FDA 1572


 MISTIE

Regulatory Documents

- CV, medical licenses
- Laboratory normal values
- Delegation of Responsibility log
- Recruitment Logs



Investigator Responsibilities



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MISTIE

INVESTIGATOR RESPONSIBILITIES

- Qualified by education, training, and experience
- Thoroughly familiar with n-PA and its use
- Aware of and comply with GCP/ICH
- Permit monitoring and auditing
- Maintain co-investigator list and authorization on delegated authority
- Able to recruit required number of subjects
- Have time to conduct and complete trial
- Maintain source documents
- Maintain trial documents
- Change or correct related data
- Conduct the trial in compliance with the protocol
- Report all serious adverse events
- Not implement any deviation without sponsor agreement
- Ascertain and report reasons for subject withdrawals prematurely
- Obtain IRB / Ethics Committee approval
- Provide documents to IRB / Ethics Committee during the trial
- Record all investigational related adverse events
- Inform institutions of trial completion and final reports

Read this date and signed:

Principal Investigator: _____ Date: _____



Investigator Responsibilities

- Take a minute to review 18 points
- Respond to Webinar poll
- Represents electronic signature
- Future electronic signature capability:
www.mistietrial.com

Surgical Center Review



- Suzanne Kempisty, RN
- Mario Zuccarello, MD
- U. Cincinnati
- 1st enrollment is surgical
 - Site activity suspended for review
 - Completed in real time
- Every surgical subject is reviewed

Monitoring



- Steve Mayo, Emissary
 - Remote monitoring every subject
 - Queries/edits directly on Vision database
 - Begins in real time during treatment period
- Site visits – as needed basis

Welcome Aboard
San Antonio and Mayo Jacksonville
Cambridge, Temple and Mt Sinai



We look forward to working with you

Coordinator Monthly Teleconference
1st Tuesday at 2 p.m.

Investigator Case Reviews
Morning Teleconferences 4/year
