CLINICAL STUDY PROTOCOL

ENRICH PLUS – A Non-Randomized Controlled Trial to Examine the Safety and Suitability of Supplementing Early Minimally Invasive Parafascicular Surgery (MIPS) for Clot Evacuation of Basal Ganglia Intracerebral Hemorrhage (ICH) with Pioglitazone

Investigational Product:	Pioglitazone
Protocol Name:	ENRICH-PLUS
Indication:	Basal Ganglia Intracerebral Hemorrhage (ICH)
Phase:	2a
Therapeutic Area:	Neurosurgery
Sponsor/PI:	Dr. J. Marc Simard
	University of Maryland, Baltimore
	22 South Greene Street
	Baltimore, MD 21201
Protocol Version:	1.0
Date:	July 11th, 2022

This clinical study will be conducted in accordance with the International Conference on Harmonization Good Clinical Practices Guidelines.

ENRICH PLUS – A Non-Randomized Controlled Trial to Examine the Safety and Suitability of Supplementing Early Minimally Invasive Parafascicular Surgery (MIPS) for Clot Evacuation of Basal Ganglia Intracerebral Hemorrhage (ICH) with pioglitazone

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

_____ _____

J. Marc Simard, MD, PhD

Principal Investigator

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
aPTT	partial thromboplastin time
AVM	arteriovenous malformation
CT	Computed tomography
DNR	Do Not Resuscitate
DSMB	Data Safety Monitoring Board
EMR	Electronic medical record
EVD	external ventricular drain
HUI3	Health Utilities Index Mark 3
ICH	Intracerebral Hemorrhage
ICP	intracranial pressure
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally Authorized Representative
MIPS	Minimally Invasive Parafascicular Surgery
MIS	Minimally Invasive Surgery
mRS	modified Rankin Scale
NICU	Neuro Intensive Care Unit
NIHSS	National Institutes of Health Stroke Scale
PRN	pro re nata (as needed)
GCS	Glasgow Coma Scale
mRS	Modified Rankin Scale
QALY	quality-adjusted life-years
SAE	Serious Adverse Event
T2DM	type 2 diabetes mellitus
TLKN	Time Last Known Normal
TZD	Thiazolidinedione
ULN	Upper Limit of Normal
uw-mRS	utility-weighted modified Rankin Scale

PROTOCOL SYNOPSIS	
Title:	ENRICH PLUS – A Non-Randomized Controlled Trial to Examine the Safety and Suitability of Supplementing Early Minimally Invasive Parafascicular Surgery (MIPS) for Clot Evacuation of Basal Ganglia Intracerebral Hemorrhage (ICH) with pioglitazone
Principal Investigators	J. Marc Simard MD, PhD - Study PI Timothy Chryssikos, MD - Site PI
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Study Sites:	University of Maryland, Baltimore MD
Indication:	Basal Ganglia Intracerebral Hemorrhage (ICH)
Study Objectives:	**Primary Efficacy Goal:** Demonstrate a trend toward improvement in functional outcome in Group 1 compared to the control arm (Group 2) as measured by the utility-weighted mRS (uw-mRS) at 180 days. **Secondary Efficacy Goal:** Demonstrate a trend toward more rapid hematoma clearance or a trend toward reduced perihematomal edema in Group 1 compared to the control arm (Group 2) as measured by serial CT scans during hospitalization.
Study Design:	A single center non-randomized controlled clinical trial comparing early (<24 hours) MIPS plus perioperative pioglitazone (Group 1) to a matched cohort of MIPS alone subjects from the ENRICH trial (Group 2)
Study Arms:	**Group 1:** Subjects will undergo MIPS for evacuation of ICH using the BrainPath access device plus perioperative pioglitazone for 3 weeks **Group 2:** Subjects will undergo MIPS for evacuation of ICH using the BrainPath access device as part of the ENRICH trial

PROTOCOL SYNOPSIS	
Study Population:	Male or female patients between the ages 18 to 80 years, inclusive, with primary basal ganglia ICH who will receive early MIPS in combination with perioperative pioglitazone treatment.
Study Duration:	Approximately 24 months, including recruitment.
Outcome Measures	Primary Outcome Measure - Efficacy ● utility-weighted mRS (uw-mRS) at 180 days[1] Secondary Outcome Measure – Efficacy ● residual clot on CT at day 7 ● perihematomal edema on CT at day 7 Secondary Outcome Measures – Safety ● 30-day mortality (30 days from intervention)[1] ● increase in hemorrhage volume between index CT and 24-hour follow-up CT[1] ● 30-day bacterial brain infection (30 days from intervention) ● Moderate hypoglycemia (<70 mg/dL) ● Severe hypoglycemia (<50 mg/dL) requiring recue therapy ● Drug toxicity Secondary Outcome Measures – Economic ● cost per quality-adjusted life-years (QALY)[1] Tertiary Outcome Measures ● length of ICU stay during hospitalization ● length of hospitalization ● ICU-related complications ● requirement for EVDs ● requirement for hyperosmolar therapies [1] These outcomes are based on the ENRICH trial (NCT02880878); others are specific to ENRICH-PLUS
Sample Size:	20 evaluable subjects
Inclusion Criteria:	1. Age 18-80 years 2. CT scan demonstrating an acute, spontaneous, primary basal ganglia ICH 3. ICH volume between 30 – 80 mL as calculated by the ABC/2 method

PROTOCOL SYNOPSIS	
	4. Study intervention can reasonably be initiated within 24 hours after the onset of stroke symptoms. In situations with unclear time of onset, then the onset will be considered the time that the subject was last known to be well 5. Glasgow Coma Score (GCS) 5 - 14 6. Historical Modified Rankin Score 0 or 1 7. Consent by patient or LAR to MIS evacuation of the ICH based on best medical practice[1] Time to pioglitazone treatment ≤ 24 hours from symptom onset or TLKN[1]
Exclusion Criteria:	1. Ruptured aneurysm, arteriovenous malformation (AVM), vascular anomaly, moyamoya disease, hemorrhagic conversion of an ischemic infarct, or bleeding into a known neoplastic lesion 2. NIHSS < 5, bilateral fixed dilated pupils, extensor motor posturing, unstable mass or evolving intracranial compartment syndrome 3. Intraventricular extension of the hemorrhage estimated to involve >50% of either of the lateral ventricles (External ventricular drain (EVD) to treat intracranial pressure (ICP) or hydrocephalus is allowed) 4. Primary thalamic ICH or infratentorial intraparenchymal hemorrhage including midbrain, pons or cerebellum 5. Evidence of active bleeding involving a retroperitoneal, gastrointestinal, genitourinary, or respiratory tract site 6. Severe kidney or liver disease (serum ALT > 2.5 x ULN) with active coagulopathy 7. Patients requiring long-term anti-coagulation that needs to be initiated < 5 days from index ICH; patient must not require Coumadin (anticoagulation) during the first 30 days (reversal of anticoagulation is permitted for medically stable patients who can safely tolerate the short-term risk of reversal) 8. Use of anticoagulants that cannot be rapidly reversed, uncorrected coagulopathy or known clotting disorder 9. Platelet count < 75,000 10. International Normalized Ratio (INR) > 1.4 after correction or inability to sustain INR ≤ 1.4 using short- and long-active procoagulants (such as, but not limited to, NovoSeven, fresh frozen plasma, vitamin K, Kcentra or Feiba) 11. Untreatable elevated activated partial thromboplastin time (aPTT) 12. Patients with a mechanical heart valve (presence of bioprosthetic valve(s) is permitted)

PROTOCOL SYNOPSIS	
	13. Positive urine or serum pregnancy test in female subjects without documented history of surgical sterilization or is post-menopausal 14. Participation in a concurrent interventional medical investigation or clinical trial 15. Known life-expectancy of less than 6 months, no reasonable expectation of recovery, Do-Not-Resuscitate (DNR), or comfort measures only prior to randomization 16. Inability or unwillingness of subject or legal guardian/representative to give written informed consent 17. Homelessness or history of drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements 18. Known serious hypersensitivity to pioglitazone or any ingredient in the formulation; intolerance or allergy to any TZD[1] 19. T2DM treated with insulin or an oral medication including Glyburide, unless the NICU physician deems it safe to *replace* the T2DM medication with pioglitazone[1] 8. heart failure (symptomatic or NYHA Class I–IV or newly diagnosed on admission TTE screening)
Concomitant Medications:	● Gemfibrozil and ketoconazole both cause significant increases in pioglitazone concentrations and should be avoided. (They act through CYP2C8 inhibition) ● Rifampin will cause a significant decrease in pioglitazone concentrations and should be avoided. (Acts through CYP2C8 induction) ● Avoid the use of hypertonic saline because it biases macrophages toward the M1, away from the M2 phenotype. Use mannitol for ICP control 20. Avoid hyperglycemia because it biases macrophages toward the M1, away from the M2 phenotype.
Study Periods:	Screening Period Treatment Period Day 0-21 Follow-up Period (telephone) 30 Day Follow up 90 Day Follow up 120 Day Follow up 180 Day Follow up

PROTOCOL SYNOPSIS	
Investigational Drug:	pioglitazone
Active Control:	20 subjects who have undergone MIPS for evacuation of ICH using the BrainPath access device only as part of the ENRICH trial
Study Drug Administration:	Pioglitazone will be administered 3 times daily starting ≤24 hours after ictus for a duration of three weeks.
Study Endpoints:	uw-mRS at 180 days Residual clot at 7 days Edema at 7 days AEs and SAEs
Statistical Methodology:	Generalized estimating equations (GEEs) will be used to analyze primary (uw-mRS) and secondary endpoints by comparing group 1 (treatment) and group 2 (control).
Committees:	A DSMB will assess safety and make recommendations

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1 INTRODUCTION AND RATIONALE

1.1. Introduction

Hematoma volume is a critical determinant of mortality and functional recovery after intracerebral hemorrhage (ICH).[1-4] This fact has prompted numerous clinical trials to reduce hematoma volume by conventional or minimally invasive surgery (MIS), or by instilling thrombolytic agents to hasten drainage.[5-7] To date, large randomized controlled trials have failed to demonstrate a clear benefit in terms of mortality or functional outcome.[8] However, a recent meta-analysis of 15 high-quality randomized controlled trials involving 2,152 patients showed that select patients with supratentorial ICH treated with MIS had significantly more favorable morbidity and mortality compared to those with other treatments.[6] In various series that examined an intervention, the degree of clinical benefit correlated with the extent of clot evacuation.[9-11]

ENRICH (Early miNimally-invasive Removal of IntraCerebral Hemorrhage) is an ongoing multicenter, randomized, adaptive clinical trial comparing standard medical management to early (<24 hours) surgical hematoma evacuation using minimally invasive parafascicular surgery (MIPS) for the treatment of spontaneous acute basal ganglia, thalamic or lobar ICH (NCT02880878). The ENRICH trial will compare the outcomes between early surgical intervention using the BrainPath® Approach (i.e., MIPS) and a medically managed cohort. The surgical approach includes a combination of available technologies, including the FDA-cleared NICO BrainPath® for non-disruptive access and NICO Myriad® to achieve the goal of maximum clot evacuation. The medically managed cohort will be treated according to the Clinical Standardization Guidelines as adapted by Emory University from the 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Clinical efficacy will be determined by demonstrating a 10% improvement in functional outcome, as determined by a blinded-assessment of the 180-day utility-weighted modified Rankin Scale (uw-mRS). The methodology utilized in the ENRICH trial was validated in a series of 39 patients treated for spontaneous supratentorial ICH and retrospectively reviewed,[12] and the results from the retrospective study were replicated in a single center series of 18 patients.[13]

1.2. Pioglitazone

Monocytes can differentiate into M1 or M2 macrophages that exhibit pro- or anti-inflammatory functional phenotypes, respectively.[14] The M2 macrophage phenotype is pro-phagocytic and is largely responsible for hematoma clearance in ICH.[13] Treatments to bias the macrophage phenotype away from the pro-inflammatory M1 toward the pro-phagocytic M2 phenotype have the potential to enhance MIS procedures for ICH clot removal by accelerating clearance of residual hematoma and necrotic debris, and reducing neuroinflammation.

In preclinical studies, several strategies have been employed to accelerate hematoma clearance in ICH (see review[16]). Arguably the most druggable pathway known to influence macrophage phenotype is the PPARγ (peroxisome proliferator-activated receptors) pathway.

The thiazolidinediones (TZD) are a class of drugs that selectively activate PPARγ. Of three available TZDs, pioglitazone (Actos) and rosiglitazone (Avandia), both currently FDA-approved for type 2 diabetes mellitus (T2DM), are the most promising for study in ICH. Work on this topic originated from the laboratory of Dr. Jaroslaw Aronowski.[15-18] They were the first to demonstrate in a mouse ICH model that rosiglitazone promotes hematoma resolution, decreases neuronal damage, and improves functional recovery.[15] Their work on PPARγ in ICH has been replicated and expanded.[13, 19-21]

The Aronowski group also conducted a prospective, randomized, blinded, placebo-controlled, dose-escalation safety trial of pioglitazone in non-surgical ICH patients: "Safety of Pioglitazone for Hematoma Resolution In Intracerebral Hemorrhage (SHRINC)" (NCT00827892).[22] The study enrolled 84 patients. The study was not powered for clinical efficacy. Nevertheless, this early phase study showed that pioglitazone was safe and well tolerated in the ICH patient population (unpublished; personal communication from JA).

1.3. Study Rationale

In patients with intracerebral hemorrhage (ICH), increasing evidence suggests that the best outcomes are obtained when most of the clot is evacuated promptly. Minimally invasive surgery (MIS) to evacuate the ICH remains under active study, as in the ongoing ENRICH trial detailed above. Despite effective MIS clot evacuation, improving outcomes in patients with supratentorial ICH remains challenging, likely due to the multi-factorial secondary effects of the initial blood clot, residual clot components, and neuroinflammation.

We *hypothesize* that outcomes from MIPS for ICH would be enhanced by concurrently addressing the secondary effects by treating patients with a drug therapy designed to accelerate innate mechanisms of phagocytosis to remove post-operative residual blood and necrotic tissue debris, and to reduce neuroinflammation. The PPARγ agonist, pioglitazone, which has been shown to enhance phagocytosis and clearance of hemorrhagic debris, is well suited for this purpose.

We propose an exploratory non-randomized pilot study, called "ENRICH-PLUS", to examine the potential benefit and safety of combining MIPS, exactly as performed in the ENRICH trial, with pioglitazone, as administered in the SHRINC trial. To enhance homogeneity in this pilot trial, only patients with ICH involving basal ganglia will be enrolled (not thalamic or lobar hemorrhages). In ENRICH-PLUS, all other inclusion/exclusion (I/E) criteria will be identical, and the surgical technique will be identical to ENRICH. Thus, it will be feasible and appropriate to compare outcomes of subjects in ENRISH-PLUS to those of matched subjects from the ENRICH trial.

This exploratory study is not powered to determine the benefit of MIPS plus pioglitazone vs. MIPS alone. It is intended to provide actionable pilot data for a future grant application for a larger, definitive trial to be submitted to StrokeNET (NIH/NINDS).

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to determine if there is a trend toward improvement or non-inferiority in functional outcome in Group 1 (ENRICH-PLUS) compared to Group 2 (controls from ENRICH) as measured by the utility-weighted mRS (uw-mRS) at 180 days.

2.2 Secondary Objectives

The secondary objective of this study is to determine if there is non-inferiority or a trend toward more rapid hematoma clearance and perihematomal edema in Group 1 compared to the control arm (Group 2) as measured by serial CT scans during hospitalization.

3 STUDY DESIGN

3.1 Overall Study Design

This is an exploratory single-center prospective study of 20 subjects with primary basal ganglia ICH who will receive early MIPS in combination with perioperative pioglitazone treatment. Outcomes will be compared to matched subjects with basal ganglia ICH who undergo MIPS alone as part of the ENRICH trial. This study will take approximately two years to complete.

Study Arms:

Group 1: 20 Subjects will undergo MIPS for evacuation of ICH using the BrainPath access device plus perioperative pioglitazone for 3 weeks

Group 2: Subjects will undergo MIPS for evacuation of ICH using the BrainPath access device as part of the ENRICH trial (NCT02880878). These subjects will be enrolled at an ENRICH trial site independent of our Institution. Deidentified patient information from 20 subjects in this group, who will be matched to those in the ENRICH-PLUS group, will be provided to the principal investigator for comparison of outcomes.

Consent for study participation will be obtained from the patient or the LAR only after fulfilling all inclusion and exclusion criteria either before or after MIPS, which will be scheduled as a standard institutional procedure outside the realm of the study.

Study participants will be administered pioglitazone (15 mg tablet) either p.o. or enteral (via nasogastric tube). The first dose may be administered prior to surgery or within 3 hours of the end of surgery but must be administered within 24 hours of the index event or time last known normal (TLKN). Pioglitazone (15 mg tablet) administration will continue 3 times daily for 3 weeks, including after hospital discharge, if applicable.

Following completion of pioglitazone, subjects will be followed at days 30, 90, 120 and 180 post MIPS. In addition to AE monitoring during these follow up's, a utility-weighted mRS (uw-mRS) at 180 days will serve as the primary end point.

3.2 Study Stopping Criteria

Enrollment will stop when:

- 20 subjects have been enrolled
- the DSMB determines that pioglitazone is causing patient harm
- the Sponsor withdraws support

4 SELECTION OF SUBJECTS

Male or female patients between the ages 18 to 80 years, inclusive, with a primary basal ganglia ICH confirmed by CT scan, who will receive early MIPS for evacuation of ICH using the BrainPath, will be considered for enrollment in this study. Patients should have had the onset of ICH within 24 hours prior to the first dose of pioglitazone. Specific inclusion and exclusion criteria of this study are listed in Section 4.1 and Section 4.2, respectively.

4.1 Inclusion criteria

Inclusion criteria for enrollment in this study are as follows:

1. Age 18-80 years
2. CT scan demonstrating an acute, spontaneous, primary basal ganglia ICH
3. ICH volume between 30 – 80 mL as calculated by the ABC/2 method
4. Study intervention can reasonably be initiated within 24 hours after the onset of stroke symptoms. In situations with unclear time of onset, then the onset will be considered the time that the subject was last known to be well
5. Glasgow Coma Score (GCS) 5 - 14
6. Historical Modified Rankin Score 0 or 1
7. Consent by patient or LAR to MIS evacuation of the ICH based on best medical practice[1]
8. Time to pioglitazone treatment ≤ 24 hours from symptom onset or TLKN[1]

4.2 Exclusion criteria

The study will exclude patients with any of the following criteria:

1. Ruptured aneurysm, arteriovenous malformation (AVM), vascular anomaly, moyamoya disease, hemorrhagic conversion of an ischemic infarct, or bleeding into a known neoplastic lesion
2. NIHSS< 5, bilateral fixed dilated pupils, extensor motor posturing, unstable mass or evolving intracranial compartment syndrome
3. Intraventricular extension of the hemorrhage estimated to involve >50% of either of the lateral ventricles (External ventricular drain (EVD) to treat intracranial pressure (ICP) or hydrocephalus is allowed)
4. Primary thalamic ICH or infratentorial intraparenchymal hemorrhage including midbrain, pons or cerebellum
5. Evidence of active bleeding involving a retroperitoneal, gastrointestinal, genitourinary, or respiratory tract site
6. Severe kidney or liver disease (serum ALT > 2.5 x ULN) with active coagulopathy
7. Patients requiring long-term anticoagulation that needs to be initiated < 5 days from index ICH; patient must not require Coumadin (anticoagulation) during the first 30 days (reversal of anticoagulation is permitted for medically stable patients who can safely tolerate the short-term risk of reversal)
8. Use of anticoagulants that cannot be rapidly reversed, uncorrected coagulopathy or known clotting disorder
9. Platelet count < 75,000
10. International Normalized Ratio (INR) > 1.4 after correction or inability to sustain INR ≤ 1.4 using short- and long-active procoagulants (such as, but not limited to, NovoSeven, fresh frozen plasma, vitamin K, Kcentra or Feiba)
11. Untreatable elevated activated partial thromboplastin time (aPTT)
12. Patients with a mechanical heart valve (presence of bioprosthetic valve(s) is permitted)
13. Positive urine or serum pregnancy test in female subjects without documented history of surgical sterilization or is post-menopausal
14. Participation in a concurrent interventional medical investigation or clinical trial
15. Known life-expectancy of less than 6 months, no reasonable expectation of recovery, Do-Not-Resuscitate (DNR), or comfort measures only prior to randomization
16. Inability or unwillingness of subject or legal guardian/representative to give written informed consent
17. Homelessness or history of drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements
18. intolerance or allergy to any TZD[1]

19. T2DM treated with insulin or an oral medication including Glyburide, unless the NICU physician deems it safe to *replace* the T2DM medication with pioglitazone[1]
20. heart failure (symptomatic or NYHA Class I–IV or newly diagnosed on admission TTE screening)[1]

5 STUDY PROCEDURES

5.1 Schedule of Procedures

	Screening (Prior to Consent)	Enrollment </= 24 Hr post onset / TLKN	Day 0 (MIPS)[2]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 (1st or Discharge, which ever is first)	Discharge	Day 10 (+/- 24 hours)	Day 30 (+/- 7 days) PHONE	Day 90 (+/- 14 days) PHONE	Day 120 (+/- 14 days) PHONE	Day 180 (+/- 14 days) PHONE
Review Inclusion/Exclusion	X															
Informed Consent		X														
Pioglitazone (15mg TID)		X[1]														
MIPS			X[2]													
Charleson Comorbidity Index		X														
Demographic Data		X														
Medical History	X															
Laboratory results[3]	X			X												
Hematology	X			X												
Chemistry	X			X												
Coagulation	X															
Pregnancy Test	X															
Head CT	X[4]			X[4]						X						
FUNC/ICH/APACHE Scores	X															
NIHSS	X[4]			X						X						
HUI3											X		X	X	X	X
uw - mRS	X[5]										X		X	X		X
GCS	X[4]			X						X						
Glucose Finger Sticks			X[6]													
sCD163 Blood Sample		X					X					X[7]				
Height/Weight		X														
Vitals[8]		X	X													
Concomitant Therapies			X													
Concomitant Medications*			X													
Adverse Event Monitoring*			X													
Serious Adverse Events*			X													
Hospital Utilization Form											X					

1. 15mg TID. Must be administered within 24 hrs of onset OR TLKN. First dose may be administered up to 24 hours prior to MIPS surgery or within 3 hours of end of surgery. Given for a total of 3 weeks, including after discharge, if applicable
2. Day 0 will begin at end time of SOC MIPS surgery
3. Any lab result conducted as SOC may be used to fufill a study timepoint
4. Data from Standard of Care
5. Historic mRS - The historical mRS will be estimated during the screening process. The historical score, which will be determined by investigator interview with the subject's LAR, is based on the subject's level of functioning prior to the onset of symptoms.
6. Prior to each drug administration (within 30 minutes), for at least 3 days. Will continue if hypoglycemia is detected; will cease if hypoglycemia is not detected for 72 hours (9 doses of Pioglitazone)
7. Only collected if patient is still admitted
8. Vitals will be collected daily from day 0 - Day 7 and will include BP, Resp, HR

* Concomitant medications, AE's, and SAE's will be documented starting at time of first administration of pioglitazone and ending at day 180. All medications will be captured.

5.2 Screening

Patients presenting with primary basal ganglia ICH 30 – 80 mL, as demonstrated on admission CT scan, will be assessed to determine if they are an appropriate candidate to undergo MIPS for evacuation of ICH using the BrainPath, prior to consideration for enrollment into the clinical trial. Only those patients who are planned to undergo MIPS, and who also meet all study Inclusion and Exclusion criteria, will be approached for enrollment into the study. The following routine scans and assessments, that will be conducted as standard of care outside the study, will be reviewed by the study principal investigator, and sub-investigators, to determine eligibility into the trial:

- Head CT
- Laboratory testing: PT, PTT, INR, HCG when applicable (Urine or Serum), CBC, complete metabolic profile including ALT and AST
- Glasgow Coma Score (GCS)
- NIH Stroke Scale score (NIHSS)
- mRS (historical)

  A historical mRS will be used during the screening process. The historical score, which will be determined through an interview with the subject's LAR, is based on the subject's level of functioning prior to the onset of symptoms.
- FUNC Score
- The Intracerebral Hemorrhage (ICH) Score
- APACHE II

Should an assessment needed for eligibility purposes not be done as standard of care prior to consent, the assessment will be conducted only after obtaining informed consent for research purposes but prior being formally enrolled into the study. No assessment or test will be administered for study related purposes until after informed consent has been obtained.

5.3 Enrollment / Informed Consent

- All patients with basal ganglia ICH who are deemed likely to benefit from surgical resection will be offered and consented for MIPS. The indication for MIPS surgery will be based on standard of care for basal ganglia ICH, whether or not the patient is eligible for ENRICH-PLUS.
- Subsequently, if a patient consents to MIPS and if they meet eligibility for ENRICH-PLUS, they will be offered and consented for enrollment in ENRICH-PLUS. If an eligible patient undergoes MIPS emergently, he/she can be offered and consented for

enrollment in ENRICH-PLUS after surgery, as long as drug can be started within 24 hours of the index event.

5.3.1 Informed Consent

Patients who are eligible will be asked if they are willing to participate in this study. Participation will be fully voluntary, and rejection will not affect the availability of other treatment modalities that may be appropriate. Should a patient be unable to consent themselves, their legally authorized representative will be approached. The study staff will maintain a screening log of all subjects consented to be included in the study.

5.3.2 Baseline Assessments

After consent but prior to drug administration, the following will be collected, only if not already done so as standard of care:

- Charleson Comorbidity Index
  Demographic Data
- Vitals including Height and Weight
- sCD163 Blood Sample

5.4 Treatment Period

Patients who consent and are enrolled in ENRICH-PLUS will be administered the first dose of the pioglitazone regimen prior to surgery or within 3 hours after MIPS surgery, at the discretion of the treating physicians

The treatment period will begin at the time of the first dose of pioglitazone. From the beginning of the treatment period through the end of the study at day 180, the following data will be captured:

Concomitant medications
Concomitant Therapies
Adverse Events
Serious Adverse Events

5.4.1 Glucose Testing

- Finger sticks for glucose will be performed by the ICU nurse caring for the patient. The results will be recorded in the patient's electronic medical record (EMR).
- Within 15 minutes before administering each dose of pioglitazone, a fingerstick for blood glucose will be performed to rule out hypoglycemia (< 70 g/dL) (see exception below)
- If hypoglycemia is not present, pioglitazone will be administered

- If hypoglycemia is diagnosed, whether symptomatic or asymptomatic, pioglitazone will not be administered, and the institutional standard of care for management of hypoglycemia will be implemented, as outlined in section 7.1. A patient with hypoglycemia will await the next scheduled time of drug administration, at which time he/she will be tested again to determine whether drug can be administered.
- After 9 successive glucose tests showing no hypoglycemia, routine finger sticks may be stopped

5.4.2 Study Drug Administration

- After the glucose stick has confirmed absence of hypoglycemia, pioglitazone (15 mg tablet) will be administered po or via NG tube.
- Subsequent pioglitazone dosing on a q 8-hour schedule may be based on the time of the first dose administered, or it may revert to an alternative q 8-hour schedule that is more convenient for ICU nursing care

5.4.2.1 Study Drug Administration Post Hospital Discharge

- Any subject who is discharged prior to completion of 3 weeks, or 63 doses, of pioglitazone, will be sent home with any remaining doses. Patients will be given a daily dosing log to complete to confirm compliancy. The study team will collect a copy of this log to be used as the administration log source.

5.5 Follow Up Period

Follow ups will be conducted at the following timepoints as measured from the end time of MIPS surgery. Follow up's at day 30, 90, 120 and 180 will all be conducted remotely over the phone.

5.5.1 24 Hours (+/- 6 Hours) and Day 7 (+/- 24 Hours, or Discharge, whichever is first*)*

The 24 hour and Day 7 follow up will include only a CT scan. Should a CT scan within this window be performed as standard of care, it will also be used for research purposes. In the case a CT scan is not routinely performed, one will be done for research purposes. CT scans will be analyzed using software for semi-automatic segmentation to determine hematoma volume and perihematomal edema

In addition to the CT's, safety will also be assessed using the following scales at Day 1 and Day 7(or Discharge, whichever is first):

- Glasgow Coma Score (GCS)

- NIH Stroke Scale score (NIHSS)

5.5.2 Day 30 (+/- 7 Days)

Assessments Collected at this visit:

- mRS
- Health Utilities Index Mark 3 (HUI3)
- Review of Concomitant Medications
- Review of Adverse Events

5.5.3 Day 90 *(+/- 14 Days)*

Assessments Collected at this visit:

- mRS
- HUI3
- Review of Concomitant Medications
- Review of Adverse Events

5.5.4 Day 120 *(+/-14 Days)*

Assessments Collected at this visit:

- HUI3
- Review of Concomitant Medications
- Review of Adverse Events

5.5.5 Day 180*(+/- 14 Days)*

Assessments Collected at this visit:

- mRS
- HUI3
- Review of Concomitant Medications
- Review of Adverse Events

6 CLINICAL ASSESSMENTS

- *NIH Stroke Scale score (NIHSS)*

  The NIHSS quantifies stroke severity based on weighted evaluation findings and includes a graded neurological examination assessing consciousness, eye movements, visual fields, motor and sensory impairments, ataxia, speech,

cognition, and inattention. An NIHSS will be completed during the screening period, as well as Day 1 and Day 7, in order to assess and quantify neurological deficits from baseline through treatment phase. This assessment will only be conducted by personnel trained and qualified to administer this assessment.

- *Modified Rankin Score (mRS)*

  The mRS is a functional disability scale that is weighted toward neurological disability, and will be conducted at baseline, using a historical score, as well as discharge, Day 30, 90, 120 and 180. This assessment will only be conducted by personnel trained and qualified to administer this assessment.

- *FUNC Score*

  The FUNC Score is used to predict likelihood of achieving functional independence.

  The score will be collected only at baseline utilizing the baseline GCS and neuroimaging.

- *The Intracerebral Hemorrhage (*ICH*)* Score

  The ICH Score estimates mortality based on age and CT findings.

  The score will be collected only at baseline utilizing the baseline GCS and neuroimaging.

- *APACHE II*

  APACHE II score is a general measure of disease severity based on current physiologic measurements, age & previous health conditions.

  The score will be collected at baseline for all patients who have arterial blood gas (ABG) results. If an ABG is not collected as routine standard prior to first dose or MIPS (which ever comes first), the APACHE II score will not be collected

- *Charleson Comorbidity Index (CCI)*

  The Charleson Comorbidity Index predict risk of death within 1 year of hospitalization for patients with specific comorbid conditions.

- *Health Utilities Index Mark 3 (HUI3)*

  HUI3 is a classification system for the purpose of measuring health status, reporting health-related quality of life, and producing utility scores. The ENRICH PLUS protocol will be using the “Mark 3” version of this system.

7 BIOMARKER BLOOD SAMPLE

Acute sCD163 levels may be a useful biomarker for the acute identification of patients at risk for perihematomal edema expansion and poorer short-term outcomes.[23, 24] To further evaluate this, biomarker analysis will be conducted in which blood will be collected at pre-dose, and at Day 4 ± 12 hours and Day 10 ± 24 hours (only if the subject is still admitted) from the time of the initial dose. Approximately 6 mLs of blood will be drawn at each time-point for a total of 18 mLs per subject across the entire duration of the study. These additional blood samples are voluntary.

7.1 Biomarker Collection, Processing, and Storage

For details regarding collecting, processing, and storing of samples, refer to the Biomarkers Study Manual.

8 CONCOMITANT MEDICATIONS

8.1 Protocol for Managing Hypoglycemia

Within 15 minutes before administering each dose, a fingerstick for blood glucose will be performed to rule out hypoglycemia (< 70 mg/dL). If hypoglycemia is detected, the institutional standard of care for management of hypoglycemia will be used when applicable. This includes the following:

- Glucagon 1 mg IM once PRN for blood glucose < 70 in unconscious patient without IV access
- Glucose chewable tablet 16 g every 15 minutes PRN for blood glucose < 70 in patient who is awake and able to take PO, repeat every 15 minutes until blood glucose > 70
- Dextrose 50% injection 25 mL every 15 minutes PRN IV for blood glucose < 70 in patient unable to take PO and with IV access, repeat every 15 minutes until blood glucose > 70
- Non-medication - 15 grams of fast-acting carbohydrates (8 oz of nonfat milk or 4 oz of juice or non-diet soda). Repeat POC BG in 15 minutes and repeat 15 grams of fast-acting carbohydrates every 15 minutes until blood glucose > 70

8.2 Medications to Avoid

The following treatments should be avoided during the Study

- **Gemfibrozil and ketoconazole** - These medications act through CYP2C8 inhibition and can cause significant increases in pioglitazone concentrations
- **Rifampin** - This medication acts through CYP2C8 induction and has been shown to cause a significant decrease in pioglitazone concentrations

- **Hypertonic Saline** – Because its biases macrophages toward the M1, away from the M2 phenotype, mannitol should be used for ICP control in this study.

8.3 Reporting Concomitant Medications

Medications, including frequency, dose, and route, will be reported beginning at time of admission through the 180 Day follow up.

9 CONCOMITANT THERAPIES

The following concomitant therapies will be captured from the time of enrollment through the end of day 180 follow-up:

- EVD placement/removal
- Lumbar punctures
- Mechanical ventilation
- Ventriculoperitoneal shunt placement/removal
- Feeding tube placement/removal

Documentation of concomitant therapies will include start time, end time, and indication for therapy.

10 STUDY DRUG

10.1 Storage & Accountability

The Principal Investigator will assume responsibility of inventory of all study drug dispensed during the conduct of this study. Drug inventory and storage will be maintained in a drug accountability log. Drug inventory, storage, and dispersal will be managed and maintained by Investigational Drug Services (IDS).

11 DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

11.1 Discontinuation of Study Treatment

11.1.1 Severe allergic reaction to pioglitazone
11.1.2 Heart failure
11.1.3 Refractory symptomatic hypoglycemia (<55 mg/dL)

11.2 Lost to Follow-Up

Every effort will be made to contact all subjects for study follow-up and to encourage visit compliance. A log will be kept which will include dates of attempted contact and results of that contact. After 3 unsuccessful attempts at contact (e.g., by telephone or email), the study team will send a certified letter to both the patient and the LAR to solicit

compliance. The subject will be considered "lost to follow-up" only after a certified letter has been sent to both the LAR and subject with no response within 30 days of sending.

11.3 Withdrawal of Subjects from Study

Subjects may voluntarily withdraw from the study at any time for any reason, and without prejudice to further treatment. Subject participation in the study may be terminated at any time at the discretion of the Investigator.

Possible reasons for discontinuation include,

- Withdrawal of subject/LAR consent. Subject withdrawal may occur any time the subject or LAR wishes to no longer continue with the study.

Every attempt must be made to obtain information about the reason(s) for discontinuation, and any possible AEs. The date the subject is discontinued from the clinical investigation and the reason for discontinuation will be recorded in subject chart. Subjects whose study therapy is discontinued for any reason should be treated and followed according to established medical practice.

12 POTENTIAL RISKS

Rationale for Dose of Pioglitazone

The dose of 45 mg/day (45 mg/~70 kg/day ~ 0.65 mg/kg/day) pioglitazone is the highest daily dose recommended for this drug in patients with type 2 diabetes mellitus (T2DM).

Cai et al.[25] reported a placebo-controlled dose-finding study to identify the maximum tolerated dose for pioglitazone in stroke patients with spontaneous ICH (SHRINC). Their trial enrolled 84 patients with 42 assigned to the placebo group and 42 assigned to the pioglitazone group. They found that the dose level 1.0 mg/kg/day is the dose that satisfies the proposed maximum tolerated dose (MTD) criteria, which is the dose with the mortality rate closest to that in the control group.

The highest dose used in the SHRINC trial (NCT00827892) was 30 mg/day, and they identified no untoward effects.

Based on the above, the ENRICH-PLUS trial will use 15 mg t.i.d. Pioglitazone (15 mg tablet) administration will continue 3 times daily for 3 weeks, or 63 doses, including after hospital discharge, if applicable.

12.1 Risks Related to Study Drug

Common side effects of pioglitazone include headaches, muscle pains, inflammation of the throat, and swelling of legs

Contraindications

- Initiation of therapy in patients with NYHA class III or IV heart failure. (See Boxed Warning.)
- Known serious hypersensitivity to pioglitazone or any ingredient in the formulation.

12.1.1 Hypoglycemia

- Pioglitazone increases insulin sensitivity in target tissues and decreases hepatic gluconeogenesis. It ameliorates insulin resistance associated with type 2 diabetes mellitus without increasing insulin secretion from pancreatic β cells. It does not lower glucose concentrations below euglycemia.
- The risk of hypoglycemia is low unless it is used in conjunction with other anti-diabetic drugs.

Risk Mitigation: Although pioglitazone is usually dosed once daily in patients with T2DM, the ERNICH-PLUS trial will employ t.i.d. dosing, in order to provide an opportunity to closely monitor blood glucose and skip a dose of study drug if hypoglycemia is detected. This protocol is intended to make it safer to administer up to 45 mg/day. Pioglitazone has a long half-life, 3–7 hours, and 16–24 h for its metabolically active metabolites; it has been shown to cross the blood–brain barrier.[28]

12.1.2 Heart Failure

- Thiazolidinediones, including pioglitazone, cause or exacerbate heart failure in some patients.
- Not recommended in patients with symptomatic heart failure.
- Initiation of pioglitazone is contraindicated in patients with NYHA class III or IV heart failure.

12.1.3 Hepatic Effects

- No evidence of drug-induced hepatotoxicity in controlled clinical trial database to date. However, hepatic failure with or without fatalities have been reported during post marketing experience.

12.1.4 Risk of Bladder Cancer

- Potential increased risk of bladder cancer. Do not use in patients with active bladder cancer; use with caution in patients with history of bladder cancer.
- However, recent reviews of this potential risk[27-29] concluded that the association of pioglitazone with bladder cancer is questionable.

12.1.5 Drugs Affecting Hepatic Microsomal Enzymes

- Concurrent use of potent CYP2C8 inhibitors increases pioglitazone AUC and half-life, potentially requiring dose reduction.

12.1.6 Advice to Patients

- Importance of informing patients that pioglitazone must not be used in patients with severe heart failure (NYHA class III or IV). Importance of immediately informing clinician if potential manifestations of heart failure (e.g., rapid weight gain, edema, unusual fatigue, trouble breathing, shortness of breath) occur.
- Advise patients to inform clinician if potential manifestations of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, yellowing of skin or whites of eyes) occur.
- Importance of patient not taking pioglitazone if receiving treatment for bladder cancer. Importance of patient reporting any sign of macroscopic hematuria or symptoms such as dysuria or urinary urgency that develop or increase during pioglitazone treatment.
- Risk of hypoglycemia *in patients receiving concomitant insulin or other antidiabetic therapy*. Provide instructions to patients and responsible family members regarding management of hypoglycemia, including recognition of symptoms, predisposing conditions, and treatment.
- Risk of pregnancy in premenopausal anovulatory women.
- Importance of regular eye examinations. Importance of reporting changes in vision.

13 POTENTIAL BENEFITS

Based on what is known about pioglitazone, subjects may experience more rapid clearing of blood and blood products from the brain, and reduced inflammation in the brain

14 SAFETY ASSESSMENT

14.1 Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition that occurs during the study. These include:

1. Increase in frequency or intensity of a pre-existing condition or disease
2. A medical condition that is diagnosed after study drug administration
3. Any event considered to be related to the study drug
4. Abnormal assessments that, in the opinion of the investigator, are clinically significant, and were either not present not present at baseline, or have worsened after administration of the study drug. These include abnormalities imaging, laboratory tests or clinical assessments.

14.2 Documentations of Adverse Events

Adverse Events will be reported from the fine of first initial administration of pioglitazone through the conclusion of the 180 Day follow up.

14.2.1 Grading and Causal Relationships of Adverse and Serious Adverse Events

Grading and Causal Relationship of Serious Adverse Events
The NCI CTCAE, Version 4.0, will be used for documentation purposes. The grades as assessed by the Investigator according to the definitions in NCI-CTCAE, Version 4.0 are as follows:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Life-threatening or disabling
Grade 5 = Death related to adverse event

14.3 Serious Adverse Events (SAEs)

Serious Adverse events will be reported from the fine of first initial administration of pioglitazone through the conclusion of the 180 Day follow up. All SAEs regardless of causal relationship must be reported.
An SAE is defined as any adverse event that fulfills at least one of the following criteria:

1. Fatal;
2. Life-threatening
3. Requiring patient's hospitalization or prolongation of existing hospitalization
4. Resulting in persistent or significant disability or incapacity
5. Congenital anomaly or birth defect
6. Medically significant or requires intervention to prevent at least one of the outcomes listed above.

Life-threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that, hypothetically, might have caused death if it were more severe.
Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.
Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room due to an adverse event. An additional overnight stay defines a prolongation of existing hospitalization.

14.4 Evaluation of Serious Adverse Events

14.4.1 Serious and unexpected suspected adverse reaction

In accordance with 21CFR312.32, the sponsor will report any suspected adverse reaction that is both serious and unexpected. Additionally, the sponsor will also report any adverse reaction if there is evidence to suggest a causal relationship between the drug and the adverse event.

14.4.2 Unexpected fatal of life-threatening suspected adverse reaction reports

In accordance with 21CFR312.32, any unexpected fatal or life-threatening suspected adverse reactions will be reported as soon as possible but within no more than 7 calendar days after knowledge of the event.

15 STATISTICAL METHODS AND SAMPLE SIZE CALCULATION

15.1 Masking

De-identified, coded data from subjects in ENRICH-PLUS and matched subjects from ENRICH will be provided to the statistician for analysis of outcomes. The statistician will perform an analysis of outcomes from the 20 subjects from ENRICH-PLUS and the 20 matched subjects from ENRICH to determine whether a trend, or non-inferiority, toward improved outcome may be associated with pioglitazone supplementation of MIPS clot evacuation.

15.1.1 Control Group:

Demographic data (age, sex), baseline NIHSS, and baseline hematoma size and side of subjects enrolled in ENRICH-PLUS will be used to identify 20 subjects with basal ganglia ICH from the MIPS arm of ENRICH using a weighted Euclidean matching methodology optimized for small sample size (pPAIRS©).[30, 31]

The deidentified coded dataset (age, sex, baseline NIHSS, baseline hematoma size and side) of all MIPS patients in ENRICH will be made available to Drs. Thomas A. Kent and Pitchaiah Mandava (Houston) for matching to the corresponding dataset from ENRICH-PLUS using their pPAIRS© algorithm. They will return the coded identity of the matched subjects to the statistician for data analysis.

15.2 Prior to formal analysis

Means, medians, ranges, standard deviations, and descriptive measures for non-normality will be computed for each continuous variable, as well as frequencies for categorical variables, within each group. Any data values identified as outliers will be further examined to determine if they are data entry errors, in which case they will be modified when possible. Outliers will generally be kept in the final analysis, unless substantial evidence is available for their deletion.

15.3 Drop-outs and plan for addressing missing data

Every effort will be made to minimize missing data, but missing data may nevertheless be realized. If so, analyses will be performed to explore plausible missing data mechanisms, and baseline predictors of missingness will be investigated. Furthermore, if substantial missing data is realized, multiple data imputation will be employed.[34]

15.4 Analysis strategy

Generalized estimating equations (GEEs)[35] will be used to analyze primary (uw-mRS) and secondary endpoints by comparing group 1 (treatment) and group 2 (control). Within and between cluster (matched pairs) variabilities can be accounted in GEEs approach. Note that the primary endpoint (uw-mRS) has 7 levels. Due to the situation of small sample size, the primary endpoint will be dichotomized based on pre-specified threshold. Given the available safety data from the SHRINC trial, i.e., that drug did not cause hematoma enlargement or clinical harm (personal communication from JA), a one-sided statistical test may be appropriate in this exploratory analysis.

15.5 Power analysis

The analysis strategy is able to detect a difference with around 80% power under $\alpha = 0.1$ and one-sided test for the primary endpoint with a dichotomized scale, given the log odds ratio of 1.4 when comparing group 1 to group 2. The working correlation structure of independence is used to conduct this conservative power analysis. More power will be achievable with adjustment for potential intra-cluster (matched pairs) correlations

16 DATA, QUALITY ASSURANCE, DOCUMENTATION, AND REPORTS

16.1 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be formed and will meet (biannually) to evaluate the study results and any adverse events. The DSMB will follow patient data and will have access to all data to ensure patient safety. The DSMB will be charged with independently determining whether pioglitazone worsens outcome from MIPS. The assessment may be in the form of a letter or report and should state which data were reviewed, their assessment of the study safety profile, and a recommendation regarding study continuation.

16.2 Monitoring Plan

In addition to a DSMB, the study staff will conduct periodic audits to ensure compliance with regulations and to ensure the study is conducted in accordance with Good Clinical Practice Guidelines, which is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

16.3 Electronic Medical Record (EMR)

Data in the patient's EMR that are routinely collected as part of the standard of care (result of finger sticks, length of ICU stay, length of hospitalization, ICU-related complication, bacterial brain infection, requirement for EVD, requirement for hyperosmolar therapy, death) may be accessed by the PI or co-Investigators or their designated representatives for study purposes.

16.4 Reports

Study results will be documented in a final study report.

16.5 Publications

The results of the study will be submitted for publication. The sole responsibility for the content of the publication will rest with the Principal Investigator. The sponsor will not take part in the decision to publish or in the content of the publication.

17 ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

17.1 Institutional Review Board/ Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the University of Maryland, Baltimore IRB. A signed and dated consent form will be obtained from the subject or subject's LAR in compliance with local requirements and as approved by the IRB.

17.2 Record Retention

The investigator will retain all study records required by the applicable regulations in a secure and safe facility. All records are to be retained by the Investigator for the longer of the following periods: (i) at least 2 years after the FDA/local health authority approves the New Drug Application; or (ii) at least 2 years following the termination or withdrawal of the health regulatory agency exemption (e.g., Investigational New Drug or clinical trial application) under which the study was conducted.

17.3 Patient Confidentiality

Any evaluation forms, laboratory specimens, reports, or other records as required for the study will be identified only by the Study Patient Number (SPN) to maintain subject confidentiality. Any computer entries will be identified using SPNs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, or other relevant health authority representative.

17.4 Legislation and Guidelines Directing the Study

This study will be conducted according to the principles of the "Declaration of Helsinki" Somerset-West) and with the laws and regulations of each participating country. A copy of the Declaration of Helsinki will be provided in the investigator folder, if necessary. The investigator will follow ICH/GCP guidelines.

17.5 Notification of the Authorities, Approval, and Registration

Before start, the study will be registered at clinicaltrials.gov. In accordance with federal guidelines, the registration and information regarding this study will remain up to date, reflecting any modifications, protocol changes, or changes in study status.

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