AWARD NUMBER: W81XWH-19-1-0539

TITLE: Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity After Severe TBI

PRINCIPAL INVESTIGATOR: Charles S. Cox, Jr., MD

CONTRACTING ORGANIZATION: University of Texas Health Science Center, Houston, TX

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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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October 2023	Annual	01-SEP-2022 to 31-AUG-2023

4. TITLE AND SUBTITLE

Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity After Severe TBI

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W81XWH-19-1-0539

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Charles S. Cox, Jr., MD

E-Mail: Charles.s.cox@uth.tmc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas Health Science Center at Houston

8. PERFORMING ORGANIZATION REPORT NUMBER

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Severe traumatic brain injury (TBI) is a leading cause of death and disability that often occurs in conjunction with multiple other injuries, with and without hemorrhagic shock. Current guideline-based neurocritical care is designed to minimize intracranial hypertension using a tiered escalation in therapies, and seeks to avoid factors that aggravate the initial injury (hypotension and hypoxia). Our project seeks to measure the shed component of the microvascular barrier/glycocalyx (syndecan-1 and thrombomodulin) as a predictor of the edemagenic status of the post-TBI neurovascular unit. The ultimate goal is to be able to use a simple blood test that identifies the shed components of the microvascular barrier to rapidly identify the subset of severe TBI patients that require high intensity management—the "malignant ICP phenotype." The global hypothesis for this project is syndecan-1 release predicts the cerebral edema/therapeutic intensity level for intracranial hypertension phenotype after TBI. The presence of hemorrhagic shock/resuscitation exacerbates the edemagenic phenotype. To date, Phase 1 of the study (n=25) has been completed. Phases 2/3 initiated enrollment in October 2021 (Year 3) and 28/50 patients have been enrolled through the end of Y4Q4. An additional patient has been enrolled in Y5.

15. SUBJECT TERMS

Traumatic brain injury, intracranial hypertension, syndecan-1

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	70	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Severe traumatic brain injury (TBI) is a leading cause of death and disability, and often occurs in conjunction with multiple other injuries and with and without hemorrhagic shock. Current guideline-based neurocritical care is designed to minimize intracranial hypertension using a tiered escalation in therapies, and seeks to avoid factors that aggravate the initial injury (hypotension and hypoxia). This project seeks to measure the shed component of the microvascular barrier/glycocalyx (syndcan-1 and thrombomodulin) as a predictor of the edemagenic status of the post-TBI neurovascular unit. Current neurocritical care treatment paradigms focus on hyperosmolar strategies to limit cerebral edema and the resultant intracranial hypertension/tissue ischemia. To be effective, an intact microvascular barrier is essential. The ultimate goal of this project is to be able to use a simple blood test that identifies the shed components of the microvascular barrier to rapidly identify the subset of severe TBI patients that require high intensity management—the "malignant ICP phenotype." The global hypothesis for this project is syndecan-1 release predicts the cerebral edema/therapeutic intensity level for intracranial hypertension phenotype after TBI. The presence of hemorrhagic shock/resuscitation exacerbates the edemagenic phenotype. To accomplish this goal, we will employ continuous ICP waveform monitoring to define 3 tiers of ICP insults as defined by pressureXtime insults that predict poor outcomes, loss of autoregulation with a CPP<60 mm Hg, or high intensity interventions to reduce the ICP as quantified by the PILOTmod score>25. These data will be correlated with glycocalyx disruption in the early post-injury period. Cerebral edema imaging will be evaluated to quantify the tissue edema driving the ICP. These early data will be correlated with 6-month Glasgow Outcome Scores and DT-MRI based brain volumetric measurements to quantify injury related tissue loss. This project will enroll patients in two clinical prospective observational studies. Study 1 is a descriptive pilot study that will enroll 25 consecutive severe TBI patients and develop and validate the tools to define the tiers of the malignant ICP phenotype and represents phase 1 of this project. Study 2 is also a prospective observation study that will enroll 50 consecutive severe TBI patients and encompasses phases 2 and 3 of this project. Phase 2 is the physiological phase focused on the patient response to the ICP insults ascertained by serum albumin, syndecan-1, and thrombomodulin levels. Phase 3 will correlate these physiologic measures with structural endpoints defined by imaging. By being able to accurately and acutely predict severe TBI patients who may develop rapid progression to a malignant intracranial pressure phenotype, patients in Forward Surgical or En Route Critical Care could be rapidly triaged to facilities with neurosurgical capabilities, and/or aggressively monitored for complications of elevated ICP. We expect this project to produce a tool that rapidly predicts patients that will require high-intensity neurocritical care, and identify a cohort of more homogeneous patients for future aggressive interventions.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

traumatic brain injury, TBI, intracranial pressure, syndecan-1, intracranial hypertension

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1: Clinical Study (Phase 1)
Subtask 2: Prepare regulatory documents and research protocol
Milestone 1: Local IRB approval at UTHealth for Study 1 (target month: 1, completed prior to month 1 on 09-AUG-2019)
Milestone 2: HRPO approval for Study 1 (target month: 3, completed in month 2 on 11-OCT-2019)
Subtask 2: Finalize data management system and eCRFs
Milestone 3: Data management system completed (target month: 1, completed in month 4 on 15-DEC-2019)
Subtask 3: Perform clinical study
Milestone 4: Research staff trained (target month: 3, completed in month 4 on 15-DEC-2019)
Milestone 5: 1st participant consented, screened and enrolled (target month: 4, completed in month 9 on 26-MAY-2020, 100% completed)
Milestone 6: Enrollment and data collection completed for Study 1 (target month: 18, 25/25 patients consented and enrolled as of 19-JUN-2021, 100% completed in month 22)
Subtask 4: Report results from clinical study
Milestone 7: Report Study 1 results from data analyses (target month: 24, 100% completed in month 28)

Major Task 2: Clinical Study (Phases 2-3)
Subtask 1: Prepare for study
Milestone 8: Protocol for Study 2 developed and approved (target month: 15, 100% completed in month 25 on 30-SEP-2021)
Subtask 2: Conduct Study
Milestone 9: 1st participant consented, screened and enrolled in Study 2 (target month: 15, 100% completed in month 26 on 29-OCT-2021)
Milestone 10: Study 2 enrollment and data collection completed (target month: 36, 28/50 consented and enrolled by 31-AUG-2023, 56% completed)
Subtask 3: Report results from clinical study
Milestone 11: Report Study 2 results from data analyses (target month: 36, 0% completed)

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major activities during the past year and quarter were enrollment of patients into Study 2.

Screening for Study 2 began in Y3Q1 on 15-OCT-2021. Through 31-AUG-2023, all patients were screened in the STICU and Neuro ICU, 66 were determined to be eligible and 28 of those consented and were enrolled. Seven patients were enrolled in the past quarter.

One patient was initially consented in Y3Q1, but later determined to not be eligible due to their non-traumatic injury. That patient was withdrawn from the study prior to the baseline MRI and therefore was a minor deviation that resulted in no additional risk to the patient. Two additional patients were withdrawn by their LARs prior to the initial MRI.

One additional patient was enrolled in September 2023, making the total enrolled 29. This patient will be listed on the next report.

	During this Quarter	**Overall**
Eligible N	8	66
Enrolled N (% of eligible)	7 (87.5)	28 (42.4)
Not enrolled N (% of eligible)	1 (12.5)	38 (57.6)
Withdrawn eligible N (% of eligible)	0	0
Withdrawn not eligible N	0	1

Once patients are enrolled in Cohort 2, the Moberg monitor collects data for at least 96 hours after ICP placement. Blood samples are taken at baseline (ED admission) and 2, 12, 24, 48, 96 hours after ICP placement in Phase 2. For Phase 3, the patient has a DT-MRI at baseline and another at 6 months after their enrollment. Enrollment delays were due to COVID-19 being a logistical barrier to getting patients consented and enrolled within the 72 hour window during 2020-2022. Enrollment has picked up recently and we hope to capitalize on this increase in study population

Reason for non-enrollment of eligible patient	During this Quarter N (% of total eligible)	Overall N (% of eligible)
LAR/patient refused	1 (12.5)	11 (16.7)
Patient or LAR not identified	0 (0)	11 (16.7)
LAR identified but consent window expired before LAR provided consent or was able to be contacted	0 (0)	10 (15.2)
Missed	0 (0)	3 (4.5)
No Moberg available at time of eligibility/equipment issue	0 (0)	1 (1.5)
Patient became DNR before consent	0 (0)	1 (1.5)
Enrolled in another study	0 (0)	1 (1.5)
Not notified of eligible patient	0 (0)	0 (0)
TOTAL NON-ENROLLED	1 (12.5)	38 (57.6)

Reasons for non-enrollment for the 38 (1 in this quarter) who were eligible but not enrolled are found in the table below. The most common reason for not enrolling is that the consent window expired. Twenty-one patients did not have their LAR identified or were not able to be consented within the 72 hour window, which is nearly as many as the number of patients who have been enrolled. There were 11 patients/LARs who refused to date, which represents a 16.7% refusal rate overall (refusals/eligible). Compared to Cohort 1 which had a refusal rate of 8.3%, this rate is significantly higher, which could be due to the requirement for 2 DT-MRIs, the second one occurring after discharge. We are collecting reasons for refusals going forward so we can see if there are any specific concerns that we can address. We submitted an amendment to extend the timeframe for obtaining the second MRI to 18 months and added a $150 patient incentive for the second MRI compensation participants for their time after being discharged from the hospital. We hope this will improve the number of follow-up MRIs we receive. We have already scheduled 3 additional follow-up MRIs among those eligible. We have also considered examining CTs to gather more information on patients who may have missed the baseline MRI due to death.

Assessment of Subjects (Cohort 2)	N eligible by 8/31/23	N (% of eligible) completed by 8/31/23	Comments
Baseline MRI	27	20 (74.0)	2 withdrawn by LAR prior to initial MRI 3 died prior to initial MRI 1 had initial MRI but incorrect protocol was used 1 unable to perform
Follow-up MRI at 6-18 months	13*	4 (30.8)	3 scheduled 1 lost to follow-up 4 attempting to contact 1 withdrawn

*Does not include 2 previous withdrawals, 1 death and 11 patients who have not reached 6 months follow-up

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will continue to enroll patients in Phases 2/3 in the next reporting period (Y5Q1). We are running labs on the already enrolled patients so that those can be completed soon prior to the end of the second NCE.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

During Phase 1, we identified 3.2 eligible patients/month and enrolled 1.6 patients/month. Identification of eligible patients has been similar in Phase 2/3 at 2.9 patients/month, but enrollment seems to have slowed to 1.2 patients/month. Reasons for non-enrollment are similar with rate of not identifying an LAR decreasing from 20.4% to 16.7%, unable to consent within 72 hours increasing from 8.2% to 15.2% and rate of refusal increasing from 4.1% (2 of 49) to 16.7% (11 of 66). The decrease in not identifying LARs provides evidence that we have done a better job working with social workers and the clinical team. There are also fewer restrictions on visitation. However, we have been less able to obtain consent from LARs due to running out of time and refusals. We are currently exploring the reasons behind the increase in refusals, which anecdotally has affected enrollment in other studies as well. Once we complete the investigation of refusals across all studies, we will be better able to recommend a plan of action. We also have noticed that our rates of obtaining the second MRI are low, so we extended the time window for obtaining the MRI from 6 months to up to 18 months. We are also adding a patient incentive of $150 to compensate the participants for their time. We expect that these actions will help increase the rate of second MRIs and have already seen improvements.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Due to the COVID-19 shutdown and not adding personnel effort until patient enrollment was about to begin, we have spent less than expected to date. We are utilizing those funds for the no cost extensions.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No significant deviations or unexpected outcomes have occurred in the past year.

We made the following changes to the Human Use Regulatory Protocol:
1) Extended the MRI follow-up window from 6 months to 6-18 months. Approval on 17-JUL-2023.
2) We will report unrelated and expected deaths to the UTHealth Houston IRB on an annual basis at continuing review due to the observational nature of the study and the traumatically injured patient population enrolled. Approval on 12-SEP-2023

Continuing review was approved by the UTHealth Houston CPHS on 15-AUG-2023 and 09-DEC-2022 and was submitted to HRPO for acknowledgement soon there after.

The revised protocol, consent forms and CR approvals are attached in Appendix A.

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of

compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Charles Cox, MD
Project Role: PI
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 2
Contribution to Project: Dr. Cox oversaw screening and enrollment for Phase 1 and analysis of the resulting data.

Name: Charles Wade, PhD
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Wade oversaw laboratory collect and analysis for Phase 1 and analysis of the resulting data.

Name: Ryan Kitagawa, MD
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Kitagawa is an expert in trauma-related neurosurgery and assisted the team with enrolling patients into Phase 1.

Name: HuiMahn "Alex" Choi, MD
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Choi is an expert in ICP monitoring, assisted the team with enrolling patients into Phase 1, and assisted with interpretation of the ICP data.

Name: Claudia Pedroza, PhD
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Pedroza is a biostatistician. She ran the data coordinating center and supervised the analysis of data.

Name: Erin Fox, PhD
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Fox is an epidemiologist and the Project Manager. She manages the day-to-day aspects of the projects, drafts all reports, and assists in data interpretation.

Name: Steve Kosmach, RN
Project Role: Nurse Coordinator
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Mr. Kosmach consented patients in the Neuro ICU for Study 1 and collected and entered all clinical research data.

Name: Yidao Cai
Project Role: FITBIR Data Programmer
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 2
Contribution to Project: Mr. Cai is sending data to FITBIR.

Name: Jude Savarraj
Project Role: FITBIR Data Programmer
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Savarraj is responsible for downloading, managing, and analyzing the waveform data from the Moberg.

Name: Yao-Wei "Willa" Wang, MD
Project Role: Laboratory Manager
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1
Contribution to Project: Dr. Wang is the Laboratory Project Manager and oversees the day-to-day operations of the research laboratory.

Name: Symantha Lopez, Veda Pa, Garrett Woodruff, Selina Gonzalez, Kalea Dixon, Daisy Lopez
Project Role: Laboratory Research Assistants
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1 month each
Contribution to Project: Laboratory Research Assistants back up clinical RAs to provide 24/7 screening and enrollment coverage and perform all laboratory analyses

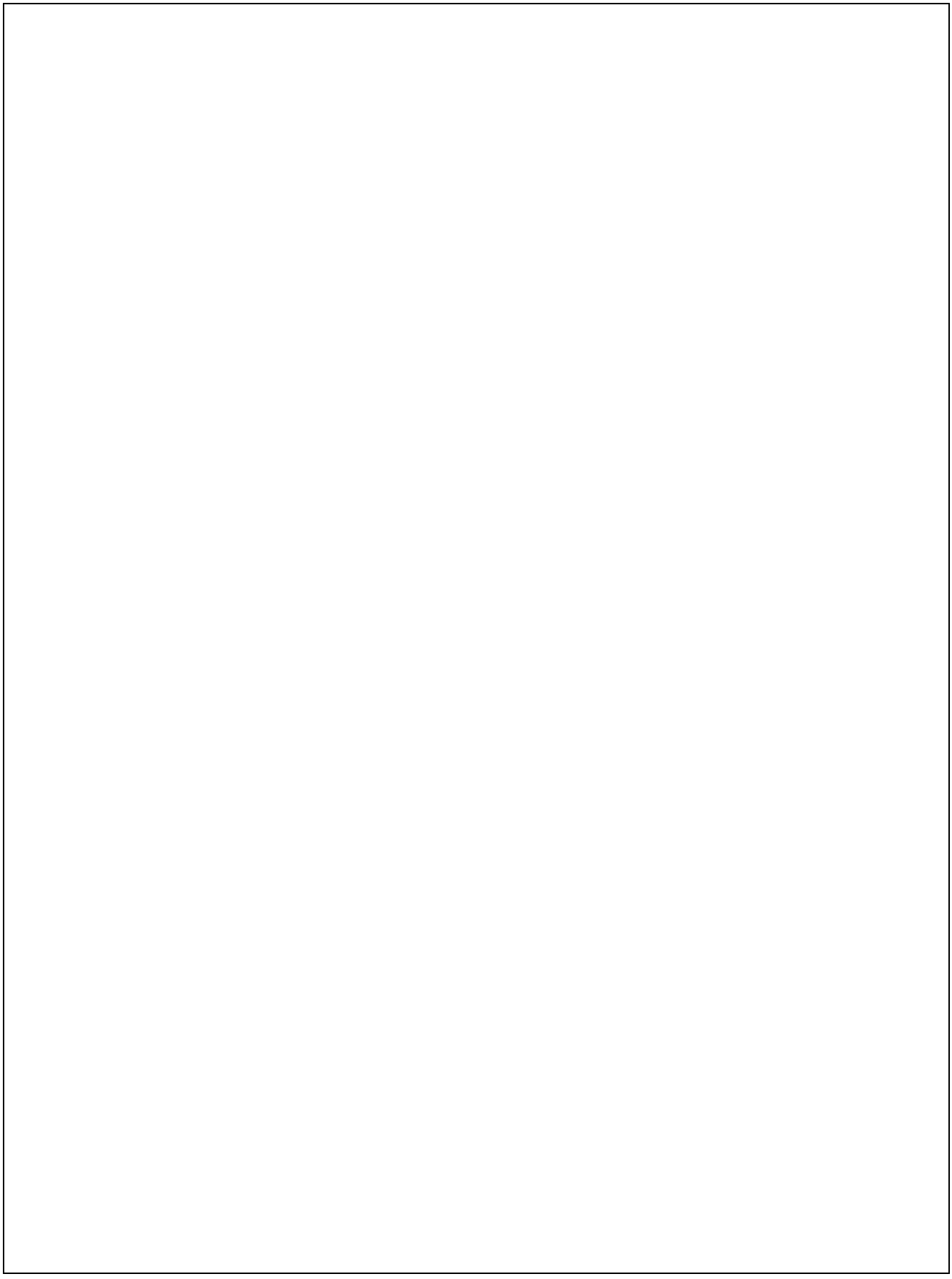
Name: Victoria Herrick, Kendra Tyner, Thet Thet Khin
Project Role: Clinical Research Assistants
Researcher Identifier (e.g. ORCID ID): Unknown
Nearest person month worked: 1 month each
Contribution to Project: Clinical Research Assistants screen patients and hook up the Moberg ICP monitoring data capture device with 24/7 coverage.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

No changes to active support

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."



Describe partner organizations – academic institutions, other non-profits, industrial or commercial escribe partner organizations – academic institutions, other non-profits, industrial or commercial Describe partner organizations – academic institutions, other non-profits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Appendix A. Regulatory documents

Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity after Severe TBI (Phase 2/3)

Protocol V 5
06 JUN 2023

Principal Investigator: **Charles Cox, MD**
Co-Investigators: **Charles Wade, PhD**
Ryan Kitagawa, MD
Claudia Pedroza, PhD
Erin Fox, PhD
HuiMahn Choi, MD
Jenifer Juranek, PhD
Jude Savarraj, PhD

Sponsor: Department of Defense

UTHealth Houston
IRB NUMBER: HSC-MS-19-0628
IRB APPROVAL DATE: 07/17/2023

Table of Contents

Abbreviations

AIS-Abbreviated Injury Scale

AF-Arcuate Fasciculus

aMRI-Anatomical Magnetic Resonance Imaging

BE-Base Excess

BMI-Body Mass Index

BTF-Brain Trauma Foundation

CC-Corpus Callosum

CNS-Central Nervous System

COP-Colloid Osmotic Pressure

CPP-Cerebral Perfusion Pressure

CRF-Case Report Form

CSF-Cerebral Spinal Fluid

CST-Corticospinal Tract

DoD-Department of Defense

DTI-Diffusion Tensor Imaging

DT-MRI-Diffusion Tensor Magnetic Resonance Imaging

DWI/DTI-Diffusion Tensor Imaging

ED-Emergency Department

EMR-Electronic Medical Record

EGL-Endothelial Glycocalyx

EoT-Endotheliopathy of Trauma

EPI-Echo Planar Imaging

FA-Fractional Anisotrophy

FDA-Food and Drug Administration

FLIRT-FMRIB's Linear Image Registration Tool

FMRIB-Functional Magnetic Resonance Imaging of the Brain

FNIRT-FMRIB's Nonlinear Image Registration Tool

FSL-FMRIB's Software Library

GCS-Glasgow Coma Score

GLMM-Generalized Linear Mixed Model

GM-Grey Matter

GOS-Glasgow Outcome Score (EC-expanded, children)

HIPPA-Health Insurance Protection and Portability Act

HRPO- Human Research Protection Office

HTS-Hypertonic Saline

ICH-Intracranial Hemorrhage

ICM+- Intracranial Monitor

ICP-Intracranial Pressure

ICU-Intensive Care Unit (P-Pediatric; ST-Shock Trauma; N-Neurotrauma)

IRB-Institutional Review Board

IR-Interventional Radiology

ISS-Injury Severity Score

LAR-Legally Authorized Representative

LLD- Lower Limit Detection

MAP-Mean Arterial Pressure

MD- Mean Diffusivity

MHH-Memorial Hermann Hospital

MPRAGE-Magnetization Prepared Rapid Gradient Echo

MRI-Magnetic Resonance Imaging

NIH-National Institutes of Health

OR-Operating Room

PILOT–Pediatric Intensity Level of Therapy

PRx-Pressure Time

ROI-Region of Interest

SBP-Systolic Blood Pressure

SLF-Superior Longitudinal Fasciculus (I, II, III)

SNPs-Single Nucleotide Polymorphisms

sTM-Soluble Thrombomodulin

TBI-Traumatic Brain Injury

TRPM4-Transient-Receptor-Potential Cation Channel Subfamily-M

WM-White Matter

Title: Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity after Severe TBI (Phase I)

A. BACKGROUND

Severe traumatic brain injury (TBI) is a leading cause of death and disability that often occurs in conjunction with multiple other injuries, with and without hemorrhagic shock. Current guideline-based neurocritical care is designed to minimize intracranial hypertension resulting from hemorrhage expansion or the development of cerebral edema. Interstitial edema (often referred to as vasogenic edema) is governed by classic Starling forces as well as the integrity of endothelial barrier function. These factors regulate microvascular fluid flux in response to vascular and oncotic/osmotic gradients across the selectively permeable microvasculature. ***Thus, maintaining appropriate vascular permeability is crucial to preventing the development of interstitial edema and subsequent intracranial hypertension.***

Endothelial Glycocalyx and Endotheliopathy of Trauma:

The endothelial glycocalyx (EGL) is a key regulator of vascular permeability, cell adhesion and inflammation. The major components of the glycocalyx are syndecans, hyaluronic acid, chondroitin sulfate, and heparan sulfate. The EGL plays a critical role in maintaining vascular integrity by serving as a (1) barrier to the transport of proteins and fluids, therefore preventing capillary leak, (2) mechanotransducer of pressure and shear stress, (3) regulator of inflammatory cell adhesion and infiltration, and (4) anticoagulant through interaction with thrombomodulin and antithrombin III. EGL breakdown causes endothelial dysfunction and disruption, which in turn results in increased vascular permeability, altering Starling forces and leading to capillary leak. Additionally, disturbances in coagulation and inflammation are triggered by the interaction of circulating cells with the exposed endothelium (Haywood- Watson, 2011;Ostrowski, 2012; Lipowsky, 2013).

Hemorrhagic shock and injury induce breakdown of the endothelial glycocalyx (EGL) (Alphonsus, 2014) leading to the systemic responses that comprise the syndrome entitled the endotheliopathy of trauma (EoT) (Holcomb, 2013), which is associated with poor outcomes and high early mortality. Other studies have also shown that increased shedding of Syndecan-1, a major component of the EGL, is associated with symptoms of EoT such as inflammation, coagulopathy and vascular leak (Ostrowski, 2012; Johansson, 2011; Rahbar, 2015). In a previous study carried out in our laboratory, we demonstrated that a Syndecan-1 level ≥40 ng/ml is associated with greater transfusions and a higher risk of death despite an absence of clinically significant differences in

admission physiology (Gonzalez Rodriguez E, 2018). Work by Rahbar *et al.* demonstrated that high circulating levels of Syndecan-1 is associated with increased permeability and reduced plasma colloid osmotic pressures (COP) due to protein leakage (Rahbar, 2014; Rahbar, 2015) in patients with severe injuries. Furthermore, patients with low COP required higher volumes of blood products and experienced worse outcomes (Rahbar, 2014). Protein leakage is mediated, in part, by the osmotic force induced by translocation of proteins like albumin from the intravascular space to the interstitial space (Rahbar, 2014; Rahbar, 2015; Vincent, 2003; Ballmer, 2001; Filho, 2013; Lipowsky, 2011; Woodcock 2012). A reduction in serum albumin or total protein concentration could indicate a state of increased vascular permeability and impaired capillary hemodynamics (Rahbar, 2014; 2015; Vincent, 2003; Ballmer, 2001; Huxley, 2000). ***Therefore, the estimation of plasma COP through albumin or serum protein concentrations could be useful to assess endothelial integrity in the acute trauma setting.***

Importance of the Microvascular Barrier and EGL in TBI:

Current neurocritical care treatment paradigms utilize hyperosmolar strategies to limit cerebral edema and the resultant intracranial hypertension/tissue ischemia. To be effective, an intact microvascular barrier is essential; early and severe disruption of the microvascular barrier is associated with increased transvascular fluid flux and tissue edema in every organ system studied. This is important because specific strategies can limit the development of edema, even in the face of microvascular barrier dysfunction. Our group and others have examined the microvascular barrier response to injury. The Alam group has shown that syndecan shedding occurs in isolated TBI in both rodent (Jepsen, 2014) and porcine models (Sillesen, 2014). Importantly, plasma COP correlates strongly with syndecan-1 shedding after injury (Rahbar, 2015). Currently, we are analyzing plasma syndecan-1 and plasma COP time-course data from a small cohort of patients with known neurocognitive outcomes and imaging data. ***Plasma COP could provide an early, non-invasive marker for cerebral edema and poor outcomes following TBI.***

Measuring ICP and the Malignant ICP Phenotype:

ICP measurement is necessary to accurately determine cerebral perfusion pressure (CPP). However, ICP measurement *per se* has not been conclusively shown to alter outcomes in head injury patients (Chestnut, 2012). This is due to a combination of factors, primarily that ICP monitoring is now so accepted for severe head injury, and forms the basis for modern brain injury management, so that it would be difficult to conduct a study with a control arm. There is a

substantial body of evidence to support the use of ICP monitoring (Carney, 2016). Several studies have reported substantially lower mortality after ICP monitoring and control was introduced. Similarly, studies have shown a lower mortality in those patients whose ICP could be controlled compared to those in which it could not. ICP monitoring is now a central part of critical care management for the severely brain injured patient. The Brain Trauma Foundation has reaffirmed the recommendations to monitor/control ICP to manage severe TBI.

Figures 1-3 below are from Guiza *et al.* and do not represent our data. However, we have extensive experience with continuous waveform data capture systems at Memorial Hermann Hospital and plan to use the Moberg CNS monitor for ICP waveform data capture. Capturing waveform data allows for the precise definition of the true ICP burden over time. Data abstracted from nursing records that assign a single value for a given hour misses cumulative insults which are associated with ultimate outcomes (Glasgow Outcome Score), in both adults (n=261 below) and children (n=99 below). It is clear from these data that even brief episodes with an ICP over 25 mmHg in adults and 20 mm Hg in children are associated with poor outcomes. Similar data are apparent with the loss of CPP in the subsequent figure. Almost any ICP insult with a CPP < 50 mm Hg is associated with a poor outcome in children, and only ICPs < 15 mm Hg are associated with potentially favorable outcomes (blue-yellow coded). ***The overall goal of this study is to determine if markers of EoT are predictive of the malignant ICP phenotype.***

Figure 1:

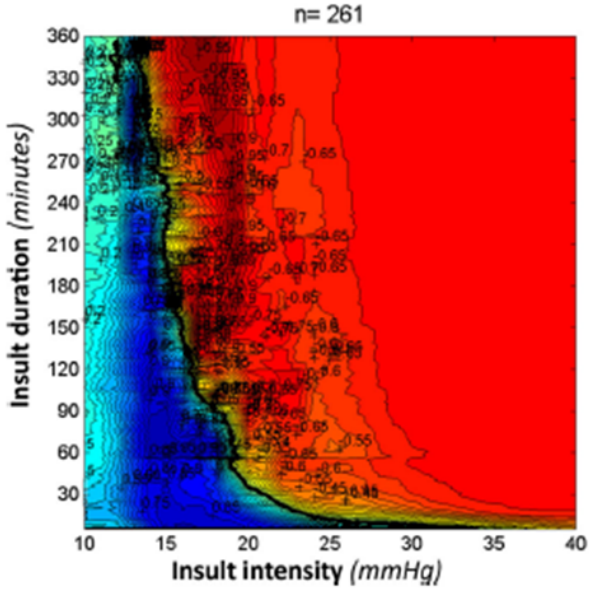
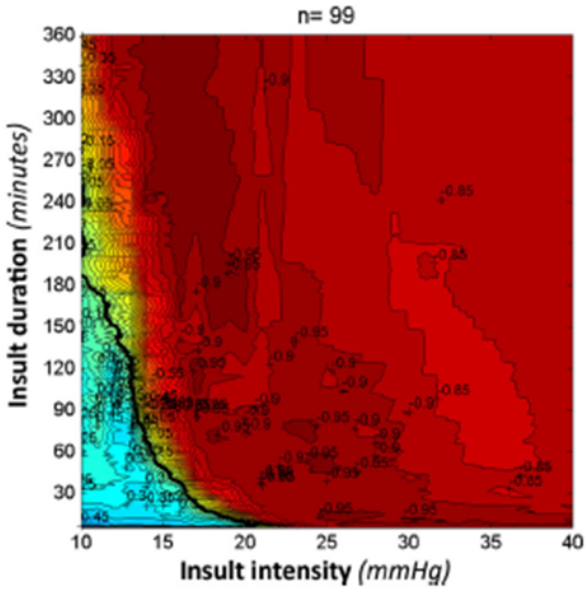


Figure 2:



Figures 1 and 2: Visualization of correlation between GOS and average number of ICP insults per GOS category. Left adult cohort (n = 261). Right pediatric cohort (n = 99). Each color-coded point in the graph refers to a number of episodes of ICP, defined by a certain ICP intensity threshold (X-axis), and a certain duration threshold (Y-axis). Such an episode is called an ICP insult. The univariate correlation of each type of ICP insult (characterized by ICP intensity and duration thresholds) with outcome is color coded. Dark red episodes mean that such ICP insults, on average, are associated with worse outcome (lower GOS categories); dark blue episodes mean that such ICP insults, on average, are associated with better outcome (higher GOS categories). The contour of zero correlation is highlighted in black, and is called the transition curve (Guiza,
et al, 2015).

Figure 3a: Adult Cohort

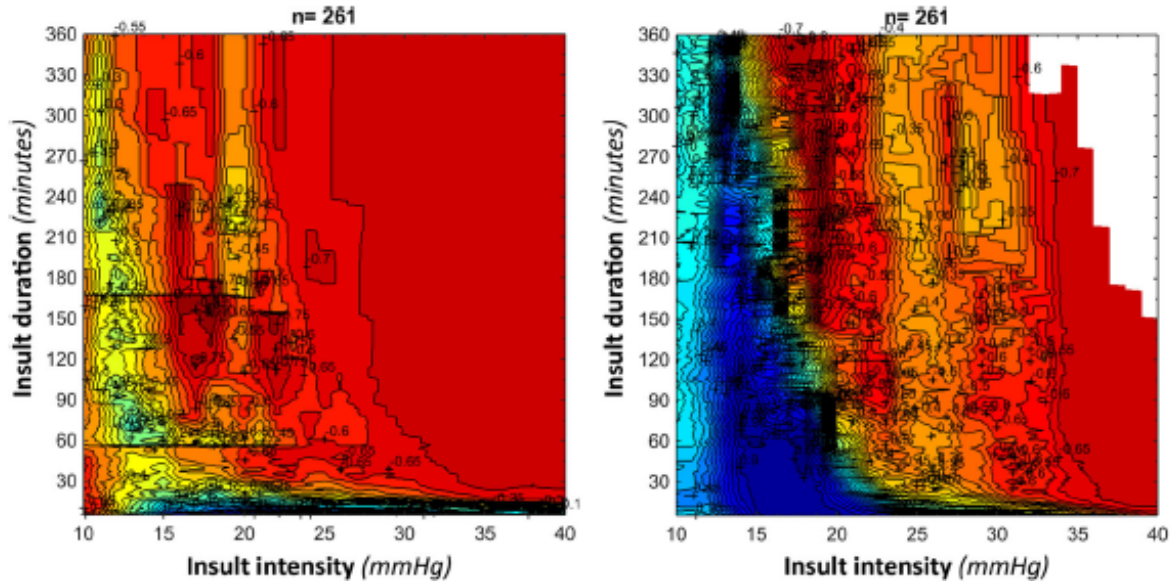
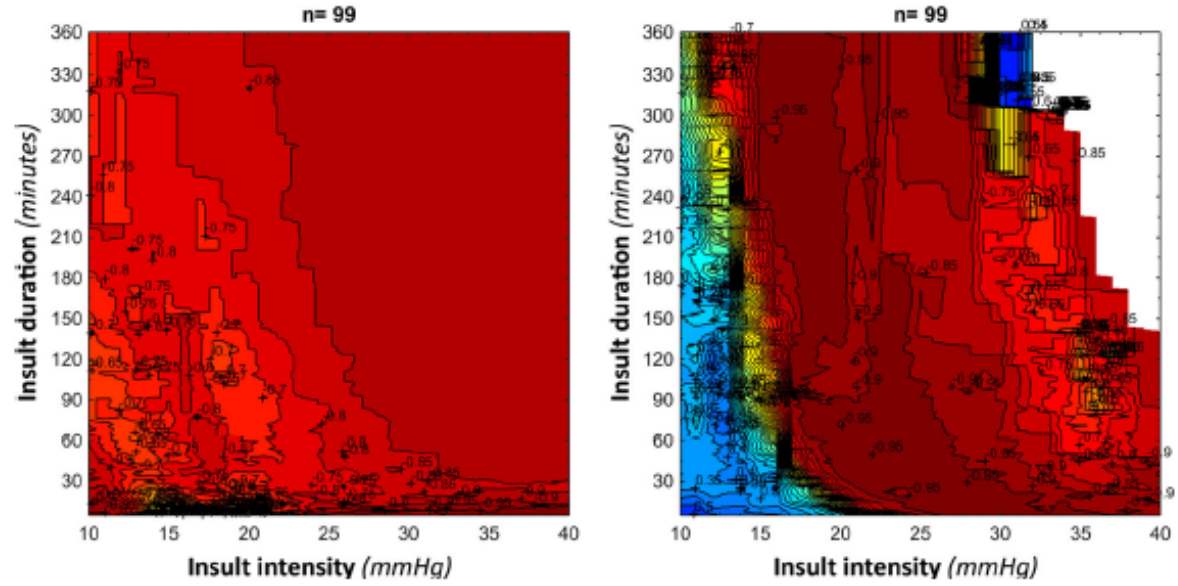


Figure 3b: Pediatric Cohort



Figures 3a-b: Visualization of correlation between GOS and average number of ICP insults per GOS category according to a cerebral perfusion pressure (CPP) threshold of 50 mmHg. The left panels in figures 3a and 3b illustrate a CPP ≤ 50 mmHg. The Right panels in figures 3a and 3b illustrate a CPP >50 mmHg (Guiza, et al, 2015)

The PILOT Scale:

The PILOT scale is presented in Table 1. All therapies from the "Guidelines for the Management of Severe TBI-4th edition" as modified from Shore et al., are organized into seven modalities: general, ventilation, osmotherapy, drainage of cerebrospinal fluid (CSF), barbiturates, surgical therapies, and other therapies. Individual therapies are assigned points based on the authors' best estimates of their relative efficacy and risks of morbidity. The PILOT scale is assessed every 24 hours; timing begins at the time of traumatic injury. When a therapy is used, the patient is awarded the corresponding number of points. Dose- related scores are based on the total dose or target (for mannitol/HTS, CSF drainage, barbiturates) or most frequently observed range of values (for $PaCO_2$ and temperature) in the 24-hr period. For example, consider a 24-hr period for a patient who is sedated, receiving neuromuscular blockade, mechanically ventilated (three $PaCO_2$ measurements of 36, 33, and 38 mm Hg), and normothermic. Assume the patient has three episodes of intracranial hypertension during that period, for which he receives two doses of mannitol (0.5 g/kg each), one dose of hypertonic saline (2-mL/kg bolus with serum sodium less than 150 mg/dl), continuous CSF drainage, and is started on a pentobarbital infusion at 1 mg/kg/hr 12 hrs into the 24-hr period. This patient would receive 1 point for sedation, 2 for neuromuscular blockade, 1 for ventilation ($PaCO_2$ most frequently 35.1– 40 mm Hg), 1 for mannitol (total dose, 1 g/kg/24 hrs), 3 for hypertonic saline, 3 for continuous CSF drainage, and 1 for low dose pentobarbital (total dose, 12 mg/ kg/24 hrs). The PILOT scale score would be 12 for this 24-hr period.

We modified the PILOT Scale shown in Table 1 to account for the changes in neurological critical care since the development of the scale, and evaluated it in a cohort of 44 patients: 16 severe TBI patients, 18 mild TBI patients and 10 extracranial trauma patients. We determined that the modified score that accounts for increasing doses of hypertonic saline to achieve therapeutic targets of serum hypertonicity resulted in an increase in 5 points and that on the 7-day PILOT scores there was a 33 point increase with an $R^2$of 0.67, meaning HTS accounted for 2/3 of the increase in the modified score relative to the original score. The rationale for the modification was that therapeutic intensity was being increased, but not being captured by the PILOT data. The $PILOT_{MOD}$ Scale is included in Appendix C.

Table 1. Pediatric Intensity Level of Therapy scale

Variable	Score	Maximum Possible Score
General—occurring at any time in 24-hr period		
Treatment of fever (temperature of > 38.5°C) or spontaneous temperature of < 34.5°C	1	4
Sedation (e.g., narcotics, benzodiazepines: any dose)	1	
Neuromuscular blockade	2	
Ventilation—most frequently observed $Paco_2$ in 24-hr period		
Intubated/normal ventilation ($Paco_2$ of 35.1–40 mm Hg)	1	4
Mild hyperventilation ($Paco_2$ of 32–35 mm Hg)	2	
Aggressive hyperventilation ($Paco_2$ of < 32 mm Hg)	4	
Osmolar therapy—total dose in 24-hr period		
Mannitol, ≤ 1 g/kg	1	6
Mannitol, 1.1–2 g/kg	2	
Mannitol, > 2 g/kg	3	
or		
Hypertonic saline (any dose or rate, regardless of serum [Na])	3	
Cerebrospinal fluid drainage—number of times in 24-hr period		
0–11 times	1	3
12–23 times	2	
≥ 24 times or continuous	3	
Barbiturates—total dose in 24-hr period		
Pentobarbital, ≤ 36 mg/kg	3	4
Pentobarbital, > 36 mg/kg	4	
Surgery—at any time in 24-hr period		
Evacuation of hematoma	4	9
Decompressive craniectomy	5	
Other—at any time during 24-hr period		
Induced hypothermia		8
Mild (≥ 35°C to 37°C)	2	
Moderate (< 35°C)	4	
Lumbar drain	2	
Induced hypertension (≥ 95th percentile for age)	2	
Total possible score	38	

Serum Albumin and Total Protein:

Admission levels of serum albumin and total protein are abnormally low in EoT+ patients and are inversely associated with circulating Syndecan-1 levels. This finding was unrelated to initial hemoglobin, total red blood cell count, ED metabolic markers or amount of pre-hospital fluids. After adjusting for possible confounding variables (age, sex, race, ISS, pre hospital vital signs, pre hospital fluids, and BMI) the magnitude of the association remained the same. Rahbar et al. reported similar findings studying plasma COP in trauma patients (Rahbar, 2014). They were able to conclude that plasma COP at approximately three times total serum protein levels could be used to assess the microcirculation and to evaluate transcapillary flux in relation to glycocalyx shedding based on findings that demonstrated a relation between endothelial damage markers and increased

endothelial permeability (Rahbar, 2014; Rahbar, 2015). As syndecan-1 levels rise, plasma COP (and total protein) decreases and results in a higher number of transfusions and higher mortality despite no clinically significant differences on arrival SBP, BE, hemoglobin or injury severity. This demonstrates the interplay between EGL disruption and capillary hemodynamics, and the need for more sensitive biomarkers to assess this relationship early and accurately (Rahbar, 2014; Rahbar, 2015; Torres, 2013; Lipowsky, 2011). While others have also reported acute low levels of albumin/total protein in patients with acute traumatic brain injury and demonstrated their association with poor outcomes (Vincent, 2003; Chen, 2014; Amavizca, 2015), the mechanisms that would explain acute low levels of albumin/total protein in the context of acute traumatic injury have been elusive.

We will use serum albumin as a screening tool to identify a group of patients (ED serum albumin ≤3.6 g/dl, sensitivity of 64.1%) that may potentially benefit from targeting EoT since commonly used markers in resuscitation fail to identify this group of patients at risk of worse outcomes. The goal is to resuscitate the microcirculation and repair the EGL and thus prevent or treat EoT in the early stages of care of the trauma patient, and improve outcomes (Ince, 2014).

Based on this information, we **hypothesize that Syndecan-1 release predicts the cerebral edema/therapeutic intensity level for intracranial hypertension phenotype after TBI. Also, the presence of hemorrhagic shock/resuscitation exacerbates the edemagenic phenotype.** To address this hypothesis, ***Aim 1*** ***will be to determine the time course of syndecan-1 release and COP in patients with severe TBI, and correlate this with pressure-time ICH exposure.*** These data will allow definition of the malignant ICP phenotype in three potential tiers: (1) "Red Zone" insult(s), (2) CPP <60 mm Hg, and (3) PILOTmod greater than 25. ***Aim 2*** ***will be to test whether the degree of microvascular barrier disruption as quantified by initial or 24 hour peak EoT results predicts the malignant ICP phenotype.*** As a secondary concept, EoT results may predict responsiveness to standard therapies for ICP as measured by Tier 2-3 BTF interventions and $PILOT_{mod}$ scores. These results will allow us to better understand the role of endothelial dysfunction in TBI and provide novel biomarkers for earlier detection and treatment of malignant ICP.

This proposal is divided into two studies in 3 distinct Phases. Study 1/Phase 1 was a pilot that enrolled 25 patients. Study 2 encompasses Phases 2 and 3 and will enroll 50 patients. The initial Pilot phase of the proposal is descriptive/logistical in nature and not hypothesis-driven as in Phases

2 and 3. The goal of Phase 1 was to validate all of the tools used to define tiers of the malignant ICP phenotype. Namely, this will be the generation of the ICP pressure-time burden contour maps that are associated with outcomes. We will add another novel tier of classification into the analysis using the $PILOT_{mod}$ scale (Appendix C) to define patients with controlled ICP, but requiring a high therapeutic intensity to maintain this control. We will then evaluate the association between different markers and the ICP cumulative dose/insult. Further, in the pilot phase we will merge the ICP and other data from the Moberg CNS monitor with our collected clinical and laboratory data.

The utility of this approach is that we will link a rapidly available, cheap biomarker screen with a sophisticated, commercially available data capture system that will serve as a useful triage and predictive tool for severe TBI patients. It is well described that the majority of patients will develop their peak ICP within the first 120 hours post-injury (most in 72 hours). We plan to follow all patients in the acute phase for the period during which an ICP monitor is in place.

B. OBJECTIVES

The overall objective of this study is to determine if markers of EoT are predictive of the malignant ICP phenotype. The objective for the Phase 1 study was to validate all of the tools used to define tiers of the malignant ICP phenotype. The objective for Phase 2 is to test whether laboratory assays in the first 24 hours after admission can predict the malignant ICP phenotype and early cerebral edema. The objective for Phase 3 is to determine whether early cytotoxic and vasogenic edema is associated with late structural CNS volumetric loss.

C. HYPOTHESIS and SPECIFIC AIMS

Global Hypothesis:

Syndecan-1 release predicts the cerebral edema/therapeutic intensity level for intracranial hypertension phenotype after TBI. The presence of hemorrhagic shock/resuscitation exacerbates the edemagenic phenotype.

Aim 1: Determine the time course of syndecan-1 release and COP in patients with severe TBI, and correlate this with pressure-time ICH exposure. These data will allow definition of the malignant ICP phenotype in three potential tiers: (1) "Red Zone" insult(s), (2) CPP <60 mm Hg and Pressure reactivity index >1.0, and (3) PILOTmod greater than 25.

Aim 2: Test whether the degree of microvascular barrier disruption as quantified by initial or 24 hour peak EoT results predicts the malignant ICP phenotype. As a secondary concept, EoT

results may predict responsiveness to standard therapies for ICP as measured by Tier 2-3 BTF interventions and $PILOT_{mod}$ scores.

Phase 1 Sub-Aims:

Sub Aim 1: Confirm that the cumulative dose (pressure X time) of ICP insults(s) is independently associated with unfavorable neurological outcome as defined by GOS 1-3.

Sub Aim 2: Stratify cumulative dose of ICP insults for CPP above/below 60 mm Hg and/or Pressure/reactivity index >1.0.

Sub Aim 3: Determine the time to peak plasma biomarker release (syndecan-1 and thrombomodulin) as well as COP and albumin depression as related to ICP burden.

Sub Aim 4: Measure the time-course of $PILOT_{mod}$ and analysis of contour mapping on ICP insult dichotomized GOS.

Phase 2 Sub-Aims:

Sub Aim 1: Confirm that initial or peak EoT laboratory results within the first 24 hours of admission can predict malignant ICP phenotype as characterized by (a)"Red Zone" (pressure X time) ICP insults; (b) loss of cerebral autoregulation as defined by a cerebral perfusion pressure (CPP) < 60 mm Hg and/or Pressure Reactivity Index≥1; (c) High therapeutic intensity level score (modified) as defined by a $PILOT_{mod}$ of greater than 25.

Sub Aim 2: Confirm that initial or peak EoT laboratory results within the first 24 hours of admission can predict cytotoxic (early) cerebral edema by DWI/DTI imaging.

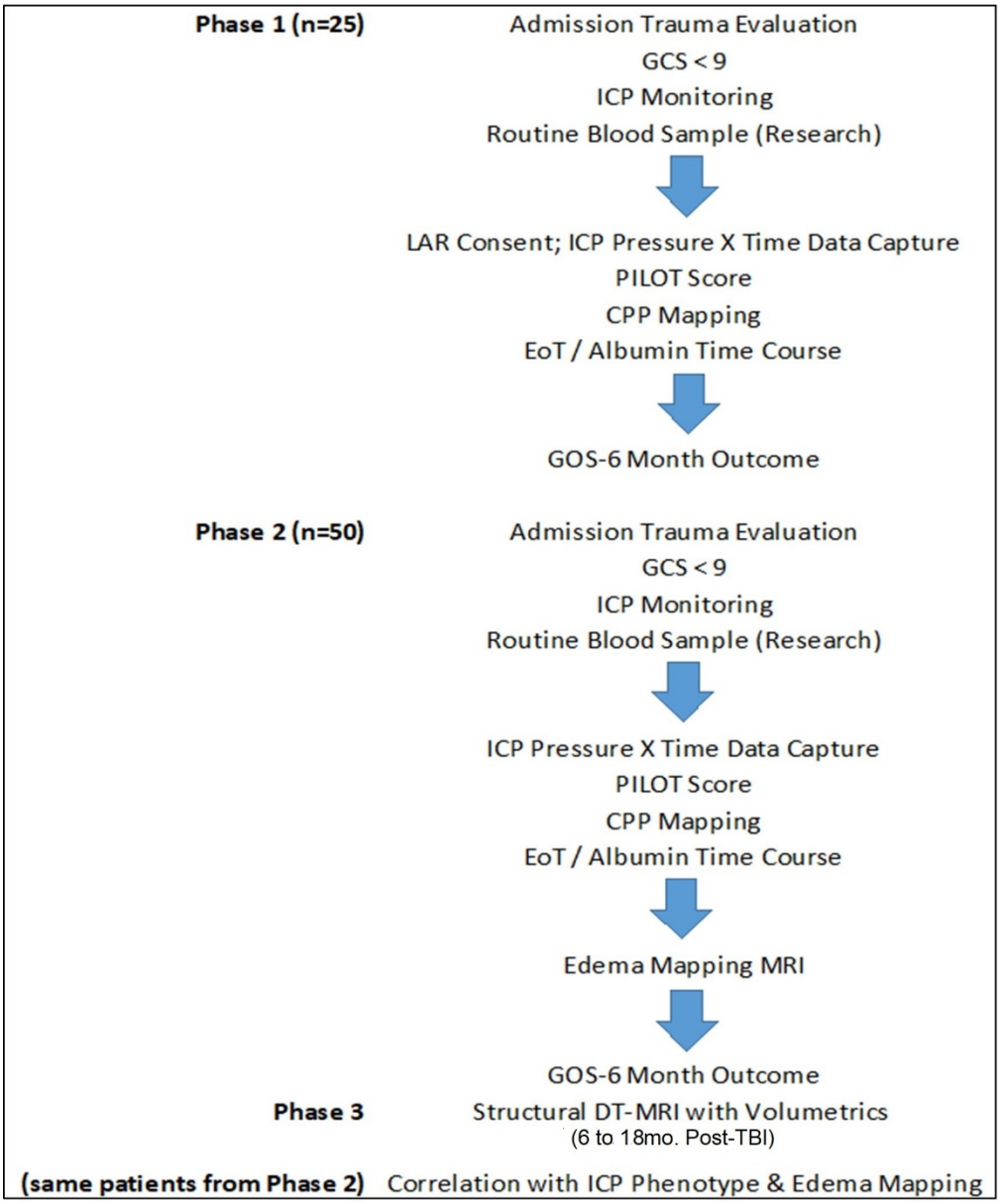
Phase 3 Sub-Aim:

Determine if malignant ICP phenotype is associated with early cytotoxic and vasogenic edema and late structural CNS volumetric loss.

D. STUDY DESIGN

This is a single center, prospective, observational study conducted at Memorial Hermann - Texas Medical Center. This study will involve continuous ICP monitoring, two brain DTI-MRI's when clinically stable, and serum biomarker collections for all enrolled subjects.

Figure 4: Study Phases



1. Study Population:

The study population is trauma patients admitted to Memorial Hermann Hospital – Texas Medical Center, Houston, Texas and meet the inclusion and exclusion criteria below:

a.) Inclusion Criteria: ***To be eligible, subjects must meet ALL of the following:***

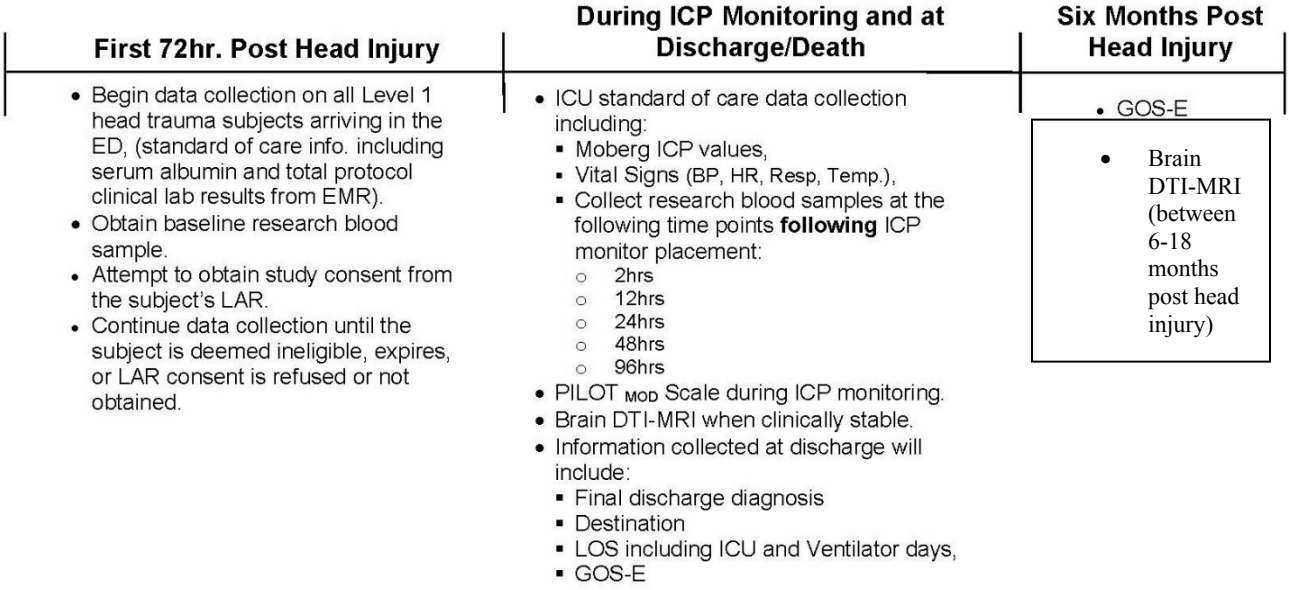
1) ≥18 years of age or older (or weight ≥50 kg if age is unknown),
2) Evidence of severe traumatic brain injury (TBI) as determined by GCS < 9 post resuscitation,
3) Requires ICP monitoring.
4) Ability to obtain legally authorized representative (LAR) consent within 72 hours of the initial injury.

b.) Exclusion Criteria: ***Subjects are ineligible if they meet ONE OR MORE of the following:***

1) Prisoners, defined as those who have been directly admitted from a correctional facility. Prisoners are excluded because of their vulnerable population status. A free-living individual who is under police observation as a suspect will remain in the study until discharge or incarcerated.
2) Known pregnancy.
3) Head injury deemed non-survivable by the trauma or neurosurgery attending and defined as patients with an initial head CT/MRI showing obliteration of the perimesencephalic cistern suggesting prolonged hypoxic ischemic insult/herniation syndrome, or initial ICP >60mmHg.
4) Greater than 20% total body surface area burns and/or suspected inhalation injury. Subjects with large and severe thermal injuries and inhalation injures require a resuscitation approach that is different from current isolated trauma resuscitation strategies. Additionally, in the absence of concomitant severe blunt trauma, these subjects are unlikely to receive blood products in the early resuscitative phase.
5) Known DNR.
6) Concurrent participation in other interventional research studies. Participation in observational studies of FDA approved drugs or devices is not an exclusion.
7) Penetrating head injuries.
8) Contraindications to MRI.

E. STUDY INTERVENTION

Figure 5: Study Flow



1. Screening Procedures:

Clinical research staff will be available in the hospital on a 24/7 basis to screen all major highest activation trauma patients with known or suspected head injuries admitted to the Emergency Department (ED). Direct subject observation and data collection will begin at time of ED arrival. For those patients who did not meet eligibility criteria, data collection will stop.

2. Clinical Data Collection Process:

Direct bedside data collection will begin at time the subject arrives in the ED and will continue until 1) it has been determined that the subject is not eligible for this trial, 2) the subject or LAR refuses to participate in the trial, 3) 72 hours post admission or 4) the subject has expired. Until deemed ineligible, data from subjects will be collected and reviewed for screening purposes. An initial brain DTI-MRI will be performed after ICP monitoring is discontinued and a second brain DTI-MRI will occur 6-18 months after the initial head injury).

3. Neuroimaging Multimodal Acquisition:

The same 3T Philips Ingenia (32 channel head coil) clinical scanner located at Memorial Hermann Hospital in Houston, TX, will be used for acquiring both longitudinal MRI data throughout the period of performance. The following 3D brain sequences will be acquired in the sagittal plane: T1-weighted FFE (1mm^3 isotropic voxel dimensions; TR: 8.1 ms; TE: 3.7 ms; flip angle: 6^0), T2-weighted turbo spin echo (1mm^3 isotropic voxel dimensions; TR: 2500 ms; TE: 388 ms; flip angle: 90^0), T2-weighted FLAIR (1mm^3 isotropic voxel dimensions ; TR: 4800 ms; TE: 323 ms; TI: 1650 ms; flip angle: 90^0). Additionally, the following will be acquired in the axial plane: 3D-Susceptibility weighted SWI (voxel dimensions: 0.75x0.75x2mm^3 ; TR: 23.4 ms; TE: 30.7 ms; flip angle: 10^0) to assess bleeds and diffuse axonal injury (DAI); pseudo-continuous arterial spin label (pCASL) sequence will also be acquired to assess cerebral perfusion dynamics without the use of contrast agent: (voxel dimensions: 1.88x1.88x5mm; flip angle: 90^0; TR: 4550 ms; TE: post-label delay: 1800 ms).

To evaluate microstructural properties of brain tissue a pair of reversed phase-encoded EPI-based spin echo sequences (b=0 s/mm^2) will be acquired for correcting geometric and eddy-based current distortions in the 32 direction EPI-based spin echo multi-shell diffusion MRI (dMRI) sequence (2.2mm^3 isotropic voxel dimensions; TR: 6000 ms; TE: 64 ms; b=0 s/mm^2, b=150 s/mm^2, b=1000 s/mm^2, b=2000 s/mm^2). The same multi-shell diffusion sequence mentioned above can be analyzed with different models of diffusion, including tensor fit (DTI), kurtosis fit (DKI), and intravoxel incoherent motion (IVIM). Each of these models have emerged to overcome underlying

assumptions of earlier models (e.g. gaussian diffusion). Thus, the DTI model uses a single shell (single b-value) dMRI sequence and assumes that diffusion is gaussian-like throughout the brain. However, ground-truth variability in diffusion profiles across different tissue types (GM, WM, CSF) and different compartments (intracellular, interstitial, blood microcirculation, perivascular glymphatic clearance) violates this underlying assumption of DTI. More sophisticated models of diffusion to account for non-gaussian-like diffusion require multiple shells (different b-values). Specifically, DKI uses multiple b-values (minimum of 3) and includes a high b-value shell (>1000 s/mm^2) to account for diffusion barriers and compartments (Jensen and Helpern 2010). Similarly, IVIM additionally incorporates low b-values (<200 s/mm2) to differentiate between multiple components including tissue diffusion and collective water flow in blood microcirculation (Le Bihan 2019). Thus far, IVIM has been most widely utilized in oncology to evaluate microvascular heterogeneity (Iima 2020) since dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced (DCE) imaging require the use of contrast agents. However, combined with susceptibility weighted imaging (SWI) for bleeds, pcASL, DTI, DKI, and high-resolution anatomical sequences (T1, T2, T2-FLAIR), a 50min MRI session has the potential to disentangle complex tissue microstructure from blood flow and glymphatic clearance in TBI patients without using contrast agents.

4. Neuroimaging Outcome Measures:

Since acute cerebral edema signals that neuroinflammatory cascades are underway, advanced neuroimaging protocols are capable of informing us about which type(s) of edema (cytotoxic or vasogenic) are evident, their respective time courses and long-term impact on brain structure and connectivity with sites distal to the primary injury. These "secondary" brain injuries are the viable targets of putative therapeutic strategies for preserving brain structure and function. Identification and classification of the predominant cause of elevated ICP in each patient (e.g. bleeds, cytotoxic edema, vasogenic edema) would be expected to have substantial prognostic value while being highly informative in precisely determining the best treatment strategy to improve long-term outcome in each individual patient. Such information about the underlying "edema profile" could advance not only the development of novel targets for therapeutic action, but also serve as an indicator of treatment efficacy during the acute and subacute stages of recovery following TBI. Traditionally, the clinical characterization of cerebral edema is generally labeled as either vasogenic or cytotoxic, depending on the underlying mechanism and the visible "signs" evident from integration of non-invasive multimodal neuroimaging sequences such as high resolution 3D-T1

3D-T2, and 3D-T2-FLAIR sequences along with diffusion weighted imaging (DWI) metrics (*e.g.* Apparent Diffusion Coefficient and mean Diffusion Weighted signal). In ischemic stroke, researchers have frequently utilized DWI MRI sequences to identify regions exhibiting restricted diffusion (low ADC values) as evidence of cytotoxic edema (e.g. intracellular influx of extracellular fluid during anaerobic conditions). Based on the ischemic stroke literature, cytotoxic edema presents acutely (<24hrs), is potentially reversible (2-4 days), and represents the "rescuable" penumbral tissue to therapeutic intervention. In contrast, vasogenic edema is marked by increased diffusion (high ADC values) due to disrupted permeability of the blood brain barrier and is less likely to recover over time.

While very little information is currently available in the TBI literature regarding vasogenic or cytotoxic edema in clinical patients, a few studies have managed to overcome the inherent challenges of acquiring multimodal MRI sequences in acute/subacute severe TBI patients as soon as they are medically stable to localize and quantify cerebral edema (Hudak et al., 2014); (Marmarou et al., 2006). In the prospective study by Marmarou and colleagues (2006), DWI measures of ADC values were obtained from adult severe TBI patients within the first 2 weeks post injury. While signs of both phenotypes of cerebral edema were evident, decreased ADC values (restricted diffusion) was determined to be the predominant contributor to brain swelling in these acute patients. Furthermore, unlike ischemic stroke, restricted diffusion was not accompanied by evidence of ischemia based on cerebral blood flow measures obtained in conjunction with the DWI. Therefore, the term "cellular edema" was deemed by these authors to be more appropriate than "cytotoxic edema".

Global Volumetric Measures

Based on our previous work with the adult TBI population, we plan to evaluate several global volumetric measures. Our planned analyses included 5 regions of interest based on segmented tissue types from the 3D-T1weighted images acquired with our imaging protocol: Cerebral white matter, total gray matter, supratentorial, supratentorial (excluding ventricular CSF), and corpus callosum (integrated over midsagittal 5mm slices).

Midsagittal Connectivity Metrics of the Corpus Callosum

Deterministic tractography methods will be used to reconstruct the connectivity of the corpus callosum at each timepoint.

Edema Imaging Metrics

The same DTI sequence imaging data used above for evaluating changes in CC connectivity over time will be used to investigate changes in Mean Diffusivity (MD), both globally (e.g. whole brain gray matter, white matter, and CSF) as well as regionally in the corpus callosum. Since there have been two distinct types of edema reported in both the stroke and TBI literature, each at opposite ends of the spectrum of MD values, we will follow the classification schema developed by Sener (2001) from over 130 MRIs to quantify volumetric changes in the amount of cytotoxic edema (low MD values $<0.60 \times 10^{-3}$ mm^2/s) and vasogenic edema (high MD values ranging from $1.28 - 2.20 \times 10^{-3}$ mm^2/s). Based on Sener's classification schema, MD values for normal appearing white matter ranges between $0.60 - 1.05 \times 10^{-3}$ mm^2/s and MD values for CSF ranges between $2.40 – 4.40 \times 10^{-3}$ mm^2/s.

Final Thoughts

While "edema imaging" in TBI patients has not yet been traditionally investigated in research studies, lessons learned from acute stroke imaging in the clinical setting could easily be applied to acute/subacute TBI patients. As in ischemic stroke, identifying bio-signatures in the acute/subacute phase post-injury has tremendous potential to guide clinical decisions and monitor efficacy of new therapeutic targets to improve long term outcomes in TBI patients.

Data will be collected on a daily basis while the ICP monitor is in place and at the time of discharge or death on all subjects who have consented to participate in the study. Information collected will include demographics, ICP monitor readings, and vital signs and routine clinical lab results. In addition to the information collected during hospitalization, the final/discharge diagnosis, discharge destination (i.e. home, long term acute care hospice, skilled facility, death), number of ventilator, ICU and hospital days, and discharge extended Glasgow outcome scale (GOSE) will be obtained at the time the subject is discharged from the hospital. A GOSE will also be completed at month 6 post ED admission. The data will be collected through 1) direct observation, 2) medical record review, 3) trauma registry database, 4) Telephone call with the subject/LAR.

5. Laboratory Sample Collection and Analysis:

Blood samples. Blood samples will be obtained to determine the best serum biomarkers to define endotheliopathy. Blood samples will be taken at time of ED admission and then 2, 12, 24, 48 and 96 hours after ICP placement *(+/- 1hr)*. Blood samples (approximately 5 – 7 ml per sample) will be collected and dispensed into appropriate vacutainer tubes. Samples will be transported to the

research laboratory and aliquots made. Plasma osmolality (Posm) will be measured by the research laboratory by freezing point depression. Blood samples will be destroyed in the event that LAR consent is not obtained. DNA genotyping will be limited to SNPs distributed across TRPM4: rs8104571 (intron-20) and rs150391806 (exon-24) and the blood sample collected after LAR consent. Leftover blood samples, if any, will be stored in a secure medical school lab for future research and for an indefinite period of time. A full list of research laboratory assays can be found in Appendix B.

F. STATISTICAL PLAN and DATA ANALYSIS

1. Outcomes:

The primary outcome is GOSE at 6 months. Secondary outcomes of interest include: discharge GOSE, final/discharge diagnosis, discharge destination (i.e. home, long term acute care hospice, skilled facility, death), number of ventilator, ICU and hospital days (within the first 30 hospital days), and 6 month mortality.

2. Sample Size:

In Phase 1, we enrolled 25 patients. This sample size is based on feasibility and number of expected patients within the first 12 months of the study. In Phase 2, we will enroll 50 patients. This sample size will allow us to detect mean group differences >0.86 SDs assuming alpha of 0.05 and 80% power. This effect size is well within range of effect sizes (ranging from 1-2.5 SDs) observed in DTI metrics in our previous TBI trial.

3. Data Analysis Plan:

Descriptive statistics of baseline characteristics will be calculated for all patients. A generalized linear model framework will be used to conduct all analyses. Random intercepts and slopes will be included for analyses of longitudinal data. We will evaluate model assumptions for each analysis.

Sub Aim 1. ICP cumulative dose will be calculated as the area under the curve (AUC) for ICP values above 25 mm Hg. To confirm the independent association between ICP cumulative dose and unfavorable neurological outcome (GOS 1-3), we will use a logistic model with dichotomized GOSE as the dependent variable and AUC as a predictor adjusting for GCS and pupil reactivity at admission. As a secondary measure of total burden, we will evaluate the PRx (using similar measures as above) as a predictor of GOSE.

ICP-GOS Visualization method: We will also calculate the number of ICP insults for each patient as described in Guiza et al. First, each time series of minute-by-minute ICP data will be segmented into different episodes, called 'ICP insults.' ICP insult will be defined as an episode where the ICP is above both thresholds of intensity and duration. We will evaluate intensity thresholds from 10 to 40 mmHg and duration thresholds from 5 to 360 minutes. For each combination of intensity and duration thresholds, we will calculate the number of insults for each patient. Then, we will use proportional odds logistic models with GOSE at 6 months as the dependent variable and the number of insults as the predictor, including a random subject effect to account for within-patient correlation. From each of these proportional odds models (one for each combination of thresholds), we will estimate log odds ranging from $-\infty$ to ∞, where negative values indicate a negative association, i.e., higher number of ICP insults (at a given threshold) is associated with lower values of GOSE; positive log odds indicate that a higher number of ICP insults is associated higher values of GOSE. We will use similar contour plots as in Guiza et al to visualize the associations at different thresholds.

Sub Aim 2. We will also produce separate contour plots of ICP insults grouped by CPP > 60 mm Hg or Pressure/reactivity index >0.2 (one group) or CPP < 60 mm Hg and Pressure/reactivity index <0.2 (second group).

Sub Aim 3. We will use mixed models to analyze longitudinal lab values of Syndecan-1, serum albumin, and total protein levels collected within the first 96 hours of ICP monitoring. To evaluate whether these biomarkers are predictive of ICP phenotype, we will fit separate linear models to the number of ICP insults and AUC of ICP episodes > 25 mm HG using the peak values of the biomarkers as predictors.

Sub Aim 4. Daily PILOTmod scores will be analyzed with mixed models. We will evaluate EoT biomarkers as predictors of PILOTmod using similar models. We will also examine the ICP insult contour plots separately for PILOTmod > 25 and $\leq$ 25.

Secondary clinical and neuroimaging (volumetrics and edema) outcomes will be analyzed with GLMs. Binary outcomes will be analyzed with logistic models; count outcomes (i.e., days) will be analyzed with Poisson or negative binomial models, and continuous variables with Normal regression models. For each outcome, we will evaluate ICP insults, % of ICP monitoring time spent above 25 mm HG, AUC of ICP, and EoT biomarkers as potential predictors, adjusting for GCS and pupil reactivity at admission.

G. DATA MANAGEMENT

Study data will be obtained from a variety of sources including laboratory results, electronic medical records, medical charts, and imaging reports and files. Data from these source materials will be entered onto a standardized set of paper Case Report Forms (CRFs) that incorporate the NINDS TBI Common Data Elements (CDE).

1. REDCap Database:

Study data will be entered into the REDCap application hosted by the UTHealth School of Biomedical Informatics Data Center. The data center is housed in a state of the art facility with environmental and physical security, enterprise class servers and routers, and database back-up and integrity check procedures.

REDCap features include subject tracking user and group level management, automated data extraction algorithms, integrated data dictionaries, automatic receding and calculated variables, data verification tools (error checks), and is compatible with SAS, SPSS, and, STATA statistical software. In compliance with HIPAA regulations, the database security features of REDCap target multiple levels including the data element (e.g., restricted access to fields), user (e.g., password authentication access), application (e.g., role-based access to features, access audit trails), and hosting services (e.g., firewall, secure sockets layer). The research project will be set up in REDCap to ensure datasets are de-identified as defined in the HIPAA privacy regulation.

The research laboratory data will be entered into a separate REDCap database created for the lab measurement component of this trial.

2. Identifiers:

The only potentially identifying data that will be collected for analysis are full dates of admission, treatment, discharge, and death. Full dates are necessary to estimate time to event and survival. Date of birth will not be collected. To protect against loss of confidentiality, the subjects' names will be replaced by a study identification number on case report forms, research biomarker samples, and in the REDCap database.

3. Confidentiality:

A small risk to any subject enrolled in this trial is breach of confidentiality. This risk is acknowledged and we have spent considerable time, effort and cost mitigating this risk. This issue will be managed and minimized in seven ways: 1) only non-sensitive health information will be

recorded during this study; 2) only clinical research staff trained to protect confidentiality will be able to access protected health information; 3) data collection will occur on computers that limit access to only trained clinical research staff by unique user id and password; 4) protected health information will be protected by encryption when not in use on the computer; 5) a study identification number will be assigned to all subjects; 6) the study ID will be the only way to link data and blood samples to a particular patient; and 7) patient identifiers such as medical record number and patient name will not be entered in the database; 8) it would be virtually impossible to identify a patient based solely on the analysis of one gene segment.

A master log linking patient medical record numbers with study ids will be maintained on a secure, zone 100, network server within the UTHealth McGovern Medical School. Access to the master linking log will be limited to the research study team.

All study documents will be physically secured within the locked offices and locked file cabinets of the research study team.

Accurate and complete study records will be maintained and made available to representatives of the UTHealth Committee for the Protection of Human Subjects, the U.S. Army Human Research Protection Office (HRPO) as part of their responsibility to protect human subjects in research, and representatives from the Department of Defense funding this study.

4. Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System:

The Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system is a collaborative effort involving the NIH Institutes and Centers (ICs) and the US Army Medical Research and Material Command (USAMRMC) to develop a biomedical informatics system and data repository for Traumatic Brain Injury (TBI) research. The purpose of FITBIR is to help accelerate TBI research by creating an infrastructure that integrates heterogeneous datasets allowing access to much more quality research data than an investigator would be able to collect independently. De-identified NINDS TBI Common Data Elements (CDEs) collected as part of this research study may be submitted to FITBIR in compliance with the funding agreement. To ensure the security of the data held by the repository, the NIH Center for Information Technology employs multiple tiers of data security based on the content and level of risk associated with the data. Datasets stored in the FITBIR informatics system are under strict security provisions, including but not limited to multiple firewalls, separate servers, and data encryption protocols. As a federal information system, FITBIR follows the recommended security controls defined by the National

Institutes of Standards 800-53r1 and related publications. FITBIR undergoes an annual independent certification and assurance audit specific to the controls defined in 800-53r1 ensuring that the defined management, data recovery, procedural, and technical controls are followed. Additionally, all FITBIR policies are reviewed on an annual basis.

5. Record Retention:

The period of paper and electronic record retention will be consistent with the record retention policies of the University of Texas Health Science at Houston and the applicable regulatory agencies for the trial, including the study sponsor.

H. HUMAN SUBJECT RESEARCH

1. Risks to Subjects:

The Phase 2 and 3 study will enroll a total of 50 subjects who have experienced a severe traumatic brain injury. Based on past data, the majority of traumatic injuries occur in male subjects 45 years of age and younger, with a penetrating injury rate of 45%, and the majority of this population will have no significant pre-existing medical history. Children estimated to be less than 18 years of age, women who are known to be pregnant, and prisoners will be excluded from this trial.

2. Protection of Human Subjects and Informed Consent Process:

Because the early data collection will occur before many subjects are able to consent due to their injury and before surrogate decision-makers are typically available to consent, we are requesting a waiver of consent to be used for: A) initial medical record review to verify eligibility, B) direct data collection in the first 24 hours, and C) blood samples within 24 hours of arrival. A Waiver of HIPAA Authorization is also requested for the extraction of research data from the medical record during the first 72 hrs of admission. Subjects whose medical conditions improve to the point of being able to make their own medical decisions will sign a consent to continue further study-related procedures. Subjects who remain critically ill, receiving continuous or intermittent sedatives, who are obtunded/disoriented from illness or injury, or are unable to dictate their own care will have proxy consent obtained from their previously appointed power of attorney (if one exists) or the subject's legally authorized representative. If there is no designated LAR, a proxy will be selected consistent with state laws.

We are requesting a waiver of informed consent for the following reasons:

1. *This non-interventional study subjects' patients to no more than minimal risk.*

This non-interventional study will subject the patient to no more than minimal risk. All data will be collected by either direct observation of clinical procedures occurring in the hospital or through daily chart review documenting the patient's remaining hospital course. With the exception of the brain MRI and research biomarker blood samples, all study data will be derived from clinically indicated procedures. MRI scans are obtained without the use of radiation and therefore pose no additional risk to subjects. This information is not sensitive in nature and data collected in this study have been or will be recorded in the medical record solely for the purpose of medical treatment. The only additional risk to patients is the potential breach of confidentiality. The strict security measures listed in the previous section will mitigate this risk.

2. *A waiver will not adversely affect the rights and welfare of the patients.*

A waiver of consent for this study will not adversely affect the rights and welfare of the patients because this study is wholly observational in nature. Participation in this study will not change in any way the care that patients receive. The results of observations recorded solely for the study will have no effect on the care of the patients being observed. Because no published prospective data are available that examine the questions raised in this study, it is difficult to determine the best clinical practice without the data that will be collected in this study.

The resulting data will allow the rational design of future intervention trials which will allow us to make improvements in clinical practice to benefit severely injured trauma patients with a TBI. Complete observational data are essential for the ethical design of the future randomized study. Results from this and the subsequent randomized study will greatly benefit future trauma patients, without jeopardizing the rights and welfare of the patients enrolled in this study.

In addition, access to and use of patient medical record information will be limited to the research study investigators and their staff who already have access to this PHI based on the clinical responsibilities of the principal investigator that extends to their research teams.

3. *This research cannot be practicably carried out without a waiver.*

Rationale for waiver of consent in ED/OR/ IR: This research cannot be practicably carried out without a waiver because we are collecting data on major trauma patients who will arrive at the ED in an altered mental state due to their injuries or the treatment of those injuries. TBI trauma patients are frequently either unconscious from the brain injury, intubated in the prehospital phase of their care or intubated in the ED.

Additionally, Legally Authorized Representatives (LARs) are generally unavailable for major trauma patients at ED admission and for the several most critical hours afterwards. If/when the patient becomes competent to consent, it may be several days after the injury when direct observation of the patient has already ended for this study.

3. Vulnerable Populations:

Children below the age of 18 or 50kg body weight will be excluded from this trial.

Obviously pregnant women will also be excluded from this trial.

Known prisoners (defined as those directly admitted from a correctional facility) will be excluded from enrollment. It is possible that subjects may be enrolled into the study who eventually come under police observation as suspects. These subjects will remain in the study until discharge (30 days) or incarcerated.

4. Potential Risks to Patients:

This is an observational, non-interventional study. The only additional potential risk is the possibility of breach of confidentiality. Strict security measures will be implemented to ensure that subject confidentiality is maintained. Electronic study data will be entered and stored in a FDA 21 CFR Part 11 compliant database with access restricted to research study members. All hard copy forms will be kept in a secure, locked office with access restricted to the research study team. DNA genotyping will be limited to SNPs distributed across TRPM4 gene.

Subjects will have no additional costs for participating in the study. Subjects, or their 3rd party payer, will be responsible for all standard-of-care charges. Subjects will not be charged for lab tests specifically performed for research purposes.

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Appendix A: Table of Study Procedures

Study Procedure	First 72hr. of Admission	96hr Post ICP Placement *(+/- 2hr)*	When Clinically Stable and ICP D/C	At Discharge/Death	6-18 Months Post TBI (+/-7 Days)
Screening	X				
LAR Consent	X				
Research Blood Samples [1]	X	X			
Brain DTI-MRI			X		X
Standard of Care Data Collection From EMR [2]	X	X	X	X	
GOS-E [3]					X

1. The baseline biomarker blood sample will be obtained shortly after ED admission and at five timepoints after ICP placement, (2hr, 12hr, 24hr, 48hr, and 96hr, +/-hr.). If LAR consent is not obtained within the first 72hr of admission data collection will cease and the blood sample will be discarded. The blood sample for genotyping will be drawn after LAR consent. Research laboratory assays are listed in Appendix B.
2. Standard of care information will be collected from the subject's EMR from admission through discharge/death. The information collected will include subject demographics, vital signs, GCS, ICP and CPP data, clinical lab and diagnostic test results and discharge information (disposition, AIS and ISS).
3. Obtained at a regularly scheduled follow-up clinic visits or by telephone call.

Appendix B: Research Laboratory Assays

Albumin

Syndecan-1

Tissue Plasminogen Activator (tPA)

Heparan Sulfate

Hyaluronic Acid

Thrombomodulin

DNA genotyping for SNPs distributed across TRPM4: rs8104571 (intron-20) and rs150391806 (exon-24)

Appendix C: PILOT $_{mod}$ Scale

Variable	Score
Treatment of Fever >38.5°C or spontaneous temperature of <34.5°C	1
Sedation by narcotics or benzodiapenes	1
Neuromuscular Blockade	2
Intubation with $PaCO_2$ of 35.1-40mm Hg	1
Intubation with mild hyperventilation and $PaCO_2$ of 32-35mm Hg	2
Intubation with aggressive hyperventilation and $PaCO_2$ <32mm Hg	4
Mannitol infusion ≤ 1g/kg	1
Mannitol Infusion 1.1-2 g/kg	2
Mannitol infusion >2 g/kg	3
HTS infusion with serum Na <150	**3**
HTS infusion with serum Na 150- 159	**5**
HTS infusion with serum Na 160- 169	**7**
HTS infusion with serum Na 170-179	**9**
CSF Drainage 0-11 times	1
CSF Drainage 12-23 times	2
CSF Drainage ≥24 times	3
Pentobarbital ≤36mg/kg	3
Pentobarbital >36 mg/kg	4
Evacuation of Hematoma	4
Decompressive Craniectomy	5
Induced mild hypothermia ≥35°-37°C	2
Induced Moderate Hypothermia <35°C	4
Lumbar drain	2
Induced hypertension (≥95th percentile for age)	2
Hypertonic saline (HTS); Cerebrospinal fluid (CSF);	
Total:	**44**

UTHealth
The University of Texas
Health Science Center at Houston

CONSENT TO TAKE PART IN RESEARCH

Simple Study Title: TBI ICP and Biomarker Study (Phase 2/3)

Full Study Title: Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity after Severe TBI (Phase 2/3)

Study Sponsor: Department of Defense

Principal Investigator: Charles Cox, Jr., MD

Study Contact: Carmen Duron, MHA, BSN, RN, (713) 500-7395

The purpose of this study is to better understand the relationship of intracranial pressure (ICP) values and blood samples that measure inflammation in individuals who have experienced a traumatic brain injury (TBI) that may be useful in predicting recovery.

If you choose to participate in this study, you will be asked to allow us to collect blood samples over the first 4 days of your hospital stay, have one brain MRI scan before discharge and another brain MRI scan at 6-18 months, and complete a brief disability assessment questionnaire at time of discharge and by telephone 6 months after the TBI. The total amount of time you will be in this study is between 6 to 18 months, depending on when the second MRI scan is completed.

This is an observational study therefore the risks are minimal however there is also the potential risk of breach of confidentiality. The only alternative is to not participate in this observational study.

Participation in this research study is voluntary. You may choose not to take part in this research study or may choose to leave the research study at any time. Your decision will not affect the clinical care you receive at the University of Texas Health Science Center at Houston (UTHealth), and/or Memorial Hermann Healthcare System.

If you are interested in participating, please continue to read below.

If you are unable to provide written informed consent, or have legally transferred authority to consent for health care decisions to another person, a Legally Authorized Representative may consent on your behalf to participate in this study. “You” refers to the patient in this consent form.

What is the purpose of this research study?

Severe head injuries can cause the brain to swell. The expanding tissue increases the pressure within the skull and can result in further brain injuries. Intracranial pressure (ICP) monitoring is standard of care for patients with severe traumatic brain injuries. Bedside monitors continuously display ICP values but this information is usually only recorded in the medical record at hourly intervals. The purpose of this study is to better understand ICP changes immediately following severe TBI by collecting very detailed information on

ICP values, (recorded every 5 seconds). Research blood samples will be tested for proteins linked to inflammation and brain swelling. This study is observational so there will be no study treatment or medications.

The Department of Defense is paying UTHealth for its work on this study.

Who is being asked to take part in this study?
You are being asked to take part in this research study because you have experienced a traumatic brain injury. This study is being conducted at UTHealth. About 50 people will take part in the study at UTHealth, and Memorial Health System.

What will happen if I take part in this study?
If you agree to participate, blood samples (about 1 ½ tablespoons) will be collected at the time of emergency department admission, and at 2, 12, 24, 48, and 96 hours after the ICP monitor was placed as standard of care. The total amount of blood withdrawn during your participation will be about 9 tablespoons.

You will also have a brain MRI scan once the ICP monitor is removed and another brain MRI scan at 6 to 18 months.

We will also complete a brief disability assessment called the Glasgow Outcome Scale (GOSE) at the time you leave the hospital and again by telephone 6 months after your TBI. The GOSE is routinely used to measure an individual's recovery following TBI and should take no more than 10 minutes to complete. In addition, we will also collect information from your medical records during your hospital stay.

The results of these research tests will not have an effect on your care. You will not receive results of these research tests, nor will the results be put in your health record. Your leftover blood samples, if any, will be stored in a secure lab at the UTHealth Medical School for future research and for an indefinite period of time.

How long will you be in the study?
If you agree to take part, your participation will last between 6 to 18 months and will involve the time you are in the hospital, and then a phone call approximately 6 months from the time you were admitted to the hospital. You will also be asked to complete the second brain MRI 6 to 18 months after your initial head injury.

What choices do you have other than this study?
The only option is to not take part in this study. You will continue to receive the standard care for traumatic brain injury.

What are the risks of taking part in this study?
Because this is an observational study, the risks are minimal. One potential risk is the possibility of breach of confidentiality. All measures are taken to protect your personal identity. The information collected will be de-identified and identified only by a unique study ID number.

MRI Scans: MRI scans are very safe procedures, and there is no radiation or contrast media involved. The MRI does involve the use of a large magnet that can interact with metal objects like dental braces or implanted devices. You will be carefully screened for the presence of metal objects in or on your body before the MRI. Some people are

uncomfortable in the scanner, as it is an enclosed space. You may require sedation or general anesthesia to complete the MRI. The risks associated with sedation and general anesthesia include respiratory depression and low heart rate and blood pressure. An Anesthesiologist will monitor you closely during the MRI scan to prevent complications from the sedation or general anesthesia.

GINA

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

What are the benefits of taking part in this study?

You may not directly benefit from participating in the study, but the knowledge gained from your participation may, in the future, help others with traumatic brain injury.

Can you stop taking part in this study?

You may decide to stop taking part in the study at any time. To withdraw from the study, please contact Charles Cox, MD at 713-500-7329.

Your doctor or the sponsor can stop the study at any time. Your doctor or the sponsor may stop your participation in the study if your condition worsens, the study is stopped, you do not meet all the requirements of the study, or the study is not in your best interest. If your participation in the study is stopped, your doctor will discuss other options for your treatment.

If you stop participating in this study, the information already collected about you will still be used in the data analysis. However, no further information will be collected without your permission.

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to stay in the study.

What happens if you are injured during the study?

If you suffer an injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment, and professional services will be available to you, just as they are to the general community. You should report any such injury to Charles Cox, MD at 713-500-7300. You will not give up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT, AND COMPENSATION

What are the costs of taking part in this study?

There will be no cost to you or to your insurance company for taking part in this research study. The sponsor will pay for the special tests and examinations that are required by this study and not otherwise part of your standard medical care. If you receive a bill that you believe is related to your taking part in this research study, please contact Charles Cox, MD, or his research staff at 713-500-7300 with any questions.

In addition, you will receive $150.00 for the six-month follow-up brain MRI visit (which can be completed between 6 to18 months after your traumatic brain injury). Transportation for follow-up study visits can be provided if needed.

How will privacy and confidentiality be protected?
Your privacy is important and your participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed.

If you sign this document, you give permission to UTHealth, Memorial Hermann Healthcare System to use and disclose (release) your health information. The health information that we may use or disclose for this research includes; prehospital information, vital signs, lab reports, procedure and diagnostic reports, lab results, discharge notes, and physician notes.

Personal identifiers such as your name and medical record number will be removed from the information and samples collected in this study. After we remove all identifiers, the information or samples may be used for future research or shared with other researchers without your additional informed consent.

People who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect your health information and may share your information with others without your permission, if permitted by laws governing them. You will not be personally identified in any reports or publications that may result from this study. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Representatives of the organizations listed below will see your name and other personal identifiers when they review your research records and medical records for the purposes of verifying study data:

- Representatives of UTHealth and/or Memorial Hermann Health System
- Representatives from the U.S. Food and Drug Administration (FDA)
- Representatives of Department of Defense

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. UTHealth and Memorial Hermann Health System may not withhold treatment or refuse treating you if you do not sign this Authorization.

Federal Interagency Traumatic Brain Injury Information System
Data from this study may be submitted to the Federal Interagency Traumatic Brain Injury (FITBIR) informatics system. FITBIR is a computer system run by the National Institutes

of Health that allows researchers studying traumatic brain injury to collect and share information with each other. With an easier way to share, researchers hope to learn new and important things about traumatic brain injury more quickly than before.

During and after the study, the researchers will send information about your health and behavior and in some cases, your genetic information, to FITBIR. However, before they send it to FITBIR, they will remove information such as name, date of birth, and city of birth, and replace that information with a code number. Other researchers nationwide can then file an application to obtain access to your study data for research purposes. Experts who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You will not benefit directly from allowing your information to be shared with FITBIR. The information provided to FITBIR might help researchers around the world treat future children and adults with traumatic brain injury so that they have better outcomes. FITBIR will report on its website about the different studies that researchers are conducting using FITBIR data; however, FITBIR will not be able to contact you about specific studies.

You may decide now or later that you do not want to share your information using FITBIR. If so, contact the researchers who conducted this study, and they will tell FITBIR, which can stop sharing the research information. However, FITBIR cannot take back information that was shared before you changed your mind. If you would like more information about FITBIR, this is available on-line at http://fitbir.nih.gov

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must contact Charles Cox, MD in writing at UTHealth, 6431 Fannin MSB 5.324, Houston, TX 77030

This Authorization will expire 6 years after the end of the study.

Whom can you contact if you have questions about the study?
If you have questions at any time about this research study, please feel free to contact the Charles Cox, MD or study staff at 713-500-7300, as they will be glad to answer your questions. You can contact the study team to discuss problems, report injuries, voice concerns, obtain information in addition to asking questions about the research.

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at (713) 500-7943.

Can we contact you in the future?
Can we contact you in the future regarding other research studies you may be interested in?

☐ **Yes,** I give my consent for future contact. ☐ **No**

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to take part in this research study. Make sure that all your questions have been answered. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of Subject	Signature of Subject	Date	Time
Printed Name of Legally Authorized Representative	Signature of Legally Authorized Representative	Date	Time
Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time

CONSENTIMIENTO INFORMADO PARA PARTICIPAR EN UN ENSAYO DE INVESTIGACION MÉDICA

Título Simple de la Investigación: Lesión Cerebral Traumática (LCT), Presión IntraCraneal (PIC) y Estudio de Biomarcadores (Fase 2/3)

Título Completo del Estudio: Biomarcadores de barreras microvasculares para predecir la intensidad terapéutica de la PIC después de una LCT grave (Fase 2/3)

Patrocinador del Estudio: Departamento de Defensa

Investigador Principal: Dr. Charles Cox

Contacto de Estudio: Carmen Duron, MHA, BSN, RN (713) 500-7395

El propósito de este estudio es para entender mejor la relación de los valores de la presión intracraneal y las muestras de sangre que miden la inflamación en individuos que han sufrido una lesión cerebral traumática (LCT) y que pueden ser útiles para predecir la recuperación.

Si elige participar en este estudio, se le pedirá que nos permita tomar muestras de sangre durante los primeros 4 días de su estancia en el hospital, hacerle una imágen del cerebro por resonancia magnética (MRI, por sus siglas en inglés) antes de darlo de alta y otro escaneo de imagen del cerebro (MRI) entre 6 a 18 meses, y completar una breve evaluación de la incapacidad al momento de ser dado de alta y por teléfono 6 meses después de la LCT. El tiempo total que permanecerá en este estudio oscila entre 6 y 18 meses, dependiendo de cuando se realice la segunda resonancia magnética.

Este es un estudio observacional, por lo tanto, los riesgos son mínimos, sin embargo, también existe el riesgo potencial de que su participación o sus datos personales puedan ser descubiertos. La única alternativa es de no participar en este estudio observacional.

La participación en este estudio de investigación es voluntaria. Puede optar por no participar en este estudio de investigación o puede optar por abandonar el estudio de investigación en cualquier momento. Su decisión no afectara la atención clínica que recibe en la University of Texas Health Science Center (UTHealth) y/o Memorial Hermann Health System.

Si está interesado en participar, siga leyendo a continuación.

Si no puede proporcionar un consentimiento (permiso) informado por escrito, o si ha transferido legalmente la autoridad para consentir las decisiones de atención médica a otra persona, un Representante Legal Autorizado puede dar el consentimiento en su nombre para participar en este estudio. “Usted” se refiere al paciente en este formulario de consentimiento.

¿Cuál es el propósito de este estudio de investigación?

Las lesiones graves en la cabeza pueden hacer que el cerebro se hinche. El tejido al hincharse puede aumentar la presión dentro del cráneo y puede provocar más lesiones cerebrales. La monitorización de la Presión Intracraneal (PIC) es la atención estándar para pacientes con lesiones cerebrales traumáticas graves. Los monitores utilizados en el cuarto del paciente muestran continuamente los niveles de presión intracraneal (PIC) pero esta información generalmente solo se registra en el expediente médico a intervalos de una hora. El propósito de este estudio es comprender mejor los cambios en la (PIC) inmediatamente después de una Lesión Cerebral Traumática (LCT) grave mediante la recopilación de información muy detallada sobre los niveles de la (PIC) (registrados cada 5 segundos). Se analizarán muestras de sangre de investigación para detectar proteínas vinculadas a la inflamación e hinchazón del cerebro. Este estudio es de observación, por lo que no habrá tratamiento, medicamento o procedimiento del estudio.

El Departamento de Defensa está patrocinando a la Universidad UTHealth por el trabajo en este estudio.

¿A quién se le pide que participe en este estudio?

Se le invita que participe en este estudio de investigación porque Ud. ha experimentado una lesión cerebral traumática. Este estudio se está realizando en la Universidad UTHealth. Alrededor de 50 personas participarán en el estudio en la Universidad UTHealth, y Memorial Health System.

¿Qué pasará si participo en este estudio?

Si acepta participar, se tomarán muestras de sangre (aproximadamente 1 ½ cucharadas) en el momento de la admisión en el departamento de urgencias, y a las 2, 12, 24, 48 y 96 horas después de que el monitor PIC se haya colocado como estándar de atención médica. La cantidad total de sangre extraída durante su participación será de unas 9 cucharadas.

También se le realizara una resonancia magnética cerebral una vez que se le retire el monitor de PIC y otra resonancia magnética cerebral entre los 6 y 18 meses.

También completaremos una evaluación breve relacionada con la discapacidad llamada Escala de Resultados de Glasgow (GOSE, por sus siglas en inglés) al momento de salir del hospital y nuevamente por teléfono 6 meses después de su LCT.

El GOSE se usa habitualmente para medir la recuperación del paciente después de una LCT y no debe tomar más de 10 minutos en completarse. Además, también recopilaremos información de su historial médico durante su estadía en el hospital. Los resultados de estas pruebas de investigación no afectarán su atención. No recibirá los resultados de estas pruebas de investigación, ni los resultados se incluirán en su registro de salud. Las muestras de sangre sobrantes, si las hay, se almacenarán en un laboratorio seguro en la Escuela de Medicina de la Universidad UTHealth para investigaciones futuras y por un período de tiempo indefinido.

¿Cuánto tiempo estará en el estudio?

Si acepta participar, su participación durara entre 6 y 18 meses e implicara el tiempo que permanezca en el hospital, y luego una llamada telefónica aproximadamente 6 meses desde el momento en que ingreso en al hospital. También se le pedirá que realice la segunda resonancia magnética cerebral entre 6 y 18 meses después del traumatismo craneoencefálico inicial.

¿Qué opciones tienes aparte de este estudio?

La única opción es no participar en este estudio. Continuará recibiendo la atención estándar para lesiones cerebrales traumáticas.

¿Cuáles son los riesgos de participar en este estudio?

Debido a que este es un estudio observacional, los riesgos son mínimos. Un riesgo potencial es la posibilidad de la perdida de la confidencialidad. Se toman todas las medidas para proteger su identidad personal. La información recopilada será desidentificada e identificada solo por un número de identificación de estudio único.

Escaneo de Imagen por Resonancia Magnética: La Imagen por Resonancia Magnética es un procedimiento muy seguro, y no hay radiación ni medios de contraste involucrados. La Imagen por Resonancia Magnética implica el uso de un imán grande que puede interactuar con objetos metálicos como aparatos ortodónticos (dentales) o dispositivos implantados. Antes de la resonancia por magnética se le examinara cuidadosamente para detectar la presencia de objetos metálicos en su cuerpo. Algunas personas se sienten incomodas en el escáner, ya que es un espacio cerrado. Es posible que necesite sedación o anestesia general para realizar la Imagen por Resonancia Magnética (MRI, conocida por sus siglas en inglés). Los riesgos asociados a la sedación y a la anestesia general incluyen la depresión respiratoria y la disminución de la frecuencia cardiaca y de la presión arterial. Un anestesista le vigilara de cerca durante el escaneo para evitar complicaciones derivadas de la sedación o la anestesia general.

GINA

Una ley federal, llamada Ley de No Discriminación de Información Genética (GINA, por sus siglas en ingles), generalmente hace ilegal que las compañías de seguros de salud, los planes de salud grupales y la mayoría de los empleadores lo discriminen en base a su información genética. Esta ley generalmente lo protegerá de las siguientes maneras:

Las compañías de seguros de salud y los planes de salud grupales no pueden solicitar la información genética que obtenemos de esta investigación.

Las compañías de seguros de salud y los planes de salud grupales no pueden usar su información genética al tomar decisiones con respecto a su elegibilidad o primas.

Los empleadores con 15 o más empleados no pueden usar su información genética que obtenemos de esta investigación al tomar la decisión de contratarlo, promoverlo o despedirlo o al establecer los términos de su empleo.

Tenga en cuenta que esta ley federal no lo protege contra la discriminación genética de las compañías que venden seguros de vida, seguros por discapacidad o seguros de atención a largo plazo.

¿Cuáles son los beneficios de participar en este estudio?

Es posible que no se beneficie directamente al participar en el estudio, pero el conocimiento obtenido de su participación puede, en el futuro, ayudar a otros pacientes con lesiones cerebrales traumáticas.

¿Puedes dejar de participar en este estudio?

Puede decidir dejar de participar en el estudio en cualquier momento. Para retirarse del estudio, llame al Dr. Charles Cox, al teléfono 713-500-7329.

Su médico o el patrocinador pueden detener el estudio en cualquier momento. Su médico o el patrocinador pueden detener su participación en el estudio si su condición empeora, el estudio se detiene, no reúne con todos los requisitos del estudio o si el estudio no es lo mejor para usted. Si se interrumpe su participación en el estudio, su médico discutirá otras opciones para su tratamiento.

Si deja de participar en este estudio, la información ya recopilada sobre usted se utilizará en el análisis de datos. Sin embargo, no se recopilará más información sin su permiso.

Mientras participa en este estudio, el equipo del estudio le notificara sobre información nueva que pueda estar disponible y que pueda afectar su disposición en permanecer en el estudio.

¿Qué sucede si se lesiona durante el estudio?

Si sufre una lesión como resultado de participar en este estudio de investigación, comprenda que no se han hecho arreglos para proporcionar un tratamiento gratuito de la lesión o cualquier otro tipo de pago. Sin embargo, las instalaciones necesarias, el tratamiento de urgencia y los servicios profesionales estarán disponibles para usted, tal como lo están para la comunidad en general. Debe informar cualquier tipo de lesión al Dr. Charles Cox, al teléfono 713-500-7300. No renunciará a ninguno de sus derechos legales al firmar este formulario de consentimiento.

COSTOS, REEMBOLSO Y COMPENSACION

¿Cuáles son los costos al participar en este estudio clínico?

La participación en este estudio de investigación no tendrá ningún costo para usted, ni para su compañía de seguro médico. El patrocinador pagara las pruebas y exámenes especiales que requiera este estudio y que no formen parte de su atención medica habitual. Si recibe una factura que cree que está relacionada con su participación en este estudio de investigación, póngase en contacto con el Dr. Charles Cox o con su personal de investigación llamando al teléfono 713-500-7300 si tiene alguna pregunta.

Además, recibirá $150.00 dólares por la visita de seguimiento de seis meses para la resonancia magnética cerebral (que puede realizarse entre 6 y 18 meses después de su lesión cerebral traumática). Si es necesario, se le proporcionara transporte para la visita de seguimiento del estudio.

¿Cómo se protegerán la privacidad y la confidencialidad?

Su privacidad es importante y su participación en este estudio se mantendrá confidencial. Sin embargo, no se puede garantizar la confidencialidad absoluta.

Su firma en este documento, autoriza al UTHealth, Memorial Hermann Healthcare System a usar y revelar (divulgar) su información de salud. La información de salud que nosotros
podemos usar o divulgar para esta investigación incluye; información pre hospitalaria, signos vitales, informes de laboratorio, procedimientos e informes de diagnóstico, resultados de laboratorio, resumen de la visita y las anotaciones del médico.

Los identificadores personales tales como su nombre y número de expediente médico se eliminarán de la información y de las muestras recolectadas en este estudio. Después de que eliminemos todos los identificadores, la información o las muestras pueden usarse para investigaciones futuras o compartirse con otros investigadores sin su consentimiento informado adicional.

Es posible que algunas personas que reciben su información no serán obligados a seguir las leyes federales de privacidad (como la Regla de Privacidad), si lo permiten las leyes que las rigen. No será identificado personalmente en ningún informe o publicación que pueda resultar de este estudio. Si toda la información que lo identifica o puede identificarlo se elimina de su información de salud, la información restante ya no estará sujeta a esta autorización y puede usarse o divulgarse para otros fines.

Los representantes de las organizaciones enumeradas a continuación verán su nombre y otros identificadores personales cuando revisen sus registros de investigación y registros médicos con el fin de verificar los datos del estudio:

- Representantes de la Universidad UTHealth y / o Memorial Hermann Health System
- Representantes de la Administración de alimentos y fármacos de los Estados Unidos (FDA por sus siglas en ingles).
- Representantes del Departamento de Defensa.

Tenga en cuenta que no tiene que firmar esta Autorización, pero si no lo hace, no podrá participar en este estudio de investigación. UTHealth y Memorial Hermann Health System no pueden retener el tratamiento o negarse a tratarlo si no firma esta Autorización.

Sistema de información federal inter-agencial sobre las lesiones cerebrales traumáticas

Los datos de este estudio pueden enviarse al sistema informático Federal Inter-agencial de Lesiones Cerebrales Traumáticas (FITBIR, por sus siglas en ingles). FITBIR es un sistema informático administrado por los Institutos Nacionales de Salud que permite a los investigadores que estudian las lesiones cerebrales traumáticas a recopilar y compartir información entre ellos. Con una forma más fácil de compartir, los investigadores esperan aprender cosas nuevas e importantes sobre las lesiones cerebrales traumáticas más rápido que antes.

Durante y después del estudio, los investigadores enviarán información sobre su salud y comportamiento y, en algunos casos, su información genética, a FITBIR. Sin embargo, antes de enviarla a FITBIR, eliminarán información tales como el nombre, la fecha de nacimiento y la ciudad de nacimiento, y reemplazarán esa información con un número de código. Otros investigadores de todo el país pueden presentar una solicitud para obtener acceso a los datos del estudio con fines de investigación. Los expertos que saben cómo proteger la información científica y de salud analizarán cada solicitud detenidamente para minimizar los riesgos para su privacidad.

No se beneficiará directamente al permitir que su información se comparta con FITBIR. La información proporcionada a FITBIR podría ayudar a los investigadores de todo el mundo a ayudar a futuros niños y adultos con lesiones cerebrales traumáticas para que tengan mejores resultados. FITBIR informará en su sitio web sobre los diferentes estudios que los investigadores están llevando a cabo y utilizando datos de FITBIR; sin embargo, FITBIR no podrá contactarlo sobre estudios específicos.

Puede decidir ahora o después que no desea compartir su información usando FITBIR. Si es así, comuníquese con los investigadores que realizaron este estudio y le dirán a FITBIR, que puede dejar de compartir la información de la investigación. Sin embargo, FITBIR no puede recuperar la información que se compartió antes de cambiar de opinión. Si desea obtener más información sobre FITBIR, puede obtenerla en línea en http://fitbir.nih.gov.

Puede cambiar de opinión y revocar (retirar) esta Autorización en cualquier momento. Incluso si revoca esta Autorización, los investigadores aún pueden usar o divulgar información de salud que ya hayan obtenido sobre usted según sea necesario para

mantener la integridad o confiabilidad de la investigación actual. Para revocar esta autorización, debe comunicarse con el Dr. Charles Cox, por escrito a la Universidad de UTHealth, 6431 Fannin MSB 5.324, Houston, TX 77030

Esta autorización se vencerá 6 años después del final del estudio.

¿A quién puede contactar si tiene preguntas sobre el estudio?

Si tiene preguntas en cualquier momento sobre este estudio de investigación, no dude en comunicarse con el Dr. Charles Cox, o el personal del estudio al 713-500-7300, ya que estarán encantados de responder sus preguntas. Puede ponerse en contacto con el equipo del estudio para analizar problemas, informar lesiones, expresar sus inquietudes, obtener información además de hacer preguntas sobre la investigación.

El Comité para la Protección de Sujetos Humanos (*Committee for the Protection of Human Subjects)* de la University of Texas Health Science Center ha revisado este estudio de investigación. Puede contactarlos para cualquier pregunta sobre sus derechos como sujeto de investigación y para discutir cualquier duda, comentario o queja sobre participando en un estudio de investigación al (713) 500-7943.

¿**Podemos contactarlo en el futuro**?

¿Podemos ponernos en contacto con usted en el futuro en relación con otros estudios de investigación en los que pueda estar interesado?

☐ Si, Yo doy mi consentimiento para contacto en el futuro. ☐ No

FIRMAS

Firme a continuación solamente si entiende la información que se le ha proporcionado sobre la investigación y elige participar en este estudio de investigación. Asegúrese de que todas sus preguntas hayan sido respondidas. Si decide participar en este estudio de investigación, se le entregará una copia de este formulario de consentimiento firmado.

Nombre Impreso del Participante	Firma del Participante	Fecha	Hora
Nombre Impreso del Representante Legal Autorizado	Firma del Representante Legal Autorizado	Fecha	Hora
Nombre Impreso de la Persona que Obtiene el Consentimiento	Firma de la Persona que Obtiene Consentimiento	Fecha	Hora

UTHealth Houston

Committee for the Protection of Human Subjects

7000 Fannin Street, Suite 1870
Houston, Texas 77030

Dr. Charles Cox Jr
UT-H - MS - Dept of Pediatric Surgery

NOTICE OF CONTINUING REVIEW APPROVAL December 09, 2022

HSC-MS-19-0628 - *Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity after Severe TBI (Phase I)*
PI: Charles Cox Jr

PROVISOS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.

APPROVED: At a convened meeting

MEETING DATE: 12/09/2022

EXPIRATION DATE: 11/30/2023

CHAIRPERSON: Charles C. Miller, III, PhD

Upon review, the CPHS finds that this research is being conducted in accord with its guidelines and with the methods agreed upon by the principal investigator (PI) and approved by the Committee. This approval, subject to any listed provisions and contingent upon compliance with the following stipulations, will expire as noted above:

CHANGES: The PI must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT: Informed consent must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. **Please note that only copies of the appropriately dated, stamped approved informed consent form can be used when obtaining consent.**

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious

harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent documents if required, in a manner which ensures subject confidentiality.

UTHealth Houston

Committee for the Protection of Human Subjects

7000 Fannin Street, Suite 1870
Houston, Texas 77030

Dr. Charles Cox Jr
UT-H - MS - Dept of Pediatric Surgery

NOTICE OF CONTINUING REVIEW APPROVAL August 15, 2023

HSC-MS-19-0628 - *Microvascular Barrier Biomarkers to Predict ICP Therapeutic Intensity after Severe TBI (Phase I)*
PI: Charles Cox Jr

PROVISOS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.

APPROVED: At a convened meeting

MEETING DATE: 08/11/2023

EXPIRATION DATE: 07/31/2024

CHAIRPERSON: Charles C. Miller, III, PhD

Upon review, the CPHS finds that this research is being conducted in accord with its guidelines and with the methods agreed upon by the principal investigator (PI) and approved by the Committee. This approval, subject to any listed provisions and contingent upon compliance with the following stipulations, will expire as noted above:

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