MISTIE III
Hanley DF, et al.
Supplemental Appendix

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1. MISTIE III Investigators

1a. MISTIE III Core Investigative Teams

** Executive committee member*

Trial Leadership
Daniel F. Hanley*
Issam A. Awad*
Mario Zuccarello*
Wendy C. Ziai*
Scott Janis*
Paul Vespa*

Operations Leadership
Karen Lane*
Nichol McBee*
Steven W. Mayo*

Operations Management
Amanda J. Bistran-Hall
Tracey Economas
Krista Vermillion
Noeleen Ostapkovich
Bing Cao
Jennifer Houser
Jamie Braun
Myriha Wrencher

Surgical Centre
Agnieszka Stadnik
P. Lynn Money
Ying Cao
Sean Polster
Julian Carrion-Penagos

Statistical Core
Richard E. Thompson*
Michael Rosenblum
Carol B. Thompson*
Gayane Yenokyan*
Elizabeth Sugar*
Joshua F. Betz
Yi Hao
Radhika Avadhani
Rachel Dlugash
Jiajun Wen
Ying Wang

Quality Assurance Core
Steven W. Mayo*
Sarah Lenington
Nicki Karlen
Carolyn Koenig
Ryan Majkowski

Outcomes Core
Kennedy R. Lees*
Jesse Dawson
Alastair Wilson

Imaging Core
Dheeraj Gandhi
W. Andrew Mould
Natalie Ullman
Hasan Ali
Saman Nekoovaght-Tak
Vikram Madan
Alexandra Baker
Krissia Rivera Perla
Christina Grabarits
Nataly Montano Vargas
Zhiyuan (Alan) Yu
Yunke Li

Safety Core
J. Ricardo Carhuapoma
Carlos S. Kase*

Safety Event Committee
Wendy C. Ziai*
Tiffany Chang
Paul Camarata
Marc Malkoff
Jennifer Jaffe
Karin Jonczak
Noeleen Ostapkovich
Tracey Economas
Carolyn Koenig

Pharmacy Core
Janet Mighty
Esther Jeon

Regional Leadership
Craig S. Anderson
(Australia and Asia)
Weimin Wang
(China)
Jeanne S. Teitelbaum
(Canada)
Andreas Unterberg
(Germany)
Pal Barzo
(Hungary)
Sagi Harnof
(Israel)
Rosario Sarabia
(Spain)
Patrick Mitchell *(UK)*
A. David Mendelow* *(UK)*
Barbara Gregson* *(UK)*

DSMB
Colin P. Derdeyn (chair)
Kyra J. Becker
James C. Torner
Brian L. Hoh

MTI-M3
Wendy C. Ziai*
Paul Nyquist
Lauren Sansing
Joshua Goldstein
Adrian Parry-Jones

1b. MISTIE III Sites and Investigators (in order of highest enrolment)
*Site Principal Investigator

Site Name	Lead Neurosurgeon	Neurointensivist/ Other Principal Investigator	Study Coordinator	Number of Subjects Enrolled
University of Texas, San Antonio	Jean-Louis Caron*		Esther E. Nanez	24
University of Alabama at Birmingham	Mark Harrigan*	David Miller	Lisa Nelson	21
University of New Mexico	Andrew Carlson*	Huy Tran	Amal Alchbli	16
University of Southampton	Diederik Bulters*	Mary Leigh Gelea	Jisha Jacob	15
NorthShore University Hospital	Salvatore Insinga	David LeDoux*	Orseola Arapi	14
University of Cincinnati	Mario Zuccarello*	Krishna K. Mohan	Lynn Money	14
Johns Hopkins University	Judy Huang	Wendy Ziai*	Mirinda Anderson White	13
Mercy San Juan Medical Center	Cully Cobb	Alex Nee*	Danielle Hornbuckle	13
Rutgers University	Gaurav Gupta	Igor Rybinnik*	Michelle Moccio	13
University of Texas, Houston	Ryan Kitagawa	Tiffany Chang*	Glenda L. Torres	12
Washington University	Michael Chicoine	Michael Diringer*	Michelle Allen	12
Salford Royal Hospital	Hiren Patel*		Victoria O'Loughlin	11
Stanford University Medical Center	Robert Dodd	Chitra Venkatasubramanian*	Rosita Thiessen	11
Kansas University Medical Center	Paul Camarata*	Michael Abraham	Jason Gorup	10
Wake Forest Baptist Health	Stacey Wolfe*	Kristi Tucker	Wendy Jenkins	10
Albert Einstein College of Medicine	David Altschul	Rishi Malhorta*	Kaitlin Dyroff	9
Maine Medical Center	Robert Ecker	David B. Seder*	Barbara McCrum	9
Saint Luke's Hospital of Kansas City	Darren Lovick*		Bridget Brion and Kelsey Titus	9
Thomas Jefferson University Hospital	Jack Jallo*	Fred Rincon	Laura Boyden and Jaime Dougherty	9
University of Pittsburgh	Brian Jankowitz*	Ashutosh Jadhav	Patricia Feineigle	9
Medical University of South Carolina	Alejandro Spiotta*	Julio Chalela	Adrian Parker and Steve Shapiro	8
Southwest Hospital of The Third Military Medical University	Rong Hu	Yi Huang/Hua Feng*	Jin Liu	8
University of Michigan	Gregory Thompson	Ventatakrishna Rajajee/Aditya Pandey*	Ron Ball	8
University of Pécs	Andras Buki*	Erzsebet Ezer	Péter Csécsei	8
University of Texas Southwestern Medical Center	Louis (Tony) Whitworth*	Christiana Hall	Katrina Van de Bruinhorst, Cecilia Hernandez, and Deanna Myer	7
Intermountain Neurosciences Institute	Joel MacDonald	Kathrine Thomas/Robert Hoesch*	Jeffrey Turner and Jacki Anderson	7
Northwestern University	Babak S. Jahromi*	Matthew B. Maas	Byron Yip and Christina Amidei	7
The Chaim Sheba Medical Center at Tel Hashomer	Lior Ungar*/Sagi Harnof*	Ahmed Maswadeh	Zehorit Tzfira	7
Duke University Medical Center	Ali Zomorodi	Michael James*	Erlinda Yeh	6
Barrow Neurological Institute	Peter Nakaji*	Shawn E. Wright	Norissa Honea	6
Weill Cornell Medical College	Jared Knopman	Halinder Mangat/Dana Leifer*	Erica Eber and Ryna Mathias	6
Henry Ford Health System	Donald Seyfried	Panos Varelas/Mohammed Rehman*	Kathleen Mays-Wilson and Janet Kandrevas	6
Inova Fairfax Hospital	James Leiphart*		Swathi Ramesh and Tricia Brennan	6
Miami Valley Hospital	Ania Pollack	John Terry*	Angela Shoen	6
Rush University Medical Center	Lorenzo Muñoz	George Lopez*	Rebecca Holtz	6
University of Wisconsin	Azam Ahmed*	Joshua Medow	Stephanie Wilbrand	6
University of Maryland School of Medicine	E. Francois Aldrich*		Kaitlyn Henry and Charlene Aldrich	6
Abington Hospital – Jefferson Health	Steven J. Barrer	Larami MacKenzie*	Karin Jonczak and Patricia Bussinger	5

Site Name	Lead Neurosurgeon	Neurointensivist/ Other Principal Investigator	Study Coordinator	Number of Subjects Enrolled
Hospital Universitari de Bellvitge	Alberto Torres Díaz*	Luisa Corral	Meritxell Santos	5
Hospital Universitario Cruces	Alejandro Carrasco Gonzalez*	Gonzalo Tamayo	Jone Iglesias and Inigo Cristobal Pomposo Gastelu	5
Hennepin County Medical Center	Walter Galicich	Thomas Bergman*	Kathryn France	5
Newcastle Royal Victoria Infirmary	Patrick Mitchell*		Valerie Hogg	5
Scripps Health	Jeffrey Schweitzer*	Scott McCaul	Kathryn Schaffer	5
University at Buffalo Neurosurgery / Kaleida Health	Jason Davies*	Eugene Gu	Mary Hartney	5
University of Chicago Medical Center	Issam Awad	Agnieszka Ardelt*	Agnieszka Stadnik	5
University of Illinois at Chicago	Sepideh Amin-Hanjani*	Fernando Testai	Maureen Hillmann	5
University of Szeged	Pal Barzo*	Krisztian Tanczos	Eniko Fako	5
Yale University	Charles Matouk	Kevin Sheth/Lauren Sansing*	Kimberly Kunze, David Mampre, Sara Jasak	5
Loyola University Chicago	Doug Anderson	Michael Schneck*	Katelynn Bragg, Tara Bernier-Lynch	4
McMaster University	Kesava Reddy*	Draga Jichici	Paula Carroll	4
NorthShore University HealthSystem – Evanston Hospital	Shakeel Chowdhry*	Steven Greenberg	Robert "Bob" Frech	4
Hospital Universitario Río Hortega de Valladolid	Rosario Sarabia*	Pedro Enriquez	Ignacio Arrese	4
Universitätsklinik Bonn	Azize Boström	Hartmut Vatter*	Azize Boström	4
University of Utah Hospital	Philipp Taussky	Safdar Ansari*	Crystal Neate, Julie Kay Martinez, Joshua Letsinger, Lilly Fagatele, Carol Eaquinto	4
Vanderbilt University Medical Center	Matthew Fusco*	Avinash Kumar	Joy Grabenstein, Matthew Warrick, Dima Sbenaty	4
Banner – University Medical Center Phoenix	Byron Willis	Douglas Franz*	Lisa Apolinar, Sherril Bierman, Stephanie Blythe	3
Hospital Universitari MútuaTerrassa	Carlos Alarcon Alba*	Baltasar Sanchez	Monica Buxeda, Gloria Tresserras Gine	3
State University of New York, Upstate Medical University	Satish Krishnamurthy	Julius Gene Latorre*	Iulia Movileanu, Mark Villwock	3
University of Alberta	Cian O'Kelly*	Peter Brindley	Leka Sivakumar	3
University of California, Los Angeles	Nader Pouratian	Paul Vespa*	Courtney Real, Elisa Yam, Susana Martinez	3
University of Debrecen	Geza Mezey	Katalin Szabo/Laszlo Csiba*	Katalin Szabo	3
Johannes Gutenberg-Universität Mainz	Naureen Keric	Thomas Kerz*	Thomas Kerz	3
University of Virginia Medical Center Hospital	Dennis Vollmer*	Daryl Gress	Jenny De Jong, Johanna Loomba	3
Virginia Commonwealth University	William C. Broaddus*		Kelly W. Mathern	3
Hospital Universitari Vall d'Hebron, Barcelona	Fuat Arikan*	Marcelino Baguena	Mireia Sanchis	3
Mayo Clinic, Jacksonville	Ronald Reimer*	W. David Freeman	Cristin Williams, Emily Edwards	2
Providence Brain and Spine Institute	David Antezana*	Lisa Yanase	Darren Larsen, Monica Rodriguez, Courtney Zerizef	2
Royal Prince Alfred Hospital	Ben Jonker	Craig Anderson*	Kylie Tastula	2
Hospital de la Santa Creu i Sant Pau, Barcelona	Fernando Muñoz Hernandez*	Indalecio Moran Chorro	Rebeca Marin	2
University of Louisville	Robert F. James*		Ann Jerde	2
Bayi Brain Hospital, Beijing Military General Hospital	Yongge Xu*	Yan Wang	Ming Liang	1
Guangzhou First People's Hospital	Jinbiao Luo*	Xuxia Yi	Xuxia Yi	1
Gwinnett Medical Center	Michael Stechison*	Arun Lakhanpal	Marsha Headlee	1
Hartford Hospital	Inam Kureshi*	Robert Brown	Laura Grenier, Sara Jasak	1
Royal Adelaide Hospital	Amal Abou-Hamden*		Aye Aye Gyi	1
Royal Melbourne Hospital	John Laidlaw*		David Jackson	1

Site Name	Lead Neurosurgeon	Neurointensivist/ Other Principal Investigator	Study Coordinator	Number of Subjects Enrolled
South Glasgow University Hospital	Roddy O'Kane*	Keith Muir	Angela Welch	1
University of Munich-Klinikum Munich Bogenhausen	David Schul	Ludwig Schuerer/Christianto Lumenta*	Barbara Kraus	1
Hospital Universitario 12 de Octubre	Alfonso Lagares Gómez-Abascal*	Juan Carlos Montejo	Pilar Ortiz Heras	
Bronson Methodist Hospital-Bronson Healthcare	Alain Fabi	Jeffrey Fletcher*	Kelly Rogers	
Carolinas Medical Center	Joe D. Bernard, Jr.	Jason Todd*	Megan Kramer	
Cedars-Sinai Medical Center	Michael Alexander*	Wengui Yu	Vicki Manoukian	
Crouse Hospital	Eric Deshaies*	Adham Kamel	Kimberly A. Kasprowicz-Shoepe	
General Hospital of Guangzhou Military Command	Weimin Wang*	Gaoquan Luo	Luihuan Zhang	
The First Hospital of Jilin University	Yunbao Guo	He Li/Kan Xu*	Yuhao Zhao	
John Muir Health	Terence Chen	Oana Spataru/Ray Stephens*	Parveen Sra and Sheila Marquez	
Froedtert & the Medical College of Wisconsin	Wade Mueller	Osama Zaidat/Ann Helms*	Tracy Larson	
Montreal Neurological Institute and Hospital – McGill University	Denis Sirhan*	Jeanne Teitelbaum	Angela Moore	
Mount Sinai Hospital	J. Mocco*	Errol Gordon	Denise Balili	
New Jersey Neuroscience Institute at JFK Medical Center	Thomas C. Steineke	Jawad Kirmani/Mohammad Moussavi*	Briana DeCarvalho	
National Neuroscience Institute	Nicolas Kon Kam King	Vincent Ng Yew Poh*	Joshua de Souza	
National University Hospital	Yeo Tseng Tsai	Sien Lwin*	Mya Aye Nyein	
Navy General Hospital	Zengmin Tian*	Weigang Ni	Rui Hui	
The Ohio State University Wexner Medical Center	Ciaran Powers	Michel Torbey*	Areej Tariq	
Rabin Medical Center	Sagi Harnof*	Georgio Rubin	Ilit Ovadia	
Rambam Medical Center	Moshe Attia	Eugenia Mahamid/Manashe Zaaroor*	Leon Levi	
The General Hospital of Shenyang Military Region	Yingqun Tao*	Dandan Gao	Youqian Zhang	
Springfield Neurological and Spine Institute	Mark Crabtree*		Jessica Ratcliff	
St. Anthony's Medical Center	Fangxiang Chen*	Maheen Malik	Carol J. Mechem	
Sutter East Bay Neuroscience Institute	Lawrence D. Dickinson*	David Bonovich	Catherine Ndungu-Case	
Tangdu Hospital, Fourth Military Medical University	Lihong Li*	Min Li	Min Li	
Temple University School of Medicine	Joseph Queenan*		Kathleen Hatala and Lijo Chandy	
University of California, San Diego	Alexander A. Khalessi*	Navaz Karanjia	Brittney Miller	
Heidelberg University Hospital	Frederik Enders	Andreas Unterberg*	Julia Mattern-Tremper	
University of Tuebingen	Martin Schuhmann	Sven Poli*	Julia Zeller	

2. Methods

2a. Eligibility Criteria (from Protocol v4.0):

Inclusion Criteria

1. Spontaneous supratentorial ICH ≥30 mL measured by the site utilising ABC/2 method using radiographic imaging (CT, CTA, etc.), with a GCS ≤14 or a NIHSS ≥6.
2. Stability CT scan done at least 6 hours after diagnostic CT showing clot stability (growth <5 mL as measured by ABC/2 method).

   If the clot volume measured on this stability CT scan increases by 5 mL or more, a second stability determination is allowed by repeat CT scan at least 12 hours later. Additional scans are permitted as needed every 12 hours to continue to monitor for stability up until the eligibility time window closes. Subsequent clot retraction remains inclusionary as long as the ICH clot size remains ≥25 mL.
3. Symptoms less than 24 hours prior to diagnostic CT (dCT) scan. An unknown time of onset is exclusionary. Use the time the patient was last known to be well for patients that awaken from sleep with symptoms.
4. Ability to randomise between 12 and 72 hours after dCT.
5. SBP <180 mm Hg sustained for six hours recorded closest to the time of randomisation.
6. Historical Rankin score of 0 or 1.
7. Age ≥18 and older.

Exclusion Criteria

1. Infratentorial haemorrhage.
2. Ruptured aneurysm, arteriovenous malformation (AVM), vascular anomaly, Moyamoya disease, haemorrhagic conversion of an ischemic infarct, recurrence of a recent (<1 year) haemorrhage, diagnosed with radiographic imaging.
3. Patients with unstable mass or evolving intracranial compartment syndrome.
4. Irreversible impaired brain stem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS ≤4.
5. Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and non-reactive pupils. Other (supranuclear) gaze abnormalities are not exclusions. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible.
6. Intraventricular haemorrhage requiring treatment for IVH-related (casting) mass effect or shift due to trapped ventricle. EVD to treat ICP is allowed.
7. Platelet count <100,000; INR >1.4.
8. Any irreversible coagulopathy or known clotting disorder.
9. Inability to sustain INR ≤1.4 using short- and long-acting procoagulants (such as but not limited to NovoSeven, FFP, and/or vitamin K).
10. Subjects requiring long-term anti-coagulation are excluded. Reversal of anti-coagulation is permitted for medically stable patients who can realistically tolerate the short term risk of reversal. Patient must not require Coumadin (anticoagulation) during the first 30 days, and normalised coagulation parameters must be demonstrated, monitored closely, and maintained during the period of brain instrumentation.
11. Use of dabigatran, apixaban, and/or rivaroxaban (or a similar medication from the similar medication class) prior to symptom onset.
12. Internal bleeding involving retroperitoneal, gastrointestinal, or genitourinary site or respiratory tract bleeding.
13. Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures, etc.) or site of recent surgical intervention.
14. Positive urine or serum pregnancy test in pre-menopausal female subjects without a documented history of surgical sterilisation.
15. Allergy/sensitivity to rt-PA.
16. Prior enrolment in the study.

17. Participation in a concurrent interventional medical investigation or clinical trial. Patients in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
18. Not expected to survive to the day 365 visit or are made DNR/DNI status prior to randomisation.
19. Any concurrent serious illness that would interfere with the outcome assessments including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrine, immunologic, and hematologic disease.
20. Patients with a mechanical heart valve. Presence of bio-prosthetic valve(s) is permitted.
21. Known risk for embolisation, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis. Atrial fibrillation without mitral stenosis is permitted.
22. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated.
23. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
24. In the investigator's opinion, the patient is unstable and would benefit from a specific intervention rather than supportive care plus or minus MIS+rt-PA removal of the ICH.
25. Inability or unwillingness of subject or legal guardian/representative to give written informed consent.

2b. Medical Management Protocol

Subjects in both groups, medical management and MISTIE/surgical management, will be treated medically using standard ICU protocols. This includes but is not limited to the following guidelines:

1. Intracranial pressure (ICP) management. Placement of an ICP monitor is recommended for subjects demonstrating obtundation, defined as GCS ≤8 on a minimum of two observations over 8 h. ICP monitoring device selection is at the discretion of the treating surgeon; however, the Camino parenchymal catheter has been pre-specified as the device of choice for the trial. The non-emergent ICP monitor would ideally be placed prior to alteplase administrations or at least 6 h after dosing. A new CT scan must be obtained after ICP monitor placement to assess stability of the current haemorrhage and to monitor for any new bleeding. If ICP is monitored, nursing assessments and ICP monitoring will be performed every 4 h, as will routine zeroing and recalibration of the system if needed. The goals of ICP management are to sustain intracranial pressure below 20 mm Hg and to improve the patient's level of consciousness.

2. Neurological status will be assessed every 4 h using GCS scoring. A neurological deterioration (neuro-worsening) is defined as any GCS decrease of greater than 2 points on the motor scale sustained for 8 h without sedation and is required to be reported as an adverse event (AE)/serious AE (SAE). Daily attempts will be made to discontinue sedation. A daily neurologic exam is recommended to be coordinated with this attempted sedation withdrawal.

3. Cardiovascular management. The patient's blood pressure must be stable to be eligible for randomisation. Blood pressure stability is defined as SBP <180 mm Hg for a period of 6 h. This 6 h period must be maintained and documented as close to but prior to randomisation as possible. Blood pressure management should conform to 2010 American Heart Association (AHA) guidelines to maintain SBP <180 mm Hg throughout the first 6 days of the ICU stay to reduce the risk of bleeding events. The systolic and diastolic pressures over the 6 h monitoring period should be documented in the medical record as source documentation.

4. Respiratory care will be directed at promoting adequate oxygenation without airway compromise, with full pulmonary inflation, and with oxygenation ≥90% on room air or supplemental O_2 by face mask of 28% or less.

5. Nutritional support will consist of optimal calories, defined as ≥30 kcal/kg and 1.5 gm protein/kg. Feeding will be achieved by the least invasive means necessary, but with the goal of reaching full nutritional support by no later than day 7 of illness.

6. Deep venous thrombophlebitis and pulmonary embolus prophylaxis will be undertaken on the day of admission with the use of sequential compression devices. For patients at high risk of thromboembolism, study center standard of care policies may govern the use of low molecular weight, fractionated, and unfractionated heparins for DVT prophylaxis during the acute treatment and follow-up periods (criteria established by the American Orthopedic Association).

7. Withdrawal of life support. Discussions of prognosis and decisions to continue, limit, or withdraw life-sustaining interventions will be conducted according to each institution's policies for end-of-life decision-making, as well as their institutional codes of medical

ethics. The study assumes any such discussion will reflect the patient's wishes and the known facts regarding prognosis. Where the principal investigator is not the managing physician, it is assumed that those individuals will confer prior to presentation of the consensus prognosis and planned course of treatment. In some situations, the investigator may choose to select a colleague to serve in the clinician role or request a review by the hospital's ethics committee or other knowledgeable expert.

Relevant AHA Guidelines[1]
1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 minutes.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure ≥60 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is no evidence of elevated ICP, then consider a modest reduction of BP (e.g. MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP, and clinically reexamine the patient every 15 minutes.

2c. Surgical Centre Oversight, Mentoring, and Qualification of MISTIE Surgeons

Joint review of MISTIE cases with the site surgeon and the surgical centre consisted of reviewing enrolment criteria and safety aspects prior to surgical intervention with the MISTIE procedure. All surgical centre reviews were performed by IAA, MZ, DH, or a backup surgeon. This consisted of reviewing the initial CT imaging and the subsequent stability imaging. Each surgical step was fully outlined in the Manual of Procedures chapter 8. Haematomas were classified by the surgical centre into one of three categories (anterior, posterior, or lobar), which dictated the trajectory to be used for initial catheter placement, determined by the site surgeon. Surgeons would then utilise the agreed-upon skull entry point and predefined trajectory to target the middle 2/3 of the longest axis of the haematoma. After catheter placement and aspiration were completed, a post-operative CT scan would confirm the placement of the catheter, which would be graded by the surgical centre into one of three categories (good, suboptimal, or poor). Catheter placement was graded as poor if the majority of the catheter's perforations were outside of the clot, thus not suitable for dosing. Suboptimal grading included eccentric placement of the catheter, but with all perforations engaging the clot, thus suitable for dosing. Good placement included all catheter perforations engaging the centre of the clot. Catheters which were poor would require repositioning before the surgical centre would clear the site to administer alteplase.

Surgeons were categorised based on their experience with the technique at the time of performance of the surgical task as (1) prequalified, (2) qualified with probation, and (3) fully qualified. Prequalified surgeons are fully trained neurosurgeons who have performed at least 3 image-guided or stereotactic catheter aspiration or placement procedures outside MISTIE and completed the MISTIE surgical training modules. Surgeons are promoted to "qualified with probation" or "fully qualified" after successfully performing the MISTIE procedure on up to 3 cases, or more than 3 cases, respectively. For each successive MISTIE procedure, prequalified surgeons were mentored by a fully qualified trial surgeon on site, or by telephone or internet, with the mentor reviewing the steps of the procedure and answering any technical questions that might arise. Details of the surgical centre protocol are outlined in the midpoint analysis of MISTIE III surgical performance by Fam et al.[2]

2d. Central Adjudication of Rankin Scale (CARS) Assessments

Adjudicated modified Rankin scale (mRS) scores were assigned using the Central Adjudication of Rankin Scale assessments (CARS) system based at the University of Glasgow. This has been described in full,[3] but briefly, mRS assessments performed at site were recorded on a digital camera and uploaded to a secure portal at the University of Glasgow. Assessments were then centrally reviewed for technical adequacy, translated into English language if needed, and then scored by a trained and blinded assessor. If this blinded score agreed with the local site score, this final common score was assigned.

Agreement was assessed automatically by the trial management after entry of the blinded score, and neither the local nor blinded central assessor knew the other's score. Where there was disagreement, the assessment was viewed by four trained and blinded assessors. If all four scores agreed, this common score was assigned. Where there was disagreement among these four scores, this was discussed in committee and a consensus score assigned.

All local and central reviewers were certified in use of the mRS.

CARS Staff

Adjudicators:
Jen Alexander (Queen Elizabeth University Hospital Glasgow, UK), Jesse Dawson (University of Glasgow, UK), Kennedy Lees (University of Glasgow, UK), Kate McArthur (University of Glasgow, UK), Terry Quinn (University of Glasgow, UK), Matthew

Walters (University of Glasgow, UK), Alastair Wilson (University of Glasgow, UK), Azmil Abdul-Rahim (University of Glasgow, UK)

Translators:
Nora Gonzalez (University of Glasgow, UK), Kerrick Hesse (University of Glasgow, UK), Nicki Karlen (Emissary LLC, Israel), Kitti Kovacs (University of Debrecen, Hungary), Annick Wyss (University of Glasgow, UK), Yuhua Fan (Sun Yat-sen University, China), Jennifer Reick (University of Edinburgh, UK), Zhiyuan Yu (Johns Hopkins University, USA)

Acknowledgments
We thank all the outcomes assessors and translators who work across our various trials. The initial CARS studies were funded by a grant from the Chief Scientist Office Scotland (CZB/4/595).

2e. Summary of Protocol Amendments: Version 1.1 to Version 4.0

- Updated MISTIE III Design to include published results of STICH II as supporting data.
- Specified that if ICH guidelines include aggressive BP reduction from INTERACT II, then it will be incorporated into MISTIE III protocol outline best practices.
- Added: information for enrolling subjects to consent to participate in ancillary study Mechanisms of Tissue Injury in MISTIE III.
- Inclusion Criteria:
    - Deleted: clot size inclusion criteria from 4.1.1 and moved it to 4.1.2.
    - Added: stability CT should be done at least 6 hours after diagnostic CT and allowances for additional scans.
    - Added: ability to randomise between 12-72 hours after dCT.
    - Added: SBP <180 mm Hg sustained for 6 hours should be recorded closest to randomisation time.
    - Edited: age from 18–80 to ≥18 (removed upper age limit).
- Exclusion Criteria:
    - Added: 4.2.2 Ruptured aneurysm, arteriovenous malformation (AVM), vascular anomaly, Moyamoya disease, haemorrhagic conversion of an ischemic infarct, recurrence of a recent (<1 year) haemorrhage, diagnosed with radiographic imaging.
    - Added: 4.2.3 Patients with unstable mass or evolving intracranial compartment syndrome.
    - Added: 4.2.4 Irreversible impaired brain stem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS ≤4.
    - Added: 4.2.11 Use of dabigatran, apixaban, and/or rivaroxaban (or a similar medication from the similar medication class) prior to symptom onset.
    - Added: 4.2.17 Participation in a concurrent interventional medical investigation or clinical trial. Patients in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
    - Added: 4.2.20 Patients with a mechanical heart valve. Presence of bio-prosthetic valve(s) is permitted.
    - Added: 4.2.21 Known risk for embolisation, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis. Atrial fibrillation without mitral stenosis is permitted.
- Study Enrolment Procedures:
    - Added: an additional surgeon in the facilities section to serve as back-up to help oversee MISTIE cases in the CCC criteria.
    - Added: if study centres are failing, sites will remain in trial for up to 9 months. At 9 months, study centres will be placed on probation with a final opportunity to enrol or be closed at 12 months.
    - Added: informed consent forms for all sites are in Appendix I with additional HIPAA templates for international enrolling centres in Appendix 2.
    - Added: if either or both are unstable, refer to page 23: Stability CT scan for clot stability and page 27: Cardiovascular management for BP stability. The first dose of study drug is administered six or more hours after the surgical procedure and only after surgical centre review.
- Interventions, Administration, and Duration:
    - Added: All subjects will still be followed daily for six days post randomisation. MRI will be performed at day 7-10 (plus or minus 1 day) or hospital discharge, whichever occurs first. Results will be compared to baseline MRI to measure oedema. The requirement to obtain MRI is waived for study centres located in Spain. See section 4.3.1 Screening procedures, item 3 above for specific sequences.
    - Added: 5.1.1 1) The non-emergency ICP monitor would ideally be placed prior to rt-PA administrations or at least six hours after dosing

- Added: 5.1.1 2) A neurological deterioration (neuroworsening) will be defined as any GCS decrease of greater than two points on the motor scale sustained for eight hours without sedation and is required to be reported as an AE/SAE
- Added: Cardiovascular management. The patient's blood pressure must be stable to be eligible for randomisation. Blood pressure stability is defined as SBP <180 mm Hg for a period of six hours. This six-hour period must be maintained and documented as close to but prior to randomisation as possible. Blood pressure management should conform to current AHA guidelines to maintain SBP <180 mm Hg throughout the first 6 days of the ICU stay to reduce the risk of bleeding events. The systolic and diastolic pressures over the six-hour monitoring period should be documented in the medical record as source documentation.
- Added: AHA guidelines for SBP and MAP referenced by Morgenstern 2010.
- Removed: patients at high risk of thromboembolism, low dose subcutaneous heparin (criteria established by the American Orthopaedic Association) can be initiated 72 hours after termination of intracerebral rt-PA therapy for those subjects randomised to surgical management. In the interest of patient safety, therapy may be initiated sooner than 72 hours after last dose of rt-PA at the discretion of the site PI but this will be documented by the EDC system as a protocol variation.
- Added: patients at high risk of thromboembolism, study centre standard of care policies may govern the use of low molecular weight, fractionated and unfractionated heparins for DVT prophylaxis during the acute treatment and follow-up periods (criteria established by the American Orthopaedic Association).
- Changed: surgical centre review of radiographic images from within 3 hours of data submission to 6 hours.
- Added: if they are two different surgical plans, site neurosurgeon must demonstrate the rationale of his/her plan before using a surgical plan different from that proposed by the surgical centre.
- Changed the post-surgical stabilisation period from 3 hours to 6 hours and should include a CT scan to confirm correct placement.
- Added: if new bleeding or bleeding expansion is seen on the post-op CT scan, wait 12 hours and repeat the CT scan. When the bleeding is stable, dosing can be initiated.
- Changed: post-operative clot from being "equal to 10m or less" to "10 to 15mL" before rt-PA cannot be given. Catheter should remain in place and open to drainage for 24-36 hours prior to removal.
- Added: replacement is defined as removal of the catheter and replacement with a better targeted catheter using the introducer method with either the same or a different trajectory of insertion. There is a one-time allowance for a new rigid cannula placement. Soft catheter placements or replacements, usually done through an existing burr hole and always done using a stylet with image guidance, do not count against this limited number of rigid cannula passes. There is no limit to the number of soft catheter placements or replacements as long as stability requirements are met. Occasionally, it may be necessary to create a new burr hole/trajectory to access the clot. This will be done only after consultation with the surgical centre. Repeat CT scan and upload DICOMs of the final catheter placement in the clot into the EDC for surgical centre review and approval of catheter location in residual haematoma prior to dosing.
- Added: 5.1.2 if repositioning or replacement does not correct the catheter-clot relation and the rigid cannula has already been replaced once during the trial, rt-PA administration must be stopped or not initiated and the catheter removed 24 hours later. This requirement will control the delivery of rt-PA only into space containing clot that can be lysed.
- Changed: the time of the catheter being left open to drain from 24 hours to 24-36 hours.
- Added the catheter may be left in place greater than 24 hours later if the catheter supports ventricular drainage as clinically required.
- Added: to limit infection risk, remove the catheter at the bedside 24 to 36 hours after the last rt-PA administration, unless the catheter supports ventricular drainage as clinically required. Send the catheter tip for culture. A CT scan must be done 24 hours post catheter removal and examined for stability, new bleeding, or haemorrhage extension.
- Added: 5.1.3 After placement or repositioning of any pre-dosing catheter a six-hour stabilisation period is required prior to first dose to assess patient clinical status and minimise rebleeding. During this time, the neurological status of the subject will be assessed to document clinical worsening or improvement. Surgical centre confirmation of catheter placement, replacement, or manipulation is also required prior to initiation of dosing. Following surgery, a CT scan is to be obtained and catheter placement approved by the surgical centre. This CT scan can be obtained any time prior to administering first dose. Furthermore, a period of at least 6 hours is to be observed prior to first dose to ensure subject is clinically stable.
- Added: 5.1.3 the drug will be administered as a sterile solution and in a sterile manner every 8 (+ 2) hours for up to 9 doses. The total volume of injectate will equal 1.0 mg rt-PA @ 1 mg/mL plus at least 3 mL of flush or as much flush is needed for the rt-PA to clear the catheter tubing.
- Added: 5.1.3 There is a two (2) hour window on either side of the eight (8) hour dosing schedule to allow for scheduling problems, stability determination, INR correction, or any other concern the PI may have regarding giving the dose on

schedule. This schedule adjustment should be used as infrequently as possible to maintain a Q8hr schedule for dosing consistency.

- Added: if a dose must be held or delayed more than 10 hours to correct an INR value above 1.4 (or other coagulopathy), hold the next scheduled dose, institute corrective therapy, and re-assess the INR. Once INR is corrected, dosing may be resumed keeping to the original dose count.

3. Statistical Methods: Severity Index Analysis

mRS 0–3 at 365 days:
As an initial step in developing our severity index for predicting mRS (0–3) at 365 days, categories for well-established "explanatory" variables age and GCS (both given as the categories used in the covariate adaptive randomisation), stability ICH (two categories), stability IVH (two categories), and clot location were employed. Additional candidate explanatory variables: presence of diabetes, presence of cardiovascular disease, and white matter disease were explored in a univariate analysis. The three additional explanatory variables were all statistically associated with mRS (0–3) in the univariate analyses; however, only the presence of diabetes and white matter disease were significant in the multivariable model.

We composed a multivariable logistic model of good outcome (mRS ≤3 versus mRS >3) at 365 days. The final categories considered were: age (<56 years, 56–<67 years, ≥67 years), GCS (3–8, 9–12, 13–15), ICH (<45 mL, ≥45 mL), IVH (≤0.4 mL, >0.4 mL), ICH location (deep, lobar), diabetes (yes, no), and white matter disease (Fazekas total score ≤2, 3, and ≥4).

Based on the coefficients of this model, the severity score was created that weighted each category as follows: Severity Index = 1.8*(1 if age <56; 0 otherwise) + 1.2*(1 if age ≥56 and <67; 0 otherwise) + 0*(1 if age ≥67; 0 otherwise) + 0.7*(1 if GCS 13-15; 0 otherwise) + 0.6*(1 if GCS 9–12; 0 otherwise) + 0*(1 if GCS 3–8; 0 otherwise) + 1.9*(1 if ICH location lobar; 0 otherwise) +0*(1 if ICH location deep; 0 otherwise) + 1.1*(1 if stability ICH <45 mL; 0 otherwise) + 0*(1 if stability ICH ≥45 mL; 0 otherwise) + 0.7*(1 if stability IVH ≤0.4 mL; 0 otherwise) + 0*(1 if stability IVH >0.4 mL; 0 otherwise) + 0.9*(1 if diabetes no; 0 otherwise) + 0*(1 if diabetes yes; 0 otherwise) + 1.2*(1 if Fazekas total score ≤2; 0 otherwise) + 0.6*(1 if Fazekas total score = 3; 0 otherwise) + 0*(1 if Fazekas total score ≥4; 0 otherwise). This severity score gives a maximum possible value of 8.8, with the highest score seen in the data at this maximum value.

Regression of the odds of mRS (0–3) gives an increase of 2.6-fold in the odds of having a 365-day mRS ≤3 for each one unit increase in the severity score, a result that is highly statistically significant (OR [95% CI] = 2.59 [2.15, 3.13], p <0.0001). No statistical difference in mean severity was seen between the medical (mean [SD] = 4.7 [1.8]) and MISTIE (mean [SD] = 4.6 [1.7]) treatment arms (p=0.534, two-sided t-test).

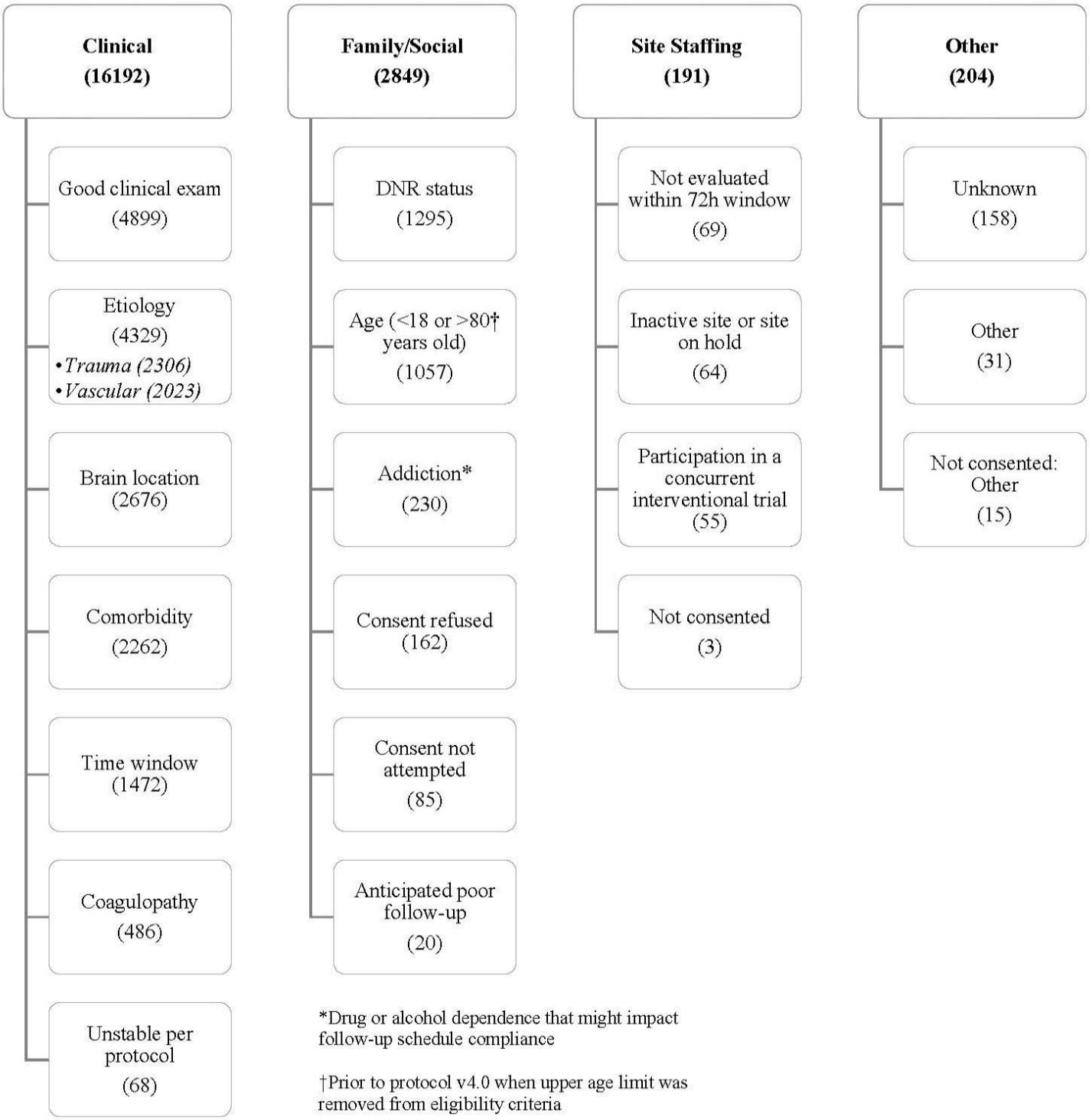
Death at 365 days:
A similar process was followed to create an index score to predict 365-day mortality. Categories of variables were slightly different than for the severity model for mRS (0–3) index. In this analysis, ICH location, IVH, and diabetes were found to be not predictive of mortality, while white matter disease (Fazekas score) and cardiovascular disease (CVD) were found to be associated with mortality. We also explored race, given the findings in the Cox proportional hazard model of mortality, and found this variable to be statistically associated with death.

Our resultant mortality score was created as follows: Mortality Index = 0.8*(1 if age ≥67; 0 otherwise) + 0*(1 if age <67; 0 otherwise) + 1.1*(1 if GCS 3-8; 0 otherwise) + 0.6*(1 if GCS 9-12; 0 otherwise) + 0*(1 if GCS 13-15; 0 otherwise) + 0.9*(1 if CVD yes; 0 otherwise) + 0*(1 if CVD no; 0 otherwise) + 0.9 *(1 if stability ICH ≥ 45 mL; 0 otherwise) + 0*(1 if stability ICH <45 mL; 0 otherwise) + 1.3*(1 if Fazekas score ≥4; 0 otherwise) + 0.7*(1 if Fazekas score = 3; 0 otherwise) + 0*(1 if Fazekas score ≤2; 0 otherwise) + 0.8*(1 if race white; 0 otherwise) + 0.1*(1 if race other, 0 otherwise) + 0*(1 if race black; 0 otherwise). This score gives a maximum possible value of 5.8, with the highest value seen in the data set at 5.8.

Regression of the odds of death at 365 days indicates just over a 2.6–fold increase in the odds of death for each one unit increase in the mortality severity score, a result that is highly statistically significant (OR [95% CI] = 2.65 [2.04, 3.42], p <0.0001). Finally, no statistical difference in mean morality severity score was seen between the medical (mean [SD] = 2.5[1.2]) and MISTIE (mean [SD] = 2.6 [1.0]) treatment arms (p=0.359, two-sided t-test).

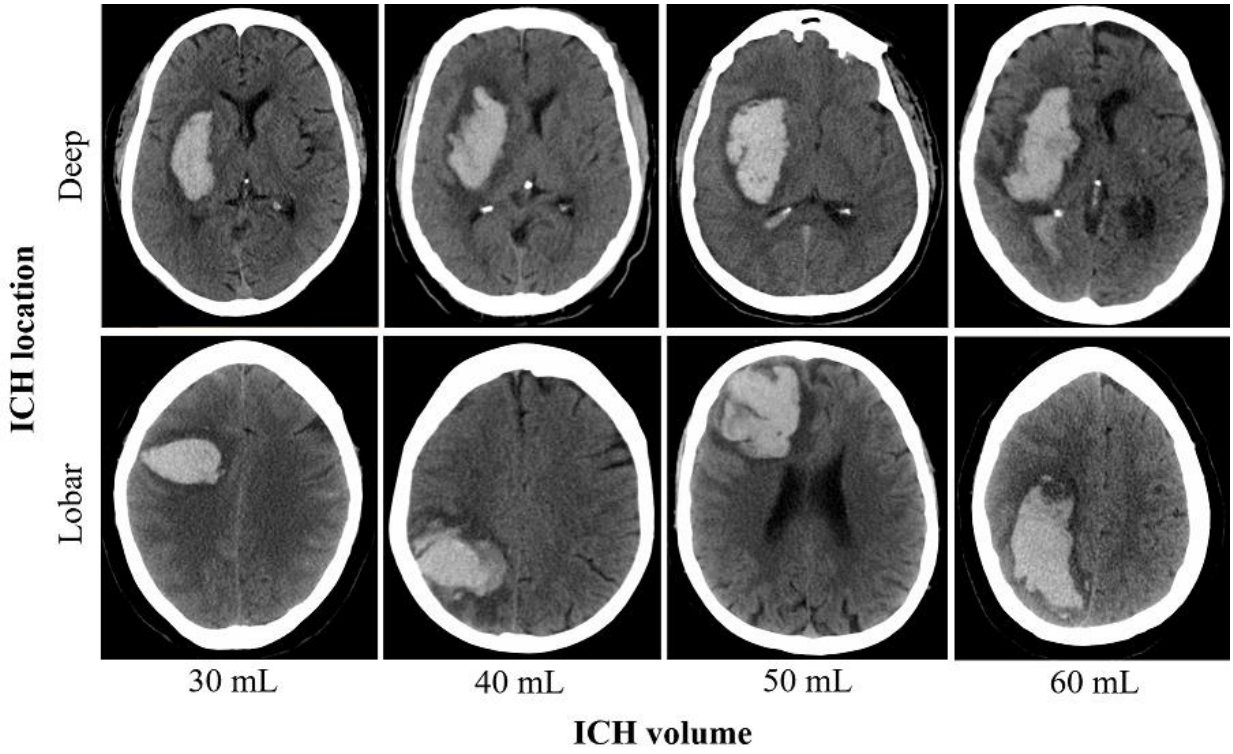
4. Patient Demographics

4a. Primary Reason for Exclusion by Count and Frequency



4b. Representative CT Scan Images of Deep and Lobar ICH

Volumetric software OsiriX MD (version 9.0.1) was used to measure clot volume by outlining and totalling each region of interest (ICH, IVH, catheter tract, and other areas of bleeding). These images are representative of ICH volumes located in the deep and lobar regions at 30, 40, 50, and 60 mL volumes.



4c. Comparison of Baseline Demographics of Screen Failure and Randomised Populations

	Screen failures (n=19,436)	Randomised (n=506)	p value
Age	66 (54-77)	62 (52-71)	<0.001
Male	10,526 (54.2%)	309 (61.1%)	0.002
Race			
Asian	1,224 (6.3%)	30 (5.9%)	0.736
black	3,559 (18.3%)	90 (17.8%)	0.763
white	13,754 (70.8%)	379 (74.9%)	0.043
other	212 (1.1%)	5 (1.0%)	0.826
mixed	10 (0.1%)	1 (0.2%)	0.167
unknown	677 (3.5%)	1 (0.2%)	<0.001
Ethnicity			
Hispanic or Latino	2,667 (13.7%)	68 (13.4%)	0.855
Not Hispanic or Latino	16,291 (83.8%)	438 (86.6%)	0.098
Not reported	478 (2.5%)	0 (0.0%)	<0.001

4d. Identification of Ineligible, Randomised Subjects

The decision to restrict the ITT analyses to only eligible subjects was pre-specified in the SAP and approved by the DSMB. An eligible subject randomised to the MISTIE arm was further defined in the SAP as exposed to surgery. The seven subjects identified as ineligible and not included in the ITT analyses are detailed below. Five of the subjects (1–5 in the table below) were identified following a systematic review of the entire cohort for compliance and eligibility with a focus on the eligibility criteria. Treatment assignment was not included as a variable in the review. Two additional subjects (6, 7 in the table below) were identified immediately post randomisation (6) and during data inspection (7).

Subject ID (de-identified)	Assignment	Reason ineligible	365d mRS
1	MISTIE	ICH too small; not exposed	3
2	Medical	ICH too small	3
3	MISTIE	ICH too small; not exposed	4
4	MISTIE	Aetiology (ICH due to AVM)	6
5	MISTIE	Patient withdrew consent immediately after randomisation	Unknown
6	Medical	Aetiology (ICH due to amyloid angiopathy)	Unknown
7	MISTIE	Clinical exam improved; not exposed	5

5. Results

5a. Summary of Key SAP-Defined Primary and Secondary Analyses

PRIMARY				
1.1	Functional outcome	4% mRS 0-3 increase, MISTIE vs Medical	Risk difference (95% CI) = 4% (-4%, 12%) (MISTIE vs Medical)	p=0.33
1.2a-1.2f	Alternative analyses of mRS levels	mRS=6 less likely, MISTIE vs Medical	AOR=0.6 (0.4, 0.9)	p=0.03
1.2d-1.2e	Subgroup analyses	No difference by treatment arm	All subgroup results reported in sections 1.2d and 1.2e	NS
KEY SECONDARY				
2.2	All-cause mortality, 365 days	Lower hazards of death, MISTIE vs Medical	HR=0.67 (95% CI: 0.45, 0.98)	p=0.037
2.3	Clot removal AUC	Clot removal as given by AUC (time-averaged clot remaining) leads to better functional outcome at 365 days	AOR (95% CI) = 0.68 (0.59, 0.78), per 10 mL clot remaining	p<0.001
2.3a	Clot removal ≤15 mL end of treatment	MISTIE ≤15 mL end of treatment showed a greater percent 365-day mRS 0-3 vs Medical	Risk difference (95% CI) = 10.5% (1.0%, 20.0%) (MISTIE vs Medical)	p=0.03
2.6	ICU care duration	No difference	MISTIE=10 (7-17) Medical=10 (5-16) Median (IQR)	p=0.46
2.8-2.9	30-day mortality/safety	Weak evidence of less mortality with MISTIE vs Medical	MISTIE=9.4%, Medical=14.7%	p=0.07
	Safety: AEs/SAEs	More AE reported in MISTIE group than medical group More SAE reported in medical group than MISTIE group	MISTIE AE=490 (79.6%) Medical AE=385 (73.1%) MISTIE SAE=126 (20.5%) Medical SAE=142 (26.9%) n=1,143	p=0.01

Key positive and negative findings are summarised in 5a above. Section 5b on page 16 details all findings from analyses specified in the Statistical Analysis Plan. Analyses are numbered as such: 1.1 (primary), 1.2a–1.2f (additional exploratory analyses of primary outcome mRS), 2.1–2.7 (secondary), and 2.8–2.9 (safety).

5b. Primary and Secondary Analyses: Results as Ordered in SAP

	Analyses	Results	Notes	Interpretation
Primary Outcomes				
1.1 365-day mRS 0-3 vs 4-6 (TMLE model)			Dichotomised, adjudicated, cross-sectional mRS 0-3 vs 4-6 at 365 days post ictus	
Univariate treatment	Chi-square test	2% (95% CI: -6.8% to 10.7%), p=0.73		No difference
Full adjusted	Multivariable logit model	Adj. risk difference (95% CI)=4% (-4% to 12%), p=0.33	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	No difference
Additional, Exploratory Analyses of mRS at 365 days				
1.2a 365-day mRS (0-3 vs 4-6)			Dichotomised, adjudicated, cross-sectional mRS 0-3 vs 4-6 at 365 days post ictus	
Univariate analysis	Chi-square test	MISTIE=44.2%, Medical=41.7% Risk diff. (95% CI) = 2.5% (-6.3% to 11.3%), p=0.58		No difference between mRS 0-3 and treatment
Full adjusted	Multivariate logit model	Adj. OR (95% CI) = 1.26 (0.83, 1.92), p=0.28	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	No difference between mRS 0-3 and treatment, adjusted for pre-specified variables
1.2b mRS as ordinal adjudicated score (0-6) 365-day mRS 0,1,2 combined	Unadjusted proportional odds model	OR (95% CI) = 0.86 (0.62, 1.17), p=0.33 OR for mRS >K vs ≤K; MISTIE vs Medical		Null hypothesis of prop odds accepted; chi2 p=0.42
	Adjusted proportional odds model	Adj. OR (95% CI) = 0.75 (0.54, 1.05), p=0.09 Adj. OR for mRS >K vs ≤K; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume	Weak evidence that mortality may be less with assignment to MISTIE. Null hypothesis of prop odds rejected; chi2 p<0.001
	Adjusted general ordered logit model for ordered data	Adj. OR (95% CI) = 0.82 (0.49, 1.37), p=0.44 Adj. OR for mRS >2 vs ≤2; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume	Mortality is less with assignment to MISTIE
		Adj. OR (95% CI) = 0.87 (0.58, 1.30), p=0.493 Adj. OR for mRS >3 vs ≤3; MISTIE vs Medical		
		Adj. OR (95% CI) = 0.84 (0.56, 1.28), p=0.419 Adj. OR for mRS >4 vs ≤4; MISTIE vs Medical		
		Adj. OR (95% CI) = 0.60 (0.37, 0.96), p=0.03 Adj. OR for mRS >5 vs ≤5; MISTIE vs Medical		
1.2c Longitudinal (mRS 0-3 vs 4-6) 30–365 days	Unadjusted GEE model (logit mRS 0-3 vs 4-6 at 30–365 days)	OR (95% CI)=1.09 (0.79, 1.50), p=0.59		
	Adjusted GEE model (logit mRS 0-3 vs 4-6 at 30 to 365 days)	OR (95% CI) = 1.30 (0.93, 1.80), p=0.13	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	

	Analyses	Results	Notes	Interpretation
1.2d 365-day subgroup analyses (severity)	Chi-Square Test: Difference in mRS 0-3 proportion	Risk difference: Medical – MISTIE		
Stability ICH (<50 mL)		<50: MISTIE=52.74%, Medical=53.24% Risk Diff (95% CI) = 0.005 (-0.11, 0.12), p=0.93, n=292		
Stability ICH (≥50 mL)		≥50: MISTIE=32.04%, Medical=25.74% Risk Diff (95% CI) = -0.06 (-0.19, 0.06), p=0.32, n=207		
Stability IVH (<10 mL)		<10: MISTIE=45.73%, Medical=42.34% Risk Diff (95% CI) = -0.03 (-0.12, 0.06), p=0.47, n=466		
Stability IVH (≥10 mL)		≥10: MISTIE=20.00%, Medical=33.33% Risk Diff (95% CI) = 0.13 (-0.16, 0.43), p=0.39, n=33		
GCS (3-8)		GCS (3-8): MISTIE=29.69%, Medical=25.40% Risk Diff (95% CI) = -0.04 (-0.20, 0.11), p=0.58, n=127		
GCS (9-12)		GCS (9-12): MISTIE=43.64%, Medical=40.20% Risk Diff (95% CI) = -0.03 (-0.16, 0.10), p=0.61, n=219		
GCS (13-15)		GCS (13-15): MISTIE=57.33%, Medical=57.33% Risk Diff (95% CI) = 0.0 (-0.16, 0.16), p=1, n=153		
Location (Deep)		Deep: MISTIE=34.57%, Medical=31.65% Risk Diff (95% CI) = -0.03 (-0.14, 0.08), p=0.59, n=307		
Location (Lobar)		Lobar: MISTIE=62.07%, Medical=55.45% Risk Diff (95% CI) = -0.07 (-0.21, 0.07), p=0.36, n=192		
Ictus to MISTIE hours (<24 h)		<24 hrs: MISTIE=1.6%, n=4		
Ictus to MISTIE hours (24-48 h)		24-48 hrs: MISTIE=26.8%, n=67		
Ictus to MISTIE hours (>48 hrs)		>48 hrs: MISTIE=71.2%, n=178		
Diabetes (Yes)		Yes: MISTIE=29.17%, Medical=26.87% Risk Diff (95% CI) = -0.02 (-0.17, 0.13), p=0.76, n=139		
Diabetes (No)		No: MISTIE=50.28%, Medical=47.40% Risk Diff (95% CI) = -0.03 (-0.13, 0.08), p=0.59, n=360		
CVD (Yes)		Yes: MISTIE=39.47%, Medical=23.53% Risk Diff (95% CI) = -0.16 (-0.37, 0.05), p=0.15, n=72		
CVD (No)		No: MISTIE=45.02%, Medical=44.66% Risk Diff (95% CI) = -0.004 (-0.10, 0.09), p=0.94, n=427		
1.2e$_1$ 365-day subgroup analyses (demographics)	Chi-Square Test: Difference in mRS 0-3 proportion	Risk Difference: Medical – MISTIE		
Race (black)		Black: MISTIE=37.78%, Medical=43.59% Risk Diff (95% CI) = 0.06 (-0.15, 0.27), p=0.58, n=87		
Race (white)		White: MISTIE=45.26%, Medical=39.33% Risk Diff (95% CI) =-0.06 (-0.16,0.04), p=0.25, n=374		
Race (other)		Other: MISTIE=53.85%, Medical=56.52% Risk Diff (95% CI) = 0.03 (-0.31, 0.37), p=0.88, n=37		
Sex (Female)		Female: MISTIE=46.15%, Medical=45.45% Risk Diff (95% CI) = -0.007(-0.15, 0.13), p=0.92, n=194		
Sex (Male)		Male: MISTIE=43.04%, Medical=39.01% Risk Diff (95% CI) = -0.04 (-0.15, 0.07), p=0.48, n=305		
Age (≤65 yr)		≤65: MISTIE=52.63%, Medical=47.95% Risk Diff (95% CI) = -0.05 (-0.16, 0.07), p=0.42, n=307		

	Analyses	Results	Notes	Interpretation
Age (>65 yr)		>65: MISTIE=30.93%, Medical=31.91% Risk Diff (95% CI) = 0.01 (-0.12, 0.14), p=0.88, n=192		
1.2e$_2$ 365-day cross-sectional of mRS (0-3 vs 4-6) (demographics)	Chi-Square Test			
Treatment		MISTIE: mRS 0-3=44.18%, mRS 4-6=55.82% Medical: mRS 0-3=41.67%, mRS 4-6=58.33% Relative Risk (95% CI) =1.06 (0.86, 1.30), p=0.58		
Race		Black: mRS 0-3=40.48%, mRS 4-6=59.52% White: mRS 0-3=42.39%, mRS 4-6=57.61% Relative Risk (95% CI) = 1.05 (0.79, 1.39), p=0.75		
Sex (Male)		Female: mRS 0-3=45.79%, mRS 4-6=54.21% Male: mRS 0-3=41.14%, mRS 4-6=58.86% Relative Risk (95% CI) = 1.10 (0.90, 1.36), p=0.33		
Age (≤65 yr)		≤65: mRS 0-3=50.34%; mRS 4-6=49.66% >65: mRS 0-3=31.41%; mRS 4-6=68.59% Relative Risk (95% CI) = 1.60 (1.26, 2.03), p=<0.0001		Day 365 mRS 4-6: Statistically significant difference between age groups: the older the patient, the higher the probability of bad outcome. Day 365 mRS 0-3: the younger the patient, the higher the probability of good outcome.
Hispanic/Latino Ethnicity		No: mRS 0-3=43.47%, mRS 4-6=56.53% Yes: mRS 0-3=39.71%, mRS 4-6=60.29% Relative Risk (95% CI) = 0.91 (0.66, 1.25), p=0.56		
1.2f$_1$ Random effects (mRS 0-3 vs 4-6) day 365	Unadjusted Random Effects Model with site (region: U.S. vs Other) as random effect	OR (95% CI) = 1.1 (0.72, 1.58), p=0.58		No differences of mRS 0-3 attributable to site differences
	Adjusted Random Effects Model with site (region: U.S. vs Other) as random effect	Adj. OR (95% CI) = 1.2 (0.82, 1.76), p=0.34	Adjusted for age, GCS, ICH location	
1.2f$_2$ Random effects: Site experience	Logistic Regression of EOT ≤30	OR (95% CI) = 1.29 (1.10, 1.50), p<0.001. Odds of EOT ≤30 for each additional surgery performed at site		
SECONDARY OUTCOMES				
2.1a Dichotomised eGOS UGR-US vs LS-Death at 365 days				
Univariate Analysis	Chi-Square Test	MISTIE=38.52%, Medical=35.90%, Risk Diff. (95% CI) = 0.03 (-0.06, 0.11), p=0.55		No difference between eGOS 4-8 and treatment groups
Full Adjusted	Multivariate Logit Model	Adj. OR (95% CI) = 1.26 (0.82, 1.97), p=0.27	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	No difference between eGOS 4-8 and treatment groups accounting for other pre-specified variables
2.1b eGOS as Ordinal at 365 days	Unadjusted Proportional Odds Model	OR (95% CI) = 1.04 (0.76, 1.42), p=0.816 OR for eGOS >K vs ≤K; MISTIE vs Medical		Null hypothesis of prop odds accepted; chi2 p=0.087

	Analyses	Results	Notes	Interpretation
	Adjusted Proportional Odds Model	Adj. OR (95% CI) = 1.13 (0.82, 1.57), p=0.453 Adj. OR for eGOS >K vs ≤K; MISTIE vs Medical	Adj. for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume	Null hypothesis of prop odds rejected; chi2 p<0.001 (global test)
2.1c eGOS as Ordinal 365 days (Reverse Coded)	Unadjusted Proportional Odds Model	OR (95% CI) = 0.85 (0.61, 1.17), p=0.32 OR for eGOS >K vs ≤K; MISTIE vs Medical	K=1 (lower and upper good recovery), 2 (upper moderate disability, 3 (lower moderate disability), 4 (upper severe disability), 5 (vegetative state and lower severe disability), 6 (death)	Null hypothesis of prop odds accepted; chi2 p=0.361
	Adjusted Proportional Odds Model	Adj. OR (95% CI) = 0.78 (0.56, 1.09), p=0.15 Adj. OR for eGOS >K vs ≤K; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume K=1 (lower and upper good recovery), 2 (upper moderate disability), 3 (lower moderate disability), 4 (upper severe disability), 5 (vegetative state and lower severe disability), 6 (death)	Null hypothesis of prop odds rejected; chi2 p= 0.001
	Adjusted General Ordered Logit Model for Ordered Data	Adj. OR (95% CI) = 0.78 (0.33, 1.88), p=0.58 Adj. OR for eGOS >1 vs ≤1; MISTIE vs Medical Adj. OR (95% CI) = 1.07 (0.56, 2.05), p=0.83 Adj. OR for eGOS >2 vs ≤2; MISTIE vs Medical Adj. OR (95% CI) = 0.94 (0.56, 1.56), p=0.81 Adj. OR for eGOS >3 vs ≤3; MISTIE vs Medical Adj. OR (95% CI) = 0.83 (0.54, 1.26), p=0.37 Adj. OR for eGOS >4 vs ≤4; MISTIE vs Medical Adj. OR (95% CI) = 0.64 (0.40, 1.02), p=0.06 Adj. OR for eGOS >5 vs ≤5; MISTIE vs Medical	Adjusted for age, GCS, location (deep vs lobar), stab ICH (cat), stab IVH 1 = lower and upper good recovery and upper moderate disability; 2 = lower moderate disability; 3 = upper severe disability; 4 = vegetative state and lower severe disability; 5 = death	Weak evidence that mortality may be less with assignment to MISTIE
2.2 All-cause mortality 365 days	Log Rank Test	Mortality: MISTIE=19.2%, Medical=25.2%, p=0.08		Weak evidence that mortality may be less with assignment to MISTIE
	Adjusted Cox proportional HR	HR = 0.67 (95% CI: 0.45, 0.98), p=0.037	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location, diabetes, CVD, race	Less mortality with random assignment to MISTIE
2.3 Clot Removal				
Univariate Analysis	AUC/Logit Model	OR = 0.70 (0.62, 0.80), p <0.001		Difference between mRS 0-3 and AUC clot-assessment
Full Adjusted	Multivariable Logit Model	Adj. OR (95% CI) = 0.68 (0.59, 0.78), p<0.001	Adjusted for age, GCS, stability IVH volume, ICH deep location	Difference between mRS 0-3 and AUC clot-assessment accounting for other pre-specified variables
2.3a ≤15 mL vs Medical	Multivariable Logit Model	Risk Difference (95% CI) = 11.5% (3.0 %, 20.0%), p=0.0008 (MISTIE vs Medical)	Adjusted for age, GCS, stability IVH volume, ICH deep location, CVD, diabetes, and white matter disease	Average Marginal Effect: MISTIE ≤15 mL EOT showed a greater % 365 mRS 0-3 vs Medical
2.3b MISTIE subjects only: cut point ≤15 mL vs 15 mL	Multivariable Logit Model	Risk Difference = -0.12 (-0.23, -0.01), p=0.03 (Medical vs MISTIE)	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	Average Marginal Effect: MISTIE ≤15 mL EOT showed a greater % 365 mRS 0-3 vs MISTIE >15 mL

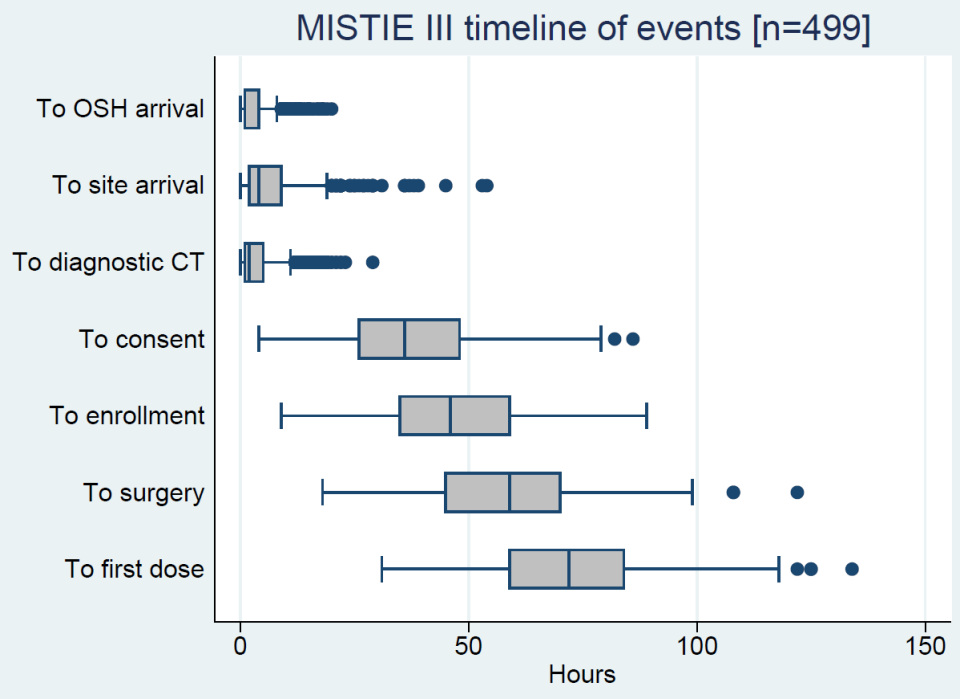
	Analyses	Results	Notes	Interpretation
2.3c MISTIE subjects only: cut point ≤20 mL vs >20 mL	Multivariable Logit Model	Risk Difference = -0.17 (-0.31, -0.03), p=0.02 (Medical – MISTIE)	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	Average Marginal Effect: MISTIE ≤20 mL end of treatment showed a greater % 365 mRS 0-3 vs MISTIE >20 mL
2.3d MISTIE subjects only: cut point ≤30 mL vs >30 mL	Multivariable Logit Model	Risk Difference = 0.002 (-0.18, 0.18), p=0.99 (Medical – MISTIE)	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	Average Marginal Effect: MISTIE ≤30 mL end of treatment did not show a greater % 365 mRS 0–3 vs MISTIE >30 mL
2.4 Patient disposition				
2.4a Home days over 365 days	Two-sample Wilcoxon rank-sum (Mann-Whitney) test	MISTIE=306 (237-329), n=166 Medical=300 (232-328), n=157 p=0.78; n=323		No difference between total home days and treatment groups
2.4b Good vs bad location at day 365 post stroke	Chi-square test	MISTIE=81.1%, Medical=84.8% Risk Diff. (95% CI) = 0.04 (-0.04, 0.11), p=0.34; n=379 (Medical – MISTIE)		No difference between good/bad location and treatment groups
2.5 180-day efficacy				
2.5a$_1$ Dichotomised, adjudicated, cross-sectional mRS 0-3 vs 4-6				
Univariate Analysis	Chi-Square Test	MISTIE=39.6%, Medical=38.3% Risk Diff. (95% CI) = -0.01 (-0.10, 0.07), p=0.76 (Medical – MISTIE)		No difference between mRS 0-3 and treatment groups
Full Adjusted	Multivariate Logit Model	Adj. OR (95% CI) = 1.25 (0.81, 1.94), p=0.31		No difference between mRS 0-3 and treatment groups accounting for other pre-specified variables
2.5a$_2$ Ordinal, adjudicated mRS 0-6 (mRS 0,1,2 combined)				
	Unadjusted Proportional Odds Model	OR (95% CI) = 0.81 (0.59, 1.11), p=0.18 OR for mRS >K vs ≤K; MISTIE vs Medical		Null hypothesis of prop odds accepted; chi-square p=0.13
	Adjusted Proportional Odds Model	Adj. OR (95% CI) = 0.69 (0.50, 0.95), p=0.02 Adj. OR for mRS >K vs ≤K; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume	Null hypothesis of prop odds rejected; chi-square p<0.001
	Adjusted General Ordered Logit Model for Ordered Data	Adj. OR (95% CI) = 0.60 (0.32, 1.11), p=0.10 Adj. OR for mRS >2 vs ≤2; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume	Mortality less with assignment to MISTIE
		Adj. OR (95% CI) = 0.85 (0.56, 1.28), p=0.42 Adj. OR for mRS >3 vs ≤3; MISTIE vs Medical		
		Adj. OR (95% CI) = 0.79 (0.52, 1.19), p=0.26 Adj. OR for mRS >4 vs ≤4; MISTIE vs Medical		
		Adj. OR (95% CI) = 0.52 (0.32, 0.86), p=0.01 Adj. OR for mRS >5 vs ≤5; MISTIE vs Medical		
2.5b$_1$ Dichotomised, adjudicated eGOS UGR, LGR, MD, LM, US vs LS, VS, Death				

	Analyses	Results	Notes	Interpretation
Univariate Analysis	Chi-Square Test	MISTIE=32.4%, Medical=31.3%, Risk Diff. (95% CI) = 0.01 (-0.07, 0.09), p=0.79 (Medical – MISTIE)		No difference between eGOS and treatment
Full Adjusted	Multivariate Logit Model	Adj. OR (95% CI) = 1.24 (0.79, 1.97), p=0.35	Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	No difference between eGOS 4-8 and treatment groups accounting for other pre-specified variables
2.5b$_2$ eGOS ordinal (reverse coded)	Unadjusted Proportional Odds Model	OR (95% CI) = 0.83 (0.60, 1.15), p=0.27 OR for eGOS >K vs ≤K; MISTIE vs Medical	K=1 (lower and upper good recovery and upper moderate disability), 2 (lower moderate disability), 3 (upper severe disability), 4 (vegetative state and lower severe disability), 5 (death)	Null hypothesis of prop odds accepted; chi-square p=0.158
	Adjusted Proportional Odds Model	Adj. OR (95% CI) = 0.71 (0.50, 1.00), p=0.05 Adj. OR for eGOS > K vs ≤K; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume K=1 (lower and upper good recovery and upper moderate disability), 2 (lower moderate disability), 3 (upper severe disability), 4 (vegetative state and lower severe disability), 5 (death)	Null hypothesis of prop odds rejected; chi-square p=0.005
	Adjusted General Ordered Logit Model for Ordered Data	Adj. OR (95% CI) = 0.81 (0.36, 1.81), p=0.60 OR for eGOS >1 vs ≤1; MISTIE vs Medical Adj. OR (95% CI) = 0.81 (0.47, 1.38), p=0.43 Adj. OR for eGOS >2 vs ≤2; MISTIE vs Medical Adj. OR (95% CI) = 0.90 (0.58, 1.39), p=0.63 Adj. OR for eGOS >3 vs ≤3; MISTIE vs Medical Adj. OR (95% CI) = 0.56 (0.34, 0.92), p=0.02 Adj. OR for eGOS >4 vs ≤4; MISTIE vs Medical	Adjusted for age, GCS, ICH location (deep vs lobar), stability ICH volume (cat), stability IVH volume 1=lower and upper good recovery and upper moderate disability; 2=lower moderate disability; 3=upper severe disability; 4=vegetative state and lower severe disability; 5=death	Mortality less with assignment to MISTIE group
2.6 Type and intensity of ICU management				
2.6a ICU days (first index stroke to discharge date duration in days)	Median Test	MISTIE=10 (7-17), n=240 Medical=10 (5-16), n=238 p=0.46; n=478	Continuity corrected Pearson chi-squared	No difference between ICU days and treatment groups
2.6b ICU management				
2.6b$_1$ ICP monitored	Chi-Square Test	MISTIE=13.6%, Medical=15.3%, p=0.60, n=72		No difference between ICP monitored and treatment groups
2.6b$_2$ Ventilation	Chi-Square Test	MISTIE=42.8%, Medical=41%, p=0.68		No difference between ventilation and treatment groups
2.6b$_3$ ICP therapies ≥1	Chi-Square Test	MISTIE=73.5%, Medical=68.4%, p=0.63		No difference between ICP therapies and treatment groups
2.6b$_4$ % subjects with any ICP ≥20 mm Hg	Chi-Square Test	MISTIE=26.5%, Medical=57.9%, p=0.01		Difference between % subjects with any ICP ≥20 mm Hg and treatment group. Higher in Medical
2.6b$_5$ % subjects with any ICP <70 mm Hg	Chi-Square Test	MISTIE=77.8%, Medical=81.6%, p=0.08		Weak evidence of a possible difference between % subjects with

	Analyses	Results	Notes	Interpretation
				any CPP <70 mm Hg and treatment groups
2.6c Hospital days (through end of study, including ICU days)	Median test	MISTIE=17 (13-27), N=250 Medical=17 (10-25), N=249 p=0.75; n=499	Continuity corrected Pearson chi-squared	No difference between treatment groups and hospital days
2.7 EQ-VAS and EQ-5D at d365				
2.7a EQ-VAS	Two-sample Wilcoxon rank-sum (Mann-Whitney) test	MISTIE=70 (50-80), n=183 Medical=70 (50-80), n=164 p=0.66; n=347		No difference between EQ-VAS and treatment groups
2.7b EQ-5D (any problem in at least one domain)	Chi-Square Test	MISTIE=176 (91.7%), n=192 Medical=155 (91.2%), n=170 p=0.87; n=362		No difference between EQ-5D and treatment groups
Safety Measurement Summary				
2.8 30-day mortality/safety				
2.8a First-week (operative) mortality	Chi-Square Test	MISTIE=0.8%, Medical=4.0%, p=0.02		Difference between mortality and treatment groups within 7 days
2.8b All-cause mortality (Within 30 days)	Chi-Square Test	MISTIE=9.4%, Medical=14.7%, p=0.07		Weak evidence of a possible difference between mortality and treatment groups within 30 days
2.8c Symptomatic brain bleed (Within 72 hours after last dose)	Chi-Square Test	MISTIE=2.4%, Medical=1.2%, p=0.33		No difference between systematic bleed rate and treatment groups
2.8d Brain bacterial infections	Chi-Square Test	MISTIE=1%, Medical=0%, p=0.16		
2.8e_1 Total SAE (within 30 days)	Mixed effects logistic regression (Clustered on Patient ID)	SAE: MISTIE=126 (20.5%), Medical=142 (26.9%), AE: MISTIE=490 (79.6%), Medical=385 (73.1%), p=0.01; n=1,143		More SAE reported in medical than MISTIE
2.8e_2 Total AE (within 30 days)				More AE reported in MISTIE than medical
2.9a Total SAE (by end of study)	Mixed effects logistic regression (Clustered on Patient ID)	SAE: MISTIE=233 (30.9%), Medical=218 (34.3%), AE: MISTIE=522 (69.1%), Medical=418 (65.7%), p=0.15; n=1,391		No difference between reported AE or SAE and treatment groups
2.9b Total AE (by end of study)				
	Accept Null			
	p<0.05: Reject Null			

Scores on the modified Rankin Scale (mRS) range from 0 (no disability) to 5 (severe disability) to 6 (death); for ordinal analysis, mRS 0 and 1 combined. Scores on the Extended Glasgow Outcome Scale (eGOS) range from upper good recovery to death. Scores on the EuroQol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) on imaginable health state.

5c. Acute Protocol Timeline Events: Measured by Hours Post Stroke



Boxplots of acute protocol timeline events. Arrival at outside hospital (OSH) is presented for subjects enrolled after transfer from another facility. The boundaries of the box are the 75th and 25th percentiles. The difference between these values is the interquartile range (IQR). The whiskers extend from the lower (upper) quartiles to the smallest (largest) value within (1.5 x IQR) of the lower (upper) quartile. All values outside of this are plotted separately. Supporting data are displayed in the table below.

Timeline event (h)	N	Mean (95% CI)	Median	Minimum	Maximum
To outside hospital arrival	308	3.2 (2.7–3.6)	1	0	20
To site arrival	499	6.8 (6.1–7.4)	4	0	54
To diagnostic CT	488	4.0 (3.5–4.4)	2	0	29
To consent	499	38.1 (36.7–39.5)	36	4	86
To enrolment	499	47.0 (45.6–48.4)	46	9	89
To surgery	249	58.3 (56.1–60.5)	59	18	122
To first dose	231	72.6 (70.2–75.1)	72	31	134

5d. Tabular Data for Modified Rankin Scale (mRS) at Days 30 and 365 Post Stroke by Treatment Group
(corresponds to Figure 2 in article)

ORDINAL

	Day 30		Day 365	
mRS	**MISTIE (n=250)**	**Medical (n=243)**	**MISTIE (n=249)**	**Medical (n=240)**
0	0 (0.0%)	0 (0.0%)	1 (0.4%)	6 (2.5%)
1	1 (0.4%)	0 (0.0%)	15 (6.0%)	6 (2.5%)
2	10 (4.0%)	9 (3.7%)	30 (12.1%)	30 (12.5%)
3	21 (8.4%)	16 (6.6%)	64 (25.7%)	58 (24.2%)
4	64 (25.6%)	60 (24.7%)	60 (24.1%)	56 (23.3%)
5	131 (52.4%)	124 (51.0%)	31 (12.4%)	22 (9.2%)
6	23 (9.2%)	34 (14.0%)	48 (19.3%)	62 (25.8%)

DICHOTOMISED

	Day 30		Day 365	
mRS	**MISTIE (n=250)**	**Medical (n=243)**	**MISTIE (n=249)**	**Medical (n=240)**
0-3	32 (12.8%)	25 (10.3%)	110 (44.2%)	100 (41.7%)
4-6	218 (87.2%)	218 (89.7%)	139 (55.8%)	140 (58.3%)

mRS scores range from 0 (no disability) to 6 (death).

The proportion of 365-day mRS 0–3 was 110 (44.2%) in the MISTIE group *vs* 100 (41.7%) in the medical group. mRS 4–6 was 139 (55.8%) in the MISTIE group and 140 (58.3%) in the medical group. mRS scores were missing for 10 out of 499 patients; of the 10, 6 subjects were lost to follow-up, and 4 refused further participation in the study.

5e. Tabular Data for Extended Glasgow Outcome Scale (eGOS) at Days 30 and 365 Post Stroke by Treatment Group
(corresponds to Figure 2 in article)

ORDINAL

		Day 30		Day 365	
eGOS	**Category**	**MISTIE (n=249)**	**Medical (n=242)**	**MISTIE (n=244)**	**Medical (n=234)**
1	Dead	23 (9.2%)	34 (14.1%)	48 (19.7%)	62 (26.5%)
2	Vegetative State	26 (10.4%)	32 (13.2%)	6 (2.5%)	3 (1.3%)
3	Lower Severe Disability	171 (68.7%)	156 (64.5%)	96 (39.3%)	85 (36.3%)
4	Upper Severe Disability	22 (8.8%)	12 (5.0%)	48 (19.7%)	37 (15.8%)
5	Lower Moderate Disability	1 (0.4%)	3 (1.2%)	21 (8.6%)	17 (7.3%)
6	Upper Moderate Disability	3 (1.2%)	2 (0.8%)	11 (4.5%)	14 (6.0%)
7	Lower Good Recovery	2 (0.8%)	1 (0.4%)	6 (2.5%)	3 (1.3%)
8	Upper Good Recovery	1 (0.4%)	2 (0.8%)	8 (3.3%)	13 (5.6%)

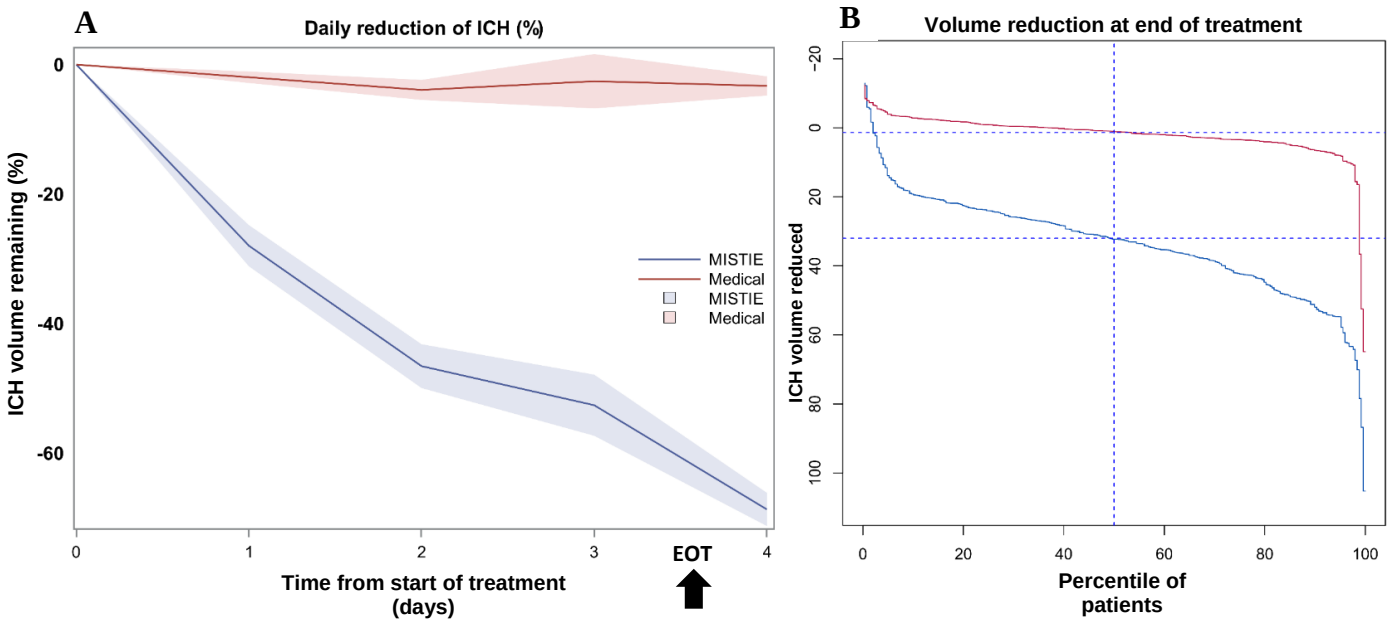
DICHOTOMISED

		Day 30		Day 365	
eGOS	**Category**	**MISTIE (n=249)**	**Medical (n=242)**	**MISTIE (n=244)**	**Medical (n=234)**
1–3	Lower Severe Disability – Dead	220 (88.4%)	222 (91.7%)	150 (61.5%)	150 (64.1%)
4–8	Upper Good Recovery – Upper Severe Disability	29 (11.7%)	20 (8.3%)	94 (38.5%)	84 (35.9%)

eGOS scores range from 8 (upper good recovery) to 1 (death). GR=good recovery. MD=moderate disability. SD=severe disability. VS=vegetative state. eGOS scores were missing for 21 out of 499 patients, out of which 11 completed the study with no eGOS reported, 6 were lost to follow-up, and 4 refused further participation.

The proportion of 365-day eGOS 4–8 (upper severe disability through upper good recovery) was 94 (38.5%) in the MISTIE group *vs* 84 (35.9%) in the medical group. eGOS scores 1–3 (lower severe disability through death) were 150 (61.5%) in the MISTIE group and 150 (64.1%) in the medical group.

5f. Graphical Display of ICH Removal: Time-Based and Cohort-Based



Percent clot removal over the treatment period (Panel A) and a cohort distribution of total amount of ICH removed at the end of treatment (EOT) time point as indicated in the first panel (Panel B). ICH=intracerebral haemorrhage. MIS=minimally invasive surgery.

(A) Percentage of clot remaining as measured with a daily CT scan after achievement of clot size stability and randomisation. Thick lines are the average daily ICH reduction for medical (red: 3.29% [95% CI 1.8–4.7%]) and MISTIE (blue: 71.25% [95% CI 68.37–74.12%]). The shaded regions are the 95% CIs of these respective groups. The black arrow marks the median time of the 24 h post-last dose time point or the EOT, which falls between days 3 and 4.

(B) The distribution of each patient's clot removal for the MISTIE (blue) and medical (red) groups. Removal is expressed as absolute volume reduction as observed on day 4 EOT CT scan. The dashed line indicates the 50th-percentile patient and respective ICH volume reductions for the MISTIE (≈33 mL) and medical care cohort (≈3 mL). All volumes were established by the core imaging laboratory. Data from all 499 randomised patients were included.

5g. Model of Relationship between Clot Removed as AUC and Proportion mRS 0–3

Model #1:
Outcome: Dichotomised mRS 0–3 (good)
Sample Size: 485
Predictors: Pre-specified variables (age, GCS, stability IVH, and deep ICH location)
Pseudo R-square: 0.212
Model p value: <0.001
AIC: 533.8
BIC: 567.4

Covariates	Odds ratio (95% CI)	Standard error	Covariate p value
AUC per 10 mL	0.680 (0.590–0.783)	0.049	<0.001
Age 56–66	0.377 (0.222–0.641)	0.102	<0.001
Age ≥67	0.126 (0.067–0.239)	0.041	<0.001
GCS: moderate (9–12)	1.693 (0.994–2.884)	0.460	0.053
GCS: severe (13–15)	2.261 (1.260–4.058)	0.675	0.006
Stability IVH volume	0.955 (0.906–1.006)	0.025	0.080
ICH location: deep	0.123 (0.072–0.212)	0.034	<0.001

Multivariate logistic regression model tests the possible relationship of clot removal or temporal duration of patient exposure to ICH, expressed as the area under the volume x time curve (AUC), and the likelihood of mRS 0–3 at 365 days. This model controls for established initial severity factors: age, GCS, IVH volume, and ICH location. To make the model clinically sensible, the AUC is defined in 10 mL volumes, as this represents clinically reasonable increments over the spectrum of ICH removed.

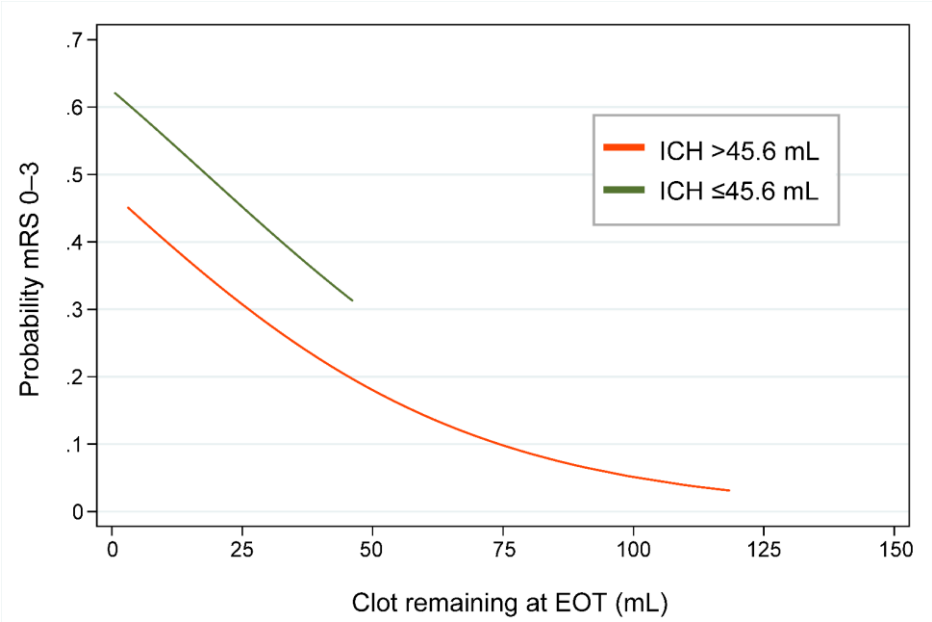
5h. MISTIE Procedure and Task Adherence Measures (Surgical Task Performance Measures): MISTIE II and III

	Aspiration alone achieved reduction to ≤15 mL	Aspiration + alteplase achieved ≤15 mL	Patients achieving ≥80% reduction	Median volume removed (25th, 75th percentile)	Median EOT volume (25th, 75th percentile)
MISTIE III	14 (5.7%)	146 (59.7%)	81 (32.7%)	32.3 (24.0, 42.3)	12.6 (7.6, 21.0)
Medical	0 (0%)	0 (0%)	0 (0%)	1.1 (-.088, 3.44)	43.7 (33.6, 56.3)

Comparison to MISTIE II

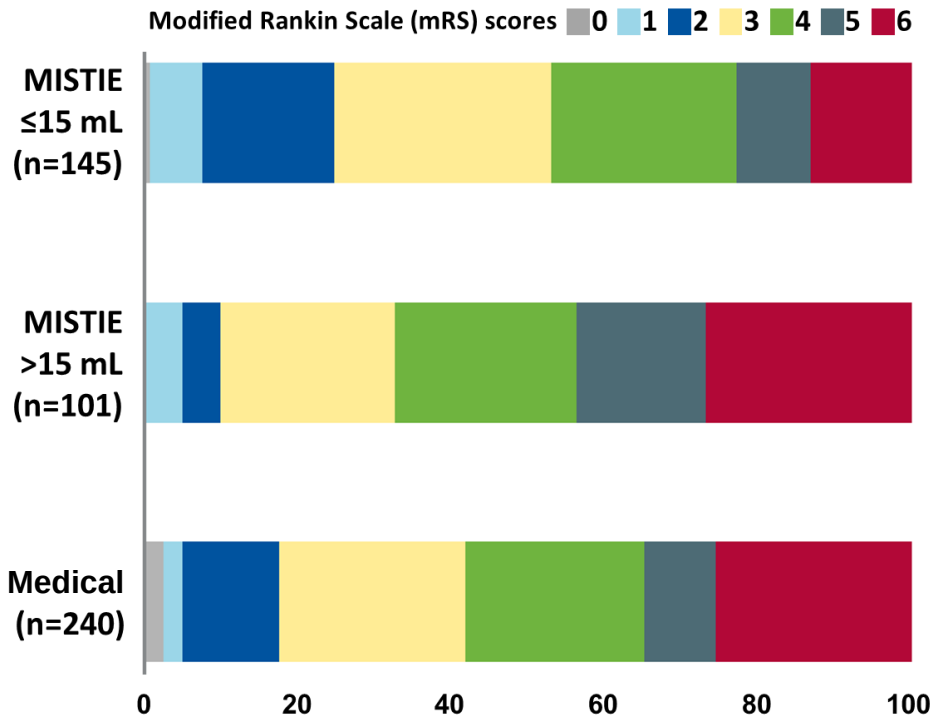
	Aspiration alone achieved reduction to ≤15 mL	Aspiration + alteplase achieved ≤15 mL	Patients achieving ≥80% reduction	Median volume removed (25th, 75th percentile)	Median EOT volume (25th, 75th percentile)
MISTIE II	8 (15%)	25 (46%)	10 (19%)	24.11 (14.3, 40.4)	16.04 (9.9, 26.9)
Medical	0 (0%)	0 (0%)	0 (0%)	1.57 (0.0, 5.4)	37.94 (29.5, 49.4)

5i. Graphical Relationship between Probability of mRS 0-3 Outcome and Clot Remaining at EOT



Plot of probability of mRS 0–3 as a function of clot remaining at the end of treatment. Probabilities are given for stability ICH size ≤45.6 mL and >45.6 mL at stability, the median stability ICH size. Probability estimates obtained from unadjusted logistic regression model of dichotomised mRS 0–3 values regressed on clot remaining at end of treatment (p=0.005).

5j1. Graphical Display of mRS Distributions at Day 365 for the As-Treated Cohort



mRS=modified Rankin Scale. mRS scores range from 0 (no disability) to 6 (death).

Figure 5j1 presents the proportion of mRS scores at 365 days for three groups: 1) MISTIE arm among those with ≤15 mL clot volume at end of treatment; 2) MISTIE arm among those with >15 mL clot volume at end of treatment; 3) medical arm. In the paper, an as-treated analysis was reported comparing MISTIE subjects achieving the ≤15 mL goal versus the control arm, with outcome being mRS 0–3 at 365 days. The result was a 10.5% (95% CI 1.0–20.0; p=0.03) increase in mRS 0–3 in the former compared to the latter, after controlling for potential confounding by baseline variables. This analysis involved fitting a weighted logistic regression model for mRS 0–3 given "exposure" (defined as 0=assignment to medical arm and 1=assignment to MISTIE and ≤15 mL clot volume) and baseline age, GCS, stability ICH volume, stability IVH volume, and clot location. The weights used in the regression fit were the inverse propensity score, which adjusted for age, GCS, stability ICH, location, white matter disease (Fazekas score), diabetes, and cardiovascular disease (CVD).

The risk difference reported above was estimated by substituting into the outcome regression model fit the baseline variables for those with exposure = 1 (MISTIE ≤15 mL clot), setting the exposure variable equal to 1, and taking the sample mean of the predicted outcome probabilities. The advantage of this weighted logistic regression method is double robustness to misspecification of the outcome regression model and the propensity score model. To have a causal interpretation, the assumptions of no unmeasured confounding, at least one of the two models being correctly specified, and positivity (non-zero probability of exposure given baseline variables) are needed, as well as outcomes being missing completely at random.

5j2. Tabular Display of mRS Distributions at Day 365 for the As-Treated Cohort

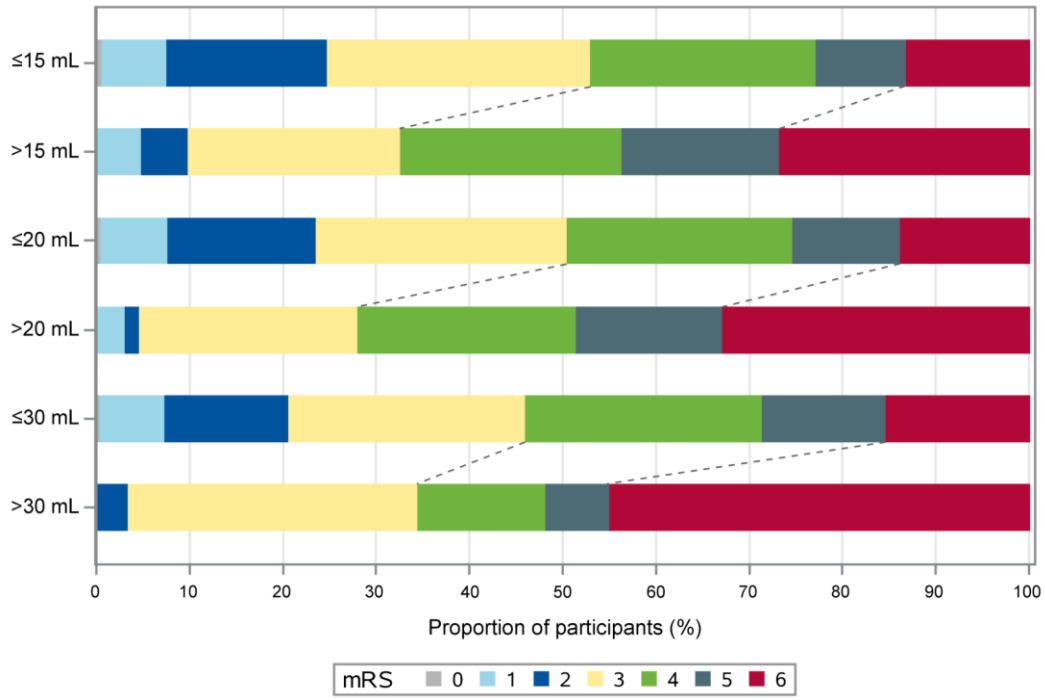
mRS	MISTIE ≤15mL (n=145)	MISTIE >15mL (n=101)	Medical (n=240)
0	1 (0.69%)	0 (0.0%)	6 (2.50%)
1	10 (6.90%)	5 (4.95%)	6 (2.50%)
2	25 (17.24%)	5 (4.95%)	30 (12.50%)
3	41 (28.28%)	23 (22.77%)	58 (24.17%)
4	35 (24.14%)	24 (23.76%)	56 (23.33%)
5	14 (9.66%)	17 (16.83%)	22 (9.17%)
6	19 (13.10%)	27 (26.73%)	62 (25.83%)

mRS scores range from 0 (no disability) to 6 (death).

In the MISTIE ≤15 mL subgroup, 3 patients had no end of treatment ICH volume recorded and 1 patient had no mRS at day 365, so there are 145 patients total.

In the medical group, 1 patient had no EOT ICH volume, 8 patients had no day 365 mRS recorded, and 1 patient had no EOT ICH volume or mRS at day 365. Thus, there are 240 patients total in the medical group.

5k1. Graphical Display of End of Treatment Volumes 15 mL, 20 mL, and 30 mL and mRS 0–3



5k2. Model of Functional Outcomes for MISTIE Group at Clot Removal Thresholds

Within 250 MISTIE subjects, 3 had missing end of treatment (EOT) volumes, and 1 had missing mRS. Proportion of 365 mRS 0–3 was 77 (53.1%) in the ≤15 mL group *vs* 33 (32.7%) in the >15 mL. mRS 4–6 was 68 (46.9%) in the ≤15 mL *vs* 68 (67.3%) in the >15 mL. Adjusted risk difference (95% CI) = 12.0% (1.2%–22.8%), p=0.03.

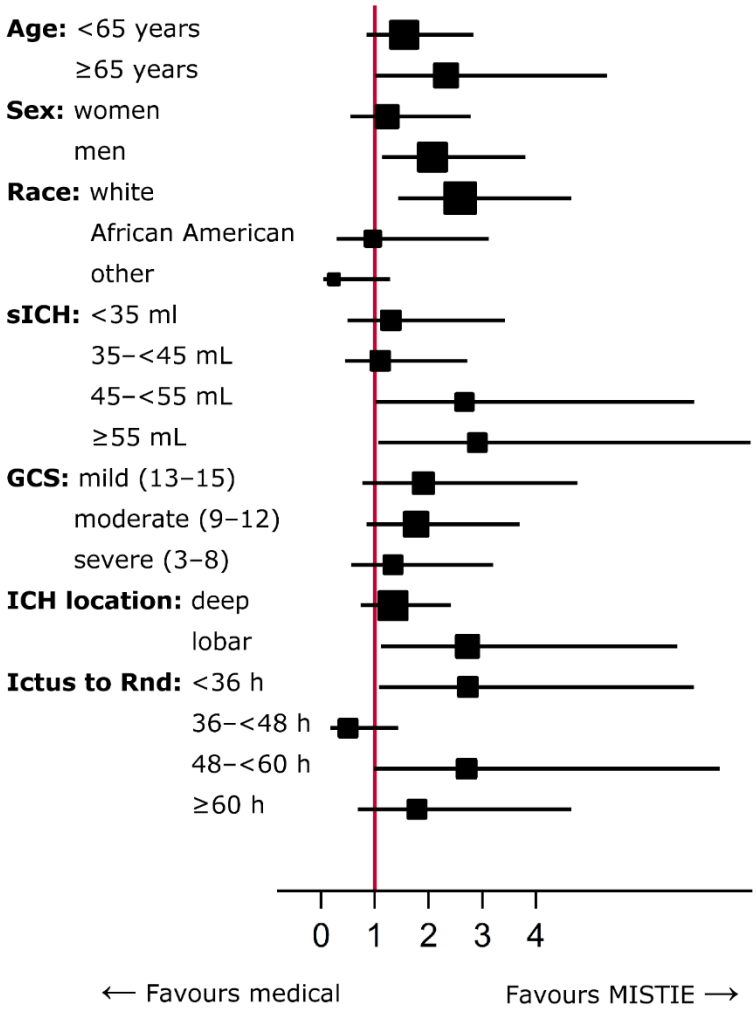
Proportion for 365 mRS 0–3 was 92 (50.6%) in the ≤20 mL *vs* 18 (28.1%) in the >20 mL. mRS 4–6 was 90 (49.5%) in the ≤20 mL and 46 (71.9%) in the >20 mL. Adjusted risk difference (95% CI) = 17.2% (3.2%–31.1%), p=0.02.

Proportion of 365 mRS 0–3 was 100 (46.1%) in the ≤30 mL group *vs* 10 (34.5%) in the >30 mL. mRS 4–6 was 117 (53.9%) in the ≤30 mL *vs* 19 (65.5%) in the >30 mL. Adjusted risk difference (95% CI) = -0.15% (-17.8% to 17.5%), p=0.99.

	Model 1: ≤15 mL	**Model 2: ≤20 mL**	**Model 3: ≤30 mL**
EOT Remain	2.03* [1.06, 3.90]	2.77* [1.17, 6.53]	0.99 [0.36, 2.76]
Age <56	[ref]		
Age 56–66	0.48 [0.23, 1.01]	0.47* [0.23, 0.98]	0.49 [0.24, 1.01]
Age ≥67	0.10*** [0.04, 0.25]	0.10*** [0.04, 0.26]	0.11*** [0.04, 0.27]
GCS 3–8	[ref]		
GCS 9–12	2.04 [0.98, 4.24]	2.16* [1.04, 4.45]	1.86 [0.90, 3.84]
GCS 13–15	3.03* [1.30, 7.05]	2.93* [1.27, 6.78]	2.66* [1.17, 6.03]
Stability ICH <35 mL	[ref]		
Stability ICH 35–<45 mL	0.48 [0.19, 1.20]	0.42 [0.17, 1.07]	0.44 [0.18, 1.08]
Stability ICH 45–<55 mL	0.38* [0.15, 0.99]	0.36* [0.14, 0.95]	0.35* [0.13, 0.90]
Stability ICH ≥55 mL	0.26** [0.10, 0.68]	0.29* [0.11, 0.75]	0.19*** [0.07, 0.49]
ICH Lobar Location	[ref]		
ICH Deep Location	0.11*** [0.05, 0.23]	0.10*** [0.04, 0.21]	0.12*** [0.05, 0.26]
Stability IVH mL	0.92* [0.86, 0.99]	0.91* [0.84, 0.99]	0.91* [0.84, 0.99]
N	246	246	246
Exponentiated coefficients; 95% confidence intervals in brackets			
* p<0.05, ** p<0.01, ***p<0.001			

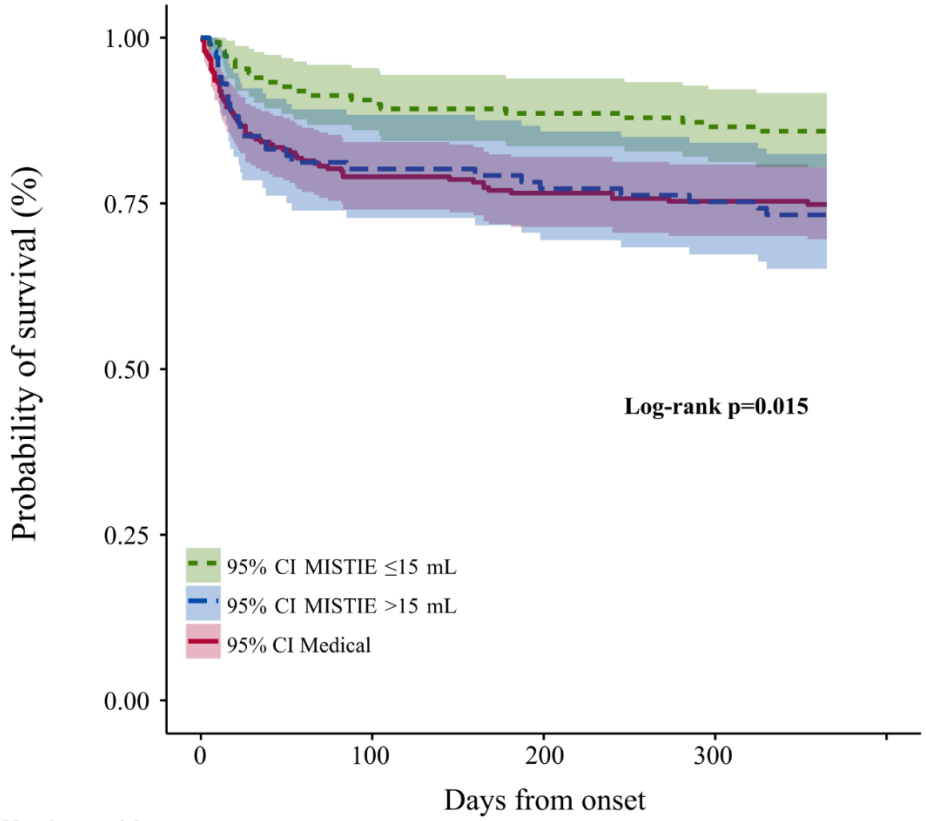
Adjusted odds ratios of mRS 0–3 versus 4–6 at ≤15 mL, ≤20 mL, and ≤30 mL end of treatment clot remaining, MISTIE subjects only. Odds ratios adjusted for ICH size, IVH size, GCS, age, and ICH location at randomisation.

5l. Forest Plot of Favourable Outcome: All Medical versus MISTIE ≤15 mL As Treated



Forest plot of interaction terms, adjusted for age, sex, ICH location, stability intracerebral haemorrhage, and Glasgow Coma Scale (GCS) score (mild, moderate, severe) at admission. The size of points indicates the relative sizes of the subgroups. GCS scores range from 15 (fully conscious) to 3 (deep coma). sICH=stability intracerebral haemorrhage. ICH=intracerebral haemorrhage. Rnd=randomisation.

5m. As-Treated Cohort: Kaplan-Meier Survival Estimates from Randomisation to Observed Day of Death



Number at risk

MISTIE ≤15 mL	149	135	132	128
MISTIE >15 mL	101	81	78	76
Medical	249	193	187	181

Estimated survival probabilities were higher throughout 365 days of follow-up with MISTIE compared to medical treatment (p=0.015). Shading shows 95% CI.

5n. Comparison of Demographics and Initial Severity Parameters of As-Treated Randomised Population

	MISTIE ≤15 mL (n=146)	MISTIE >15 mL (n=101)	Medical (n=249)
Demographic variables			
Age (years)	62 (50-69)	63 (54-73)	62 (53-71)
Men	94 (64.4%)	63 (62.4%)	146 (58.6%)
Race			
black	30 (20.6%)	15 (14.9%)	41 (16.5%)
white	106 (72.6%)	82 (81.2%)	184 (73.9%)
other	10 (6.9%)	3 (3.0%)	24 (9.6%)
missing	0 (0.0%)	1 (1.0%)	0 (0.0%)
Ethnicity: Hispanic/Latino	23 (15.8%)	11 (10.9%)	34 (13.7%)
Baseline variables			
Tobacco use	33 (22.6%)	16 (15.8%)	39 (15.7%)
Cocaine use	7 (4.8%)	4 (4.0%)	9 (3.6%)
Anticoagulated	5 (3.4%)	19 (18.8%)	10 (4.0%)
Hormone replacement therapy	0 (0.0%)	1 (1.0%)	3 (1.2%)
Hyperlipidaemia medication compliant	59 (40.4%)	37 (36.6%)	93 (37.4%)
On antiplatelet therapy	41 (28.1%)	26 (25.7%)	77 (30.9%)
Diabetes	40 (27.4%)	31 (30.7%)	67 (26.9%)
Hypertension	142 (97.3%)	96 (95.1%)	240 (96.4%)
Other cardiovascular disease	20 (13.7%)	18 (17.8%)	34 (13.7%)
Randomisation GCS score*			
3-8	38 (26.0%)	26 (25.7%)	63 (25.3%)
9-12	62 (42.5%)	47 (46.5%)	108 (43.4%)
13-15	46 (31.5%)	28 (27.7%)	78 (31.3%)
Randomisation NIHSS score	19 (15-22)	19 (16-24)	19 (15-23)
Diagnostic CT (at presentation)			
ICH volume (mL)	36.8 (29.2-49.7)	46.5 (36-66)	41.5 (30.9-55.3)
IVH volume (mL)	0 (0-1.1)	0 (0-2.9)	0 (0-1.9)
Stability CT (prior to randomisation)			
ICH volume (mL)	39.7 (33.0-50.3)	58.2 (43.3-72.2)	45.3 (35.4-57.2)
IVH volume (mL)	0 (0-1.6)	1.2 (0-4.9)	0.4 (0-3.2)
Ventilation at randomisation	65 (44.5%)	41 (40.6%)	102 (41.0%)
Blood pressure at presentation			
Systolic BP (mm Hg)	178 (154-212)	176 (156-200)	176 (158-200)
Diastolic BP (mm Hg)	100 (85-120)	98 (82-110)	98 (84-114)
Blood pressure at randomisation			
Systolic BP (mm Hg)	138 (131-147)	139 (130-148)	139 (131-148)
Diastolic BP (mm Hg)	70 (65-78)	69 (62-76)	69 (60-77)
Time from ictus to diagnostic CT (h)	2.2 (1.2-5.8)	2.2 (1.1-6.4)	1.9 (1.2-4.8)
Time from ictus to stability CT (h)	35.1 (23.4-52.8)	36.8 (23.8-50.6)	36.3 (23.6-48.6)
Clot location: deep	100 (68.5%)	62 (61.4%)	144 (57.8%)
Pre-stroke modified Rankin Scale score			
0	136 (93.2%)	92 (91.1%)	233 (93.6)
1	10 (6.9%)	9 (8.9%)	16 (6.4)

Data are n (%), mean (SD), or median (IQR). Three MISTIE subjects are missing EOT volume. *Scores on the Glasgow Coma Scale (GCS) range from 15 (fully conscious) to 3 (deep coma). GCS=Glasgow Coma Scale. NIHSS=NIH Stroke Scale. ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage.

5o. Comparison of Treatment-Related Variables by As-Treated Group

	MISTIE ≤15 mL (n=146)	MISTIE >15 mL (n=101)	Medical (n=249)
Ictus to randomisation (h)	48 (33-61)	45 (35-59)	46 (36-58)
Ictus to end of treatment (EOT) (h)*	120 (100-137)	140 (105-167)	115 (103-127)
MISTIE procedure duration (h)	1 (1-1)	1 (1-1)	NA
Number of doses	3 (2-5)	6 (3-9)	NA
EOT CT ICH volume (mL) IVH volume (mL)	 8.1 (5.8-11.6) 0.1 (0-0.8)	 22.6 (17.6-31.4) 0.6 (0-2.5)	 43.7 (33.6-56.3) 0.3 (0-1.9)
EOT ICH remaining ≤15 mL	146 (100%)	0 (0%)	2 (0.8%)
Withdrawal of care	10 (6.9%)	15 (15%)	35 (14%)
Days in ICU	10 (6-16)	13 (9-19)	10 (6-18)
Days to return home	49 (32-83)	66 (42-135)	62 (35-100)
ICP monitored % subjects with any ICP ≥20 mm Hg % subjects with any CPP <70 mm Hg % ICP readings ≥20 mm Hg† % CPP readings <70 mm Hg†	16/146 (11%) 4/16 (25%) 9/16 (56%) 9/319 (3%) 31/319 (10%)	18/101 (18%) 5/18 (28%) 12/18 (67%) 14/371 (4%) 33/371 (9%)	38/249 (15%) 22/38 (58%) 31/38 (82%) 67/711 (9%) 159/711 (22%)
One or more ICP therapies	12 (75%)	13 (72%)	26/38 (68%)

*Median EOT calculated as 24 hours after last dose for MISTIE subjects who received alteplase dosing. Medical group EOT was calculated from randomisation time plus median surgical EOT time in order to standardise comparison for medical subjects and MISTIE subjects. This achieved a "virtual" dosing endpoint without alteplase dosing for each individual medical subject. †Adjusted for number of readings per subject.
Three MISTIE subjects are missing EOT volume.
ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage. ICU=intensive care unit. ICP=intracranial pressure. CPP=cerebral perfusion pressure.

5p1. Additional Outcome Variables by mITT Group

	MISTIE	Medical	p value
eGOS[1] ≥4 (upper severe disability) at 365 days	94 (38.5%)	84 (35.9%)	0.553
Time to home[2]	55 (34-105)	62 (35-100)	0.846
Location at day 365			
home	154 (76.2%)	145 (77.5%)	
rehab unit	9 (4.5%)	6 (3.2 %)	
acute	1 (0.5%)	0 (0.0%)	0.055
long-term-care facility	37 (18.3%)	27 (14.4%)	
missing[3]	1 (4.5%)	9 (4.8%)	
EuroQoL Visual Analog Scale (EQ-VAS) at 365 days	70 (50-80)	70 (50-80)	0.662
EQ-5D (some+extreme problems) at 365 days			
mobility	138/192 (71.9%)	121/170 (71.2%)	0.883
self-care	117/192 (60.9%)	112/170 (65.9%)	0.330
activities	161/192 (83.8%)	144/170 (84.7%)	0.824
pain	95/192 (49.5%)	89/170 (52.4%)	0.585
anxiety	88/192 (45.8%)	86/170 (50.6%)	0.366
any problems	176/192 (91.7%)	155/170 (91.2%)	0.868
Barthel Index at 365 days	80 (40-100)	80 (40-100)	0.487

Data are n (%) or median (IQR).
[1]Scores on the Extended Glasgow Outcome Scale (eGOS) range from upper good recovery to death. [2]25th percentile provided in place of IQR. Data censored at 180 days for analysis, and 75% of subjects were not yet home. [3]Missing includes subjects who withdrew or were lost to follow-up. [4]Scores on the EuroQol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) on imaginable health state. [5]Scores on the Barthel Index range from 0 (unable to perform any) to 100 (able to perform all) for activities of daily living.

5p2. Additional Outcome Variables by As-Treated Group

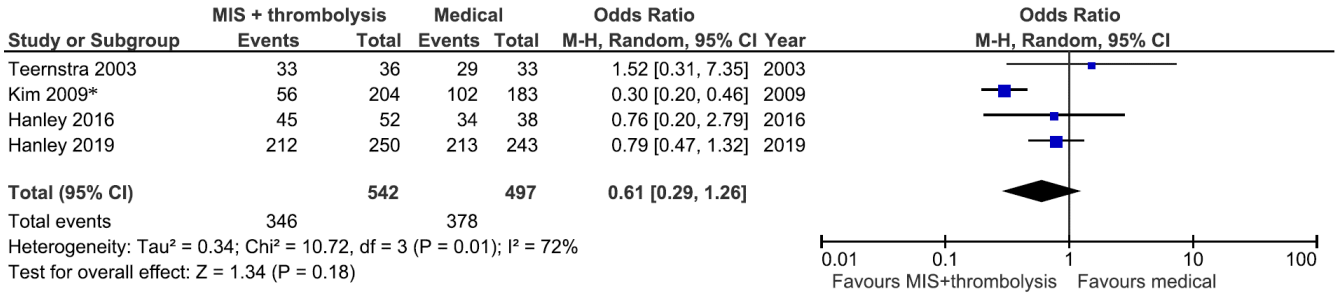
	MISTIE ≤15 mL	MISTIE >15 mL	Medical
eGOS[1] ≥4 (upper severe disability) at 365 days	68 (47.9%)	26 (26.3%)	84 (35.9%)
Time to home[2]	49 (32-83)	66 (42-135)	62 (35-100)
Location at day 365			
home	101 (69.2%)	52 (51.5%)	145 (58.2%)
rehab unit	5 (3.4%)	4 (4.0%)	6 (2.4%)
acute	1 (0.7%)	0 (0.0%)	0 (0.0%)
long-term-care facility	19 (13.0%)	18 (17.8%)	27 (10.8%)
missing[3]	1 (0.7%)	0 (0.0%)	5 (2.0%)
EuroQoL Visual Analog Scale (EQ-VAS) at 365 days	70 (50-80)	60 (50-80)	70 (50-80)
EQ-5D (some+extreme problems) at 365 days			
mobility	79/119 (66.4%)	58/72 (80.6%)	121/170 (71.2%)
self-care	65/119 (54.6%)	51/72 (70.8%)	112/170 (65.9%)
activities	95/119 (79.8%)	65/72 (90.3%)	144/170 (84.7%)
pain	55/119 (46.2%)	39/72 (54.2%)	89/170 (52.3%)
anxiety	58/119 (48.7%)	29/72 (40.3%)	86/170 (50.6%)
any problems	109/119 (91.6%)	66/72 (91.7%)	155/170 (91.2%)
Barthel Index[5] at d365	85 (48-100)	63 (20-95)	80 (40-100)

Data are n (%) or median (IQR).
[1]Scores on the Extended Glasgow Outcome Scale (eGOS) range from upper good recovery to death. [2]25th percentile provided in place of IQR. Data was censored at 180 days for analysis, and 75% of subjects were not yet home. [3]Missing includes subjects who withdrew or were lost to follow-up. [4]Scores on the EuroQol Visual Analog Scale (EQ-VAS) range from 0 (worst) to 100 (best) on imaginable health state. [5]Scores on the Barthel Index range from 0 (unable to perform any) to 100 (able to perform all) for activities of daily living.

5q. Adverse Event Summaries

ADVERSE EVENTS	Stroke to day 30		Stroke to end of follow-up	
Body system classification	**MISTIE (n=255)**	**Medical (n=251)**	**MISTIE (n=255)**	**Medical (n=251)**
Blood and lymphatic system disorders	2 (0.8%)	0 (0.0%)	2 (0.8%)	0 (0.0%)
Cardiac disorders	3 (1.2%)	5 (2.0%)	3 (1.2%)	5 (2.0%)
Gastrointestinal disorders	5 (2.0%)	7 (2.8%)	5 (2.0%)	7 (2.8%)
General disorders and administration site conditions	17 (6.7%)	12 (4.8%)	17 (6.7%)	12 (4.8%)
Hepatobiliary disorders	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.8%)
Immune system disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
Infections, non-neurologic	10 (3.9%)	26 (10.4%)	11 (4.3%)	27 (10.8%)
Injury, poisoning, and procedural complications	1 (0.4%)	2 (0.8%)	1 (0.4%)	4 (1.6%)
Investigations	1 (0.4%)	7 (2.8%)	1 (0.4%)	7 (2.8%)
Metabolism and nutrition disorders	3 (1.2%)	6 (2.4%)	3 (1.2%)	6 (2.4%)
Musculoskeletal and connective tissue disorders	2 (0.8%)	0 (0.0%)	2 (0.8%)	0 (0.0%)
Neoplasms: benign, malignant, unspecified (incl cysts/polyps)	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)
Nervous system disorders	108 (42.4%)	47 (18.7%)	113 (44.3%)	55 (21.9%)
Psychiatric disorders	6 (2.4%)	5 (2.0%)	6 (2.4%)	5 (2.0%)
Renal and urinary disorders	3 (1.8%)	2 (0.8%)	3 (1.2%)	2 (0.8%)
Respiratory, thoracic, and mediastinal disorders	32 (12.5%)	33 (13.1%)	32 (12.5%)	33 (13.1%)
Skin and subcutaneous tissue disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
Vascular disorders	14 (5.5%)	13 (5.2%)	14 (5.5%)	13 (5.2%)

6. Meta-Analysis of MISTIE Procedure (MIS Plus Thrombolysis) from Currently Available, Published Clinical Trials



*Kim et al. limitations: 1) ICH ≤30 cm^3; 2) GCS 13–15; 3) use of rescue surgical therapy; 4) outcome dichotomised at 0–2 vs 3–6

High-quality evidence from well-conducted stroke trials is limited. In a recent meta-analysis in Stroke,[4] only three of 14 studies identified met all Cochrane Review criteria. Thus, we performed our own meta-analysis and added the data from this trial. We searched scientific databases, including PubMed, the CENTRAL (Cochrane Central Register of Controlled Trials), Chinese National Knowledge Infrastructure (CNKI), VIP, and Wanfang, using the Cochrane systematic approach and the PRISMA 2009 guidelines for randomised controlled trials of MIS treatment of supratentorial spontaneous ICH published between 1987 and 2018. The search was done in November 2018 using different combinations of the following terms: spontaneous or intracranial or intracerebral or cerebral or brain or putaminal or intraparenchymal or basal ganglia or thalamic or h(a)emorrhage or h(a)emorrhagic or stroke or hypertensive intracranial h(a)emorrhage or h(a)ematoma or minimally invasive or minimal surgical procedures or endoscopy(ic) or stereotaxy(ic) or aspiration or keyhole or burrhole or craniopuncture or evacuation or randomised or controlled or surgery.

All of the publications were independently identified by three reviewers and assessed for quality using the Cochrane evaluation. The following inclusion criteria were followed for publications: adult patients (at least 18 years of age), supratentorial ICH confirmed by neuroimaging, spontaneous aetiology, minimally invasive surgical procedure plus thrombolysis, multicentre or large single-site studies, and an mRS score taken at 6 months or later.

The outcome for both MISTIE trials was dichotomised mRS 0–3 versus 4–6. However, to produce comparisons across the same cut point, we utilised mRS 0–2 versus 3–6 for all trials, as Kim used that dichotomy and the trial data was not available.

7. References

1. Morgenstern LB, Hemphill III JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; 41: 2108–29.

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3. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet* 2017; 389: 603–11.

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