

IHAST2 Update

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IHAST2

INTRAOPERATIVE HYPOTHERMIA
for
ANEURYSM SURGERY TRIAL

Inside

	page
1. Early Postoperative NIHSS	2
2. "Practice" Patients/Screening	3
3. Center Activation	4
4. Intercurrent Events	6
5. Physician Investigator On-Call	7
6. Temperature, Forms and Blinding	8
7. IHAST2 Web Site	8
8. New Center in IHAST2	8

We're "back in business"

Following the delay introduced by the OPRR-consent issues, we are clearly "back in business". As of March 15, 2000, eleven centers have completed at least one "practice" patient. Of these centers, St. Vincent's Hospital (Australia), University of Western Ontario (Canada), and The Alfred (Australia) have enrolled "real" patients. Given the unavoidable delays, this is pretty good. We would like to congratulate all of these centers! Congratulations also to St. Vincent's Hospital for entering the first "real" patient in IHAST2!

Hopefully, everyone else will complete all criteria needed to start enrollment. We sincerely hope to have all centers ready and operating before June.

We would like to thank all of you for the extra work that you have done to comply with the changes that OPRR requested in our Consent Document. At this time, 30 of the 31 centers have submitted revised Consent Documents to their local IRBs. Two thirds of these have been reviewed and approved. Thanks again for your patience and understanding!

Please File Your IHAST2 Updates

Just a reminder. Please file one copy of each edition of the *IHAST2 Update* in your Site Regulatory Binder (See Chapter VII.A.5 of the Operations Manual).

1. Early Postoperative NIHSS

PROTOCOL CHANGES!

Delay in Initial Postoperative NIHSS Exam Until 3 to 6 Hours Following Surgery

Change in Handling NIHSS Exams in Anesthetized and/or Paralyzed Postoperative Patients

We have encountered some unforeseen problems with respect to the immediate postoperative 2-hour NIHSS. It is clear from "practice" patient data that the use of the PolarAir unit is resulting in more rapid (and hence longer lasting) cooling than we saw in the pilot trial. While we selected the PolarAir unit for just this purpose, it is also making it more difficult to rewarm patients.

The original protocol required that the NIHSS exam be performed \approx 2 hours after surgery. This was based on pilot trial data indicating that hypothermic patients would warm by this point in time. However, this is not proving to be true, as several "practice" patients were still cold at the time of the 2-hour exam. The exam MUST NOT be performed on a patient who is still cold because this would result in the coordinator or neurologic examiner becoming unblinded as to group assignment. Also, to prevent shivering it has been necessary to maintain deep sedation (e.g. with propofol) in some patients for longer than was originally anticipated. Unfortunately, the NIHSS exam cannot be reasonably performed on a deeply anesthetized or pharmacologically paralyzed patient. Needless to say, this has resulted in conflict – a mandated examination that cannot be performed.

To resolve this dilemma, we are making two protocol changes:

- 1) The initial postoperative examination is to be performed between 3 and 6 hours after the completion of surgery.
- 2) The NIHSS exam should not be performed in patients who are anesthetized and/or paralyzed

These have some obvious implications.

We are now delaying the "earliest" point at which the NIHSS exam can be done - moving it back from 2 hours to 3 hours. Again, this is being done to maintain blinding; if everyone knows that patients can't be rewarmed by 2 hours, anyone asked to do an NIHSS exam at 2 hours will immediately know that this was a normothermic patient. If the exam is delayed to 3 hours for all patients, when everyone should be warm, this problem disappears.

This delay also makes it less likely that the first postoperative NIHSS exam will be contaminated by "residual anesthesia".

The three-hour window provides some flexibility. A patient who is undergoing a procedure (e.g. CT scan or angiography) at 3 hours need not be tested during that procedure (which is often impossible) - just wait until the procedure is completed before doing the NIHSS.

The "can't perform" issue not only applies to patients in the early post-operative period, but also later in their hospital course. If a patient, 3 days after surgery, is receiving pentobarbital, morphine, pancuronium and controlled ventilation to treat severe intracranial hypertension, the NIHSS exam can be "waived".

There are two caveats:

First, the new 3-6 hour window needs to be firm, and the exam needs to be done in this window. If it is not possible to perform the NIHSS during this period, a comment must be written indicating why it was impossible to perform. Delayed exams beyond this time will simply confuse things and blur the distinction between the postoperative exam and the 24hr exam.

Second, with respect to waiving the NIHSS, you need to distinguish between “residual sedation” and “active anesthesia”. A reduced level of consciousness in a post-operative patient is often attributed to “residual drug effects”. However, it is often impossible to distinguish between residual sedation and real neurologic dysfunction. The NIHSS exam should **NEVER** be waived simply because a patient **MIGHT** be comatose because of residual sedation – although you can now wait a while in the case of uncertainty. **Unless the patient is actively receiving anesthetic doses of drugs such as propofol, pentobarbital, etc. with the intent of rendering them unconscious, or is receiving neuromuscular blockers, the NIHSS must be performed.**

In the situation where the NIHSS cannot be performed, please NOTE ON THE CORRESPONDING NIHSS FORM that the scheduled examination cannot be performed. Second, a brief explanation of why the examination could not be performed must be entered on the COMMENTS screen located on the IHAST2 web site.

2. "Practice" Patients/Screening

Many centers are now approved to start "practice" patient enrollment. Following are brief instructions on getting started:

- 1. Screening:** Once your center is approved to begin "practice" patients, you need to begin screening patients for eligibility to participate. Screening should start as soon as you are approved to enroll "practice" patients. Please complete a SCREENING form on all patients scheduled to undergo an open craniotomy for the clipping of an intracranial aneurysm, regardless of whether or not they are eligible. In addition, please complete an ELIGIBILITY form if the patient has experienced a SAH, again regardless of whether or not they are eligible.

We have provided you with a limited number of SCREENING and ELIGIBILITY forms (50 of each) for use on patients that are not enrolled. You can save us a fair amount of money if you would photocopy the SCREENING and ELIGIBILITY forms for use during the “practice” patient phase only, rather than using the carbonless NCR (white with canary-colored copy behind it) CRF forms. However, once you are approved to start "real" patients, please begin using the carbonless NCR CRF forms.

- 2. Forms:** For enrolled "practice" patients make sure that the following "form completion" steps have been performed (this will make it much easier for us to get people approved to do "real" patients):

- a) Complete all forms in the "Practice" Patient Notebook.
- b) Fax Page 6 of the ANESTHESIOLOGIST form to the CCC, along with any required IE forms (any Severe or Indicator event, items 1-10 on page 6 of the ANESTHESIOLOGIST form). The FAX number is 319-384-8072.
- c) Make photocopies of all of the completed forms from the "Practice" Patient Notebook.
- d) **Federal Express** the following materials to the DMC:

Copies of all the completed forms

The sealed envelope containing the TEMPERATURE Form from the **opened** RANDOMIZATION ENVELOPE

The **unopened** RANDOMIZATION ENVELOPE

The sealed Study Packet containing the anesthesia record and the postoperative recovery or critical care records

Copies of all IE forms, even if they have already been FAX'd.

We are asking that the material be sent Federal Express to expedite the process of reviewing "practice" patients.

We will contact you as soon as possible concerning data correction issues, errors, etc.

Also, please don't forget that you need to make a confirmation call to the DMC no more than 24hrs after making the initial enrollment call.

3. Discharge Summary for "Practice" Patients: While the "practice" patients are being done, largely for procedural

reasons (to help centers "get ready"), we need to pay close attention to various safety issues in these patients. We do not want to create a data collection nightmare, however do feel that we need some additional follow-up information.

For this reason, we request that you please mail or FAX a copy of each "practice" patient's discharge summary to the DMC as soon as it becomes available.

Make sure you remove the patient's name, and that you clearly write the patient's ID Number on each page of the discharge summary.

3. Center Activation

"Practice" vs. "Real" Patients

A number of centers have called the CCC/DMC on an emergent basis, telling us that they were ready to enroll either their first "practice" patient or their first "real" patient, but were not able to access the telephone randomization system. The reason that they were not able to obtain a response from the automated telephone system is because their center had not yet been "activated" in the computer that manages the system. We would like to clarify a few issues about what is required for a center to be activated (i.e. before you can enroll patients).

"Practice" Patients: "Practice" patients can be enrolled after a center has a certified anesthesiologist, a certified neurosurgeon and a certified study coordinator and all are available for the case. In addition, all required Human Studies Approval materials must be completed and copies received by the CCC. Also, we would prefer if you have a neurologic examiner appointed at this time but one is not required for the "practice" patients.

A certified neuropsychology examiner is not needed to enroll "practice" patients.

Comment: Because of the recent discussions with OPRR, the requirement regarding Human Studies approval is critical. We **MUST** have a copy of the official approved consent documents **IN OUR FILES** before you can start. The entire trial would be in jeopardy of being terminated, if OPRR discovered that patients were being enrolled without these documents on file.

"Real" Patients: "Real" (i.e. randomized) patients can be enrolled only after the following requirements have been met:

1. A neuropsychology examiner has been identified and approved by the UI neuropsychologist.
2. A neurologic examiner has been certified.
3. Two "practice" patients must have been enrolled and studied. Data on these "practice" patients must be complete through the end of the post-operative evaluation. Page 6 of the ANESTHESIOLOGIST Form must have been faxed to the CCC, and all completed CRFs, the two randomization envelopes, and the anesthesia records must have been received by the DMC. **Please Federal Express these records.**
4. The records for the "practice" patients must have been reviewed by the DMC and CCC, and the DMC must have communicated with the center regarding any problems with CRF completion.

Note: With rare exceptions, the DMC will contact you within 24hrs after receiving the "practice" patient CRFs. In general this means that you should be able to start enrollment of

"real" patients approximately 48-72hrs after enrollment of your second "practice" patient.

Factors that could delay approval are:

1. A delay in getting the CRFs to the DMC.
2. Significant errors in the CRFs indicating that further education may be required. We do not need to wait until all Data Edit Reports have been completed.

The entire purpose of the "practice" patients is to "work out the bugs" at each center **BEFORE** "real" patients are enrolled and real data are collected. This will help insure that the data that is entered into the final database is of the highest quality. We feel that we would defeat the purpose of entering "practice" patients if centers proceed with enrollment of "real" patients **BEFORE** the DMC has had an opportunity to review the "practice" patient CRFs and to provide the centers with appropriate feedback.

We realize that centers are in a hurry, and that everyone is anxious to get moving! However, we need to ask for your patience. Do the "practice" patients and send your CRFs to us **ASAP (use Federal Express)**. We promise - to the best of our ability - to let you know whether there are problems in data collection within no more than 24hrs after we receive the forms.

4. Intercurrent Events (IEs)

In IHAST2, all Intercurrent Events (IEs) are identified by code numbers and have defined diagnostic criteria. The complete set of IE code numbers and diagnostic criteria is provided in the Operations Manual. Because of the large number of centers participating in IHAST2, it is essential (in fact, required) that each PCC consistently apply these codes and criteria when diagnosing and reporting IEs. Without consistent diagnostic and reporting criteria, variations among centers, physicians, hospitals, countries, laboratories, *etc.*, with regard to diagnosis, will render our outcome data unreliable. Consistent criteria are also essential to assure that patient safety data are reliable.

In all instances possible, IE diagnostic criteria are based on published guidelines, standards, or consensus statements. When no standards exist, IE definitions were established with the goal of maximizing specificity over sensitivity. In other words, the IE criteria were designed to make sure the patient really has the condition and the condition is likely to be clinically meaningful.

INTERCURRENT EVENT form completion: Most of the time, IE forms will be completed by the Local Study Coordinator based on preoperative (POST-ADMIT SCREEN) and postoperative (DAILY POST-OP SCREEN) evaluations of the patient's status.

Primary IEs are those which are considered to be the principal, fundamental, or underlying problem or event. Primary IEs are the key, central, or initiating event. Accordingly, most of the time, only a single IE code should be entered as a Primary IE. If necessary, two

codes may be entered as Primary IEs. However, if there are more than two primary IEs occurring simultaneously, complete additional IE forms for all other primary IEs. In most instances, Primary IEs will be a clinical condition or event, rather than a procedure. (Typically, clinical conditions or events lead to procedures).

Related/concurrent IEs are those that occurred as a result of the Primary IE, or occurred in such close association with the Primary IE that they cannot be separated from it. In most instances, procedures that occur as a result of the Primary IE will be coded as related/concurrent IEs. In all cases, please provide a written narrative in the space provided on the IE form that provides a description of events in temporal sequence. Please provide sufficient information to support all diagnoses.

Emergent Reporting: Two types of IEs must be reported "emergently" to the CCC (*i.e.*, by the next working day); these are "**Indicator IEs**" and **Severe IEs**. "**Indicator IEs**" are events that literature suggests are most likely to be affected by intraoperative temperature management (major cardiovascular complications, bleeding, infection). "Indicator IEs" are highlighted on the IE code list and in the IE definitions table. Items 1-10 on page 6 of the ANESTHESIOLOGIST form are also all "Indicator IEs," (see below). Using an INTERCURRENT EVENTS form, it is mandatory that all "Indicator IEs" be promptly reported (faxed) to the CCC, regardless of their clinical impact (mild, moderate, severe, death). "**Severe IEs**" are those where the event or procedure was either life-threatening, permanently disabling, or substantively prolonged in-patient hospitalization. Any and all IEs which are considered to be **severe** or to have resulted in **death** must be promptly reported (faxed) to the CCC, even if the IE is

not an “Indicator IE,” and even if all supporting information is not available at the time of the initial report.

Routine IEs: “Routine” IEs do not need to be faxed to the CCC. “Routine IEs” are **NON**-Indicator IEs that are judged as being either “mild” or “moderate” based upon their net clinical impact on the patient. Mild—the event or procedure was well tolerated by the patient and did not appear to substantially influence the patient's overall clinical course. Moderate--the event or procedure was sufficient to interfere with the patient's recovery. For most moderate events, some new treatment is necessary and/or the duration of hospitalization may be slightly prolonged because of the event.

IEs from the ANESTHESIOLOGIST form: Section H (page 6) of the ANESTHESIOLOGIST form is a list of perioperative IEs. To aid Anesthesiologists in completing page 6 of the ANESTHESIOLOGIST form, an abbreviated set of IE criteria will soon be provided to all centers. **Items 1-10** on this list are all “**Indicator IEs.**” If any item (1-10) is marked as occurring, an IE form must be completed and the IE must be promptly reported to the CCC as an “Indicator IE” (regardless of its severity), as described above. None of the items listed in 11-24 are Indicator IEs. When any of these items (11-24) are marked as occurring, IE forms need to be completed only if the Anesthesiologist considers the event(s) to have been clinically significant. (If not clinically significant, an IE form does not need to be completed). If the IE (11-24) is judged to be Severe, or to result in the patient's Death, then the IE is to be emergently reported to the CCC as described above. It is preferred that the Anesthesiologist who cared for the patient in the O.R. complete all IE forms triggered by responses to section H (page 6) of the

ANESTHESIOLOGIST form. However, the Local Study Coordinator may assist the Anesthesiologist in completing these forms provided the Study Coordinator remains unaware of patient group assignment and temperature data.

Please note that the telephone number for the CCC is incorrectly printed on the INTERCURRENT EVENTS form under question number 5. In the gray box the directions state that “All events in these categories must be promptly reported to the CCC at 319-356-0416”. This telephone number should be:

319-356-0461

5. Physician Investigator On-Call

The Physician Investigator on-call telephone number is **319-384-7116**.

If you have questions regarding eligibility or protocol issues during the hours of 8:00 A.M. to 5:00 P.M., Monday through Friday (U.S. Central Time), please call the Clinical Coordinating Center (CCC) at 319-356-0461.

If you need to reach the Clinical Coordinating Center outside regular office hours, you may reach the Physician Investigator On-Call at 319-384-7116. Either Dr. Todd or Dr. Hindman will be on call to answer emergent questions regarding eligibility and protocol issues, or assist you if you are unable to complete the automated randomization call. We ask that you please use this number for emergent issues only.

6. Temperature, Forms and Blinding

By now, everyone knows the efforts we're making to maintain "blinding" in the IHAST2 trial; without such an effort, the trial won't work. This blinding must not only involve local individuals, but people at the Clinical Coordinating Center (CCC) and Data Management Center (DMC).

In our experience with the "practice" patients, we've encountered a number of situations that indicate that centers and individuals don't entirely understand what needs to be done to maintain blinding. In particular, comments or remarks in comment boxes, either on the Web or on paper IE forms, that could identify a patient's group assignment. For example, something like: "While we were **rewarming** Mr. Jones, he developed a short run of V-tach".

A comment such as this unblinds anyone who reads it; the local coordinator, CCC personnel who receive it and DMC personnel who enter the data into the computer.

Please make a concerted effort to avoid such situations of "inadvertent unblinding".

7. IHAST2 Web Site

We welcome you to visit our web site, which was constructed by the IHAST2 Data Management Center. Posted on this web site you will find the Operations Manual and copies of the *UPDATE* Newsletters, in addition to other information. The address is:

<https://ctsdmc.public-health.uiowa.edu/IHAST2/>

8. New Center Joins IHAST2

Johns Hopkins Hospital has joined us in the IHAST-2 Clinical Trial as the 31st participating center. Their research team will be headed by Dr. Marek Mirski, PI, and Dr. Raphael Tamargo, Co-PI. Ms. Nichol McBee will serve as local study coordinator.