IRB APPLICATION

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of site prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB On-line training and the IRB has been notified.
6. That all personnel working on this protocol will follow all site IRB Policies and Procedures.
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the Site Compliance and Privacy Office , Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at site for an extended period of time.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from site without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at site. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of site. It will also approve which HIPAA identifiers may be taken outside of site with the health information or specimens.
23. If any member of study team leaves site, they are STRONGLY ENCOURAGED to use Exit Checklist.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Provide a brief description of the investigators experience in working with this population in the clinical and research arena.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

Table of Contents

Brief Summary/Abstract

There is an increasing need for improved treatments for stroke patients as stroke is the most common cause of serious long term adult disability and the third most common cause of death in the United States. Hyperglycemia is seen in approximately 40% of acute ischemic stroke patients and has been associated with worse clinical outcomes. Intravenous (IV) insulin therapy with tight glucose control has been found to improve clinical outcomes in some non-stroke acute illness trials. Current stroke guidelines emphasize the need for definitive clinical trials to determine best practice for managing hyperglycemia in acute stroke patients. A clear determination of the risk and benefit of glucose control with IV insulin would have a dramatic impact on acute ischemic stroke patient therapy.

This Phase III multicenter, randomized, controlled trial will determine the efficacy and provide further safety data on glycemic control in stroke patients. The hyperglycemic acute ischemic stroke patients that meet all eligibility criteria will receive up to 72 hours of hyperglycemia control with IV insulin therapy or control therapy with subcutaneous (SQ) insulin. Treatment will be given within 12 hours of symptom onset and within 3 hours of arrival to the emergency department (ED). The primary efficacy outcome to be assessed at 90 days will be the severity adjusted difference in favorable outcome between the groups. Favorable outcome will be defined by a previously described baseline severity adjusted dichotomized modified Rankin scale (mRS). Outcome success will depend on the severity of the initial stroke (per NIH Stroke Scale Score (NIHSS)). The primary safety outcome will be the hypoglycemic event rate. Secondary outcomes will assess additional neurological and functional status using stroke severity, functional and quality scales as well as glucose control success and adherence to the protocol dosing recommendations of the computerized decision support tool. This trial launches a highly collaborative model for stroke research providing a foundation for maximally generalizable results based on performance at academic, community, urban, rural, large and small hospitals throughout North America to produce a highly representative national population sample. A validated computer decision support tool will guide delivery of IV insulin therapy. A baseline severity-adjusted dichotomized outcome analysis (responder analysis) will adjust for variability of individual patient characteristics to allow detection of the true clinically relevant treatment effect. In this setting an absolute 7% treatment effect is recognized as a threshold at or above which a profound effect on a large stroke population would be realized.

Human Participants

1. How many subjects will sign a consent form under this protocol?

Up to __ patients will sign a consent form under this protocol.

Biomedical Research

1. Will any of the NON-RADIOLOGIC treatments/ procedures be done for research purposes only?
NO

2. Will any RADIOLOGIC treatments/examinations be performed for research purposes only?
NO

3. Will you be using viable embryos?
NO

4. Will you be using embryonic stem cells?
NO

Data and Safety Monitoring Plan

How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Serious adverse event	IRB	Within 24 hours from the time the study team received knowledge of the event.	IRB
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form.
Protocol Violations (*The IRB only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)*	IRB	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation Form
Data Breach	Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY	Corporate Compliance and Privacy Office ITC

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual.*
- *All recruitment materials will be approved by the IRB prior to use. The advertisements will be submitted to the IRB after the protocol has been approved.*
- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the site must have been granted clinical privileges to perform specific clinical privileges whether those procedures are experimental or standard.*
- *The IRB cannot grant clinical privileges.*
- *Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.*
- *Personnel on this protocol will have the appropriate clinical privileges in place before performing any procedures required by this protocol.*

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the institution. You must have "permission" to share data/ specimens outside of site other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of site even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at
http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: FDA Verification of Approval

1. What is the name of the approved drug, device or biologic?

Insulin (human regular insulin, analog rapid acting insulin, basal insulin)

2. What document have you provided to confirm FDA approval?

Package insert

3. Is the study required by the FDA?

NO

4. Is the study initiated by an investigator and not a commercial company?
YES

5. Is the study retrospective?
NO

6. Does the study involve research on a drug/ device in an already approved population/ condition?
YES

7. Does the study involve research only on a drug and NOT on a device?
YES

APPENDIX: FDA Verification of Approval-GlucoStabilizer

3. What is the name of the approved drug, device or biologic?
GlucoStabilizer

4. What document have you provided to confirm FDA approval?
510k

3. Is the study required by the FDA?
NO

4. Is the study initiated by an investigator and not a commercial company?
YES

5. Is the study retrospective?
NO

6. Does the study involve research on a drug/ device in an already approved population/ condition?
YES

7. Does the study involve research only on a drug and NOT on a device?
YES

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

1. **How do you plan to <u>identify</u> potential subjects?**
   Chart Review/Database Review from a database established for health care operations (departmental clinical database) or quality improvement.
   DHHS: Study team requests Waiver of Consent to identify potential subjects.
   HIPAA- *Allowed under Preparatory to Research*

   Patients health care provider supplies the study team with the patients contact information without patients knowledge.
   DHHS: Study team requests Waiver of Consent to identify potential subjects.
   HIPAA- *Allowed under Preparatory to Research*

   The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes. No PHI will be removed from the site

covered entity during the review. The PHI that the researcher seeks to use or access is necessary for the research purposes.

2. **How will potential subjects be <u>contacted?</u>**
   Direct contact of potential subjects by the study team by approaching in person. Members of study team ARE health care providers of patients.
   DHHS: Study team requests a Waiver of Consent to contact potential subjects
   HIPAA: *Allowed under Health Care Operations.*

   Potential subjects will be approached while at by a person who is NOT a member of their health care team.
   DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

3. **Will any additional information be obtained from a potential subject during "prescreening"?**
   NO

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?**
   NO

5. **How will the consenting process take place?**
   The study investigators will meet with the potential subject and/or, if applicable, his or her legally authorized representative to discuss the study and obtain voluntary, informed consent prior to performing any study procedures. A comprehensive discussion of the study will include information regarding the scientific basis for the study, risks and benefits, as well as overall responsibilities of study participants. Once the potential subject, or if applicable, his or her legally authorized representative, has been given sufficient time to have all of his/her questions answered, he/she will then be asked to sign the informed consent document if he/she is willing to participate in the research.

   Subjects will be given a copy of the signed informed consent form and one copy will be sent to medical records.

   The original consent form will be kept in a secured, locked office.

6. **Will subjects sign a consent form for any part of the study?**
   YES

7. **Will the study procedures be started the same day the subject is recruited for the study?**
   YES

   ►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.
   Per the study protocol, in order to be eligible to participate, subjects must be enrolled within 3 hours of hospital arrival. Given the nature of acute stroke and the time constraints in the eligibility criteria, it is likely that study procedures will be initiated on the same day that the subject gives informed consent.

   ►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.
   In order to ensure that the potential subject, and if applicable, his or her legally authorized representative, have been given enough time to make an informed decision, the investigator or study coordinator will provide a detailed explanation of study rationale, study required procedures, and the risks of participating in this study. The investigator or study coordinator will also reiterate that the patient is not required to participate in research and that the patient's quality of care will not change if

the patient decides not to participate. If time allows, the investigator or study coordinator will allow the patient to spend time reviewing a copy of the informed consent privately.

8. Do you need to perform a "dry run" of any procedure outlined in this protocol?
NO

APPENDIX: Safeguards for Cognitively Impaired

1. What additional safeguards that will be employed to protect the cognitively impaired subjects?
In this study, the following safeguards will be in place to protect cognitively impaired subjects:

- Use of a surrogate decision maker when permitted by law (i.e. a legally authorized representative)
- To the extent possible within the constraints of the enrollment window from the time of symptom onset and hospital arrival, allow for the use of waiting periods. While this will not be systematically built in, we will encourage study investigators to allow more time to consider the information given. This may also make it possible for potential participants to have time to consult with family members or friends about whether or not to participate.

2. The following steps will be taken to determine the capacity of a potential subject to give consent for themselves.

If there is concern that a potential subject/ subject may be cognitively impaired a determination of incompetence will be made after an evaluation by a person with the appropriate expertise to make such a determination as delegated by the PI. The determination of competency must be documented per site procedures.

The following methods below will be used to determine capacity for consent:

- Will rely on individual observation of and interaction with the potential subject as well as the opinion of the medical provider or caregiver, when available. The prospective subject should demonstrate competence in relation to the proposed study in order to be judged capable of providing informed consent for that study. In general, an assessment an individual's capacity to consent will be based on her/his:
  - Ability to communicate a choice;
  - Ability to understand relevant information;
  - Ability to appreciate the nature of the situation and its likely consequences; and,
  - Ability to manipulate information rationally

- The individual's abilities will be assessed by discussing the proposed study with her/him and then asking specific questions. Such questions may include:
  - Can you tell me what will happen if you agree to take part in this study?
  - How might this study help you?
  - How might this study not help you, or even hurt you?
  - Do you have to be in this study?
  - What would you do if you wanted to leave the study?
  - What will happen if you decide not to be in the study?

- An individual will be considered unable to provide consent if he or she has:
  - An inability to express or communicate a preference or choice (cannot make up his/her mind, is comatose, or has severe psychotic thought disorders, etc.);
  - An inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (does not understand that he/she may be hurt or may not be helped or cannot distinguish research from treatment); and/or,
  - An inability to provide a logical rationale for participation/no participation in a study (cannot address risk/benefit-related reasons for or against participation in a study.

3. The following steps will be taken to document the determination of competency to consent.
A note to file will be written and filed in the study files and/or medical records to describe the consenting process. The note will include a description of methods used to determine capacity of the subject to consent. The note should also include the name of the person determining competency of the subject.

4. When will subjects capacity to consent be assessed?
Prior to initial consenting process if there is a concern that the potential subject has a cognitive impairment.

APPENDIX: Privacy Plan for Studies with Consent

1. Answer the questions below to describe your/central registry's plan to protect the identifiable data from improper use and disclosure.

How will data be stored?
Data, which may include health information, will be stored with HIPAA identifiers.

Will specimens be stored at site?
NO

Will any of the data be stored electronically at site?
Yes, data will be stored electronically at a site managed server that is configured to store data regulated by HIPAA.

Will any of the data be stored in hard copy format at site?
Yes, case report forms will be stored in a secure area with limited access and questionnaires/ surveys will be stored in a secure area with limited access.

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and records management guidelines.
The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as approval is received from the sponsor to delete them.

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB?**
YES

APPENDIX: Sponsor

Sponsor Information
NIH-NINDS