IHAST2 Update

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IHAST2
INTRAOPERATIVE HYPOTHERMIA
for
ANEURYSM SURGERY TRIAL

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$$$ GREAT NEWS $$$

I hope that everyone has received the recent email – but just in case, here it is again. In June of 2000, we submitted a supplementary funds proposal to NIH. This was a request for more money to increase per patient payments to centers. I won't go into the details about why it took so long; however, the bottom line is **WE GOT IT** (finally!).

This means two things. First, we will now pay centers **$4,500** (US) per completed patient from this point forward. Second, we will be able to pay centers an *additional* $1,500 for each patient enrolled since June 1, 2000 (yeah, *back* payments!). So, basically, just figure you have been, and will continue to be, paid $4,500 per patient since JUNE 1, 2000! For some of the high volume centers, this will add up to quite a substantial and well-deserved financial compensation.

It will take time to get these payments out. First, we are waiting for the actual award from NIH to occur. Once the award is in place, we will be able to amend the existing subcontracts between Iowa and your centers. This will require sending the amendments for signed approval from your institution and then having them returned to Iowa. We will make this happen as quickly as possible.

I will also tell you that without the work done by ***all of you***, this supplement would not have been granted. We were told, in no uncertain

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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).

terms, that money would be made available to reinforce a good project that was working well – not to prop up a bad project. The fact that we are still "on target" with our accrual rates went a long way toward convincing NIH that IHAST2 was "a good horse worth backing!"

300th Patient!

On Friday, March 16th, the group at Harborview Medical Center, in Seattle, (Dr. Art Lam, Dr. Richard Winn, and Ms. Pat Tanzi) randomized the 300th patient in IHAST2. Why is this a "big deal"? This means we've reached our first interim analysis point. If you remember, interim analyses are planned after complete data are collected for 300, and then 600, patients. Since we collect data through the 3-month follow-up, we expect to have received and completed the edit process on these 300 patients by the end of this coming summer. A report will be submitted to Dr. Bill Young and the Patient Safety Monitoring Board (PSMB) by September.

However, I don't think you need to worry too much about "stopping early". The inter-group differences or "stopping boundaries" needed to halt the trial, at this early point, are almost unreachable. A two-group p-value of 0.00052 is necessary to declare an end. Even a "no difference" is not sufficient grounds to halt. Also, we will ***not*** know the results of the interim analysis. Just like you, we are blinded as to group assignments. Unless the trial is stopped (which, as indicated, is VERY unlikely), all we will be told after the interim analysis is "carry on."

So, please don't "slow down" on enrollment now – and please don't think about waiting until we are past this interim point. KEEP UP THE GOOD WORK – and keep those patients coming in!!!

New Centers

Please extend greetings to three new centers joining IHAST2!

The University of Cincinnati has been approved to begin the "practice patient" phase of the trial. The team at Cincinnati consists of Mario Zuccarello, MD, Neurosurgery (PI); Phil Bridenbaugh, MD, Anesthesia (Co-PI); and Janice Carrozzella, RN (Coordinator).

We are just about as close with University Hospitals of Cleveland. With a little luck, they will be ready to begin "practice patients" by the time you are reading this article. Their team consists of Warren Selman, MD, Neurosurgery (PI); Barbara Dabb, MD, Anesthesia (Co-PI); and Gerri Zaleski, RN (Coordinator).

Also, very close to starting enrollment, is Auckland Hospital located in Auckland, New Zealand. The team is headed by Tim Short, MD, Anesthesia (PI); Edward Mee, MD, Neurosurgery (Co-PI), and Jayne Ayto, RN (Coordinator).

Good luck to all three and welcome!

Annual Meeting And All That Jazz!

The Annual IHAST2 Investigators' Meeting will be in New Orleans this year. It will be held in conjunction with the American Society of Anesthesiologists Annual Meeting and is scheduled for Saturday, November 13, 2001. Like last year, the Study Coordinators will meet in the morning and then everyone will get together for lunch and an afternoon session.

Monitoring Visits

To date, we have completed routine monitoring visits to 9 participating centers: 1) Harborview Medical Center, Seattle, 2) University of Michigan Medical Center, Ann Arbor, 3) University of Western Ontario, London, Ontario, 4) Toronto Western Hospital, Toronto, Ontario, 5) Wake Forest University Baptist Medical Center, Winston-Salem, 6) University of Virginia Health System, Charlottesville, 7) New York Presbyterian Hospital/Cornell University, New York 8) St. Vincent's Public Hospital, Melbourne, Australia, and 9) The Alfred, Melbourne, Australia. A very warm thank-you to all the people at these participating sites! Overall, we are very pleased with data that have been reviewed and know that this project is succeeding only because of the collective effort of all centers. We are scheduled to visit 10 more centers in the next quarter. See you soon!

February and March Payments Combined

Payments for patient data received during the month of February will be combined with the payments for March. Payments for both months will be initiated on April 3rd. We apologize for this delay.

Outcome Discrepancies

In the last several weeks we have noticed potentially serious problems with a few 3-month neurologic outcome assessments. Since this is the single most important data collected in IHAST, we need to do everything possible to eliminate this problem.

I'm speaking specifically of what appear to be inconsistencies between different neurologic outcome measures at the 3-month evaluation. For example, there are several cases in which a patient was assigned a GOS of 1 and a Rankin of 2. By definition, these scores are inconsistent: A GOS of 1 means able to resume normal activities, while a Rankin of 2 indicates that they are unable to resume normal activities. (See Attachment #1). Similarly, the reverse has been encountered, *i.e.* a GOS of 2 (moderate disability) and a Rankin of 1 (no significant disability). Again, a GOS of 2 implies that they cannot participate in a variety of activities, while a Rankin of 1 indicates an ability to participate in ALL activities. We have one case of a GOS of 3 (severe disability) and a Rankin of 2 (slight disability), and another case of a GOS of 2 (moderate disability) and a Rankin of 4 (unable to walk and unable to attend to bodily needs). Related problems have also appeared between other outcome measures (NIHSS, Barthel's). For example, it is difficult to imagine a GOS of 2 and Barthel's Index of 65.

This is a major issue since it involves the primary outcome variable (GOS). Ensuring the accuracy of our GOS assignments must be a very high priority in the trial. It is critical that the 3-month outcomes be assigned "independently" by the Neurologic Examiner. Were we to formally question a specific score in a specific individual, we might bias the score in that patient. Moreover, since no narrative description of the patient's condition is provided, we have no way of knowing whether the GOS is correct, whether the Rankin is correct, or whether this might be an unusual situation where the discrepancy is, in fact, reasonable. All we can do is track the problem. We have set up formal system by which Neurologic Examiners with two such apparent discrepancies (a computerized algorithm defines the inconsistency) will be required to repeat the GOS/Rankin certification exam. Unfortunately, that is only "after the fact" and won't catch all situations.

It appears that one part of the problem may be a misunderstanding of the scores. These

scores (in particular the GOS and Rankin) are not "continuous" but definition-driven categorical scores. In other words, they cannot be treated like "visual analogue scales" in which a patient who is "a little bit worse than the other guy" is given a higher score. Scores must be strictly assigned based on the formal definitions, even if your "qualitative" sense is that the patient is better (or worse) than the score. We entirely recognize that some inconsistencies are "real". For example, the Rankin scale is not restricted to neurologic disability (for that matter, neither is the GOS). In some cases, the Neurologic Examiner must make a judgement call because of a situation that just doesn't precisely fit the definitions. Nevertheless, the number of apparent inconsistencies being encountered seems to exceed what we would consider "reasonable".

All we can ask is that you gather your group – including your Neurologic Examiners – and review this letter, review the various neurologic outcome scales and review your scoring procedures. Almost nothing in IHAST2 is more important than ensuring that these outcome measures are correctly assigned.

See Attachment #1 for Definitions

Who May Complete the 3-month Follow-up Exam

Just a reminder that the Neurologic Examination should not be completed by a Study Coordinator, even if that Study Coordinator has not had direct contact with the particular patient.

The assessments done at the 3-month postoperative visit are really the key to this study - they represent our primary outcome variables and must be defended "at all costs." The final outcome assessments (Glasgow Outcome Scale, NIHSS, Barthel's, neuropsychology battery, *etc*.) **MUST** be made by an IHAST2-certified Neurologic Examiner who is not aware of the patient's temperature group assignment and/or any intraoperative or early (first two hours) postoperative temperature data.
PLEASE UNDERSTAND - IF THIS FINAL EXAM IS NOT "DONE RIGHT" EVERYTHING THAT HAS GONE BEFORE IS A WASTE OF TIME!!!

The Neurologic Examiner performing the final assessments cannot be the Local Study Coordinator, the Local P.I., the Local Co-P.I., or any participating Neurosurgeon or Anesthesiologist. The Neurologic Examiner performing the final assessments should not be routinely involved in the day-to-day surgical, anesthetic, or postoperative care of surgical SAH patients. In general, the Neurologic Examiner performing the final assessments should be at considerable "distance" from the care of patients enrolled in IHAST2, and have virtually no chance of accidentally discovering critical aspects of specific patient management. Examples of appropriate Neurologic Examiners for the final assessment(s) include:

a. a neurology faculty, fellow, or resident not routinely involved in the postoperative care of SAH patients;
b. an Emergency Room physician not routinely involved in the postoperative care of SAH patients;
c. a neurology nurse not routinely involved in the postoperative care of SAH patients;
d. a surgical or anesthesia faculty or fellow with no routine involvement in the care of SAH patients; or

e. a neurosurgery or neuroanesthesia fellow with no clinical commitments at the time of the final outcome assessments and no prior knowledge of specific study patients.

In addition, it would be best if the Neurologic Examiner were someone with extensive medical (and ideally) neurologic experience. Anyone can be "trained" to do these exams - but the better they understand medicine and neurology, the more reliable their scores.

Determination of Pregnancy Status is MANDATORY

Please note that a pregnancy test ***must*** be performed on all pre-menopausal women who have consented to participate in IHAST2. The only exception is if the patient reports that she has had a hysterectomy or tubal ligation. For the purposes of IHAST2, either the standard lab test for your hospital or a commercial "over the counter" urine test is fine. However if *you* perform the pregnancy test using a commercial urine test (rather than using your hospital's laboratory), please note the type of test and the result in the patient chart. Or, if applicable, a history of surgical sterilization should be noted in the patient chart.

Clarification of Fisher Scale Scoring

In February 2001, we emailed Study Coordinators and Neurosurgeons to clarify how the Fisher scale should be scored. In addition, we are currently modifying the design of the Fisher scale on the NEUROSURGEON form to reduce ambiguity.

The Fisher scale used in IHAST2 is that originally described in Fisher CM, *et al.*: Neurosurgery 1980; 6:1-9. The originally described scale is as follows:

Fisher 1: “no [subarachnoid] blood detected”
Fisher 2: “a diffuse deposition or thin layer [of subarachnoid blood] with all vertical layers of [subarachnoid] blood (interhemispheric fissure, insular cistern, ambient cistern) < 1 mm thick”
Fisher 3: “Localized [subarachnoid] clots and/or vertical layers of blood ≥1 mm in thickness.”
Fisher 4: "diffuse [thin] or no subarachnoid blood, but with intracerebral or intraventricular clots.”

Fisher and co-workers published a subsequent validation paper (Kistler JP, *et al.*: Neurology 1983; 33:424-36), using a grading scale that was "…identical to [that] in the previous … study…" although a bit more description for each score was given. In both papers, the critical prognostic factor for the development of vasospasm was the amount of blood present in the subarachnoid space. Only patients who had a large amount of subarachnoid blood and/or subarachnoid clots (*i.e.*, only Fisher 3) were at substantial risk of vasospasm.

What Fisher and co-workers did not address (in either paper) is how to score patients who have a LARGE AMOUNT OF SUBARACHNOID BLOOD AND EITHER INTRACEREBRAL OR INTRAVENTRICULAR CLOT. Should such patients be scored as 3 or 4? Because the critical prognostic factor is the amount of subarachnoid blood, WE RECOMMEND THAT SUCH PATIENTS BE SCORED AS 3.

To be frank, we now recognize that on a few occasions we gave the wrong answer to people who asked us how to score patients with a large amount of blood and intracerebral or intraventricular clot. We apologize for our confusion.

Thus, to summarize: Patients who have no or small amounts of subarachnoid blood are always scored as either Fisher 1, 2, or 4. Patients are

scored as Fisher 4 ONLY if they have no/small amount of subarachnoid blood AND either intracerebral or intraventricular clot. If a patient has a large amount of subarachnoid blood, they should be scored Fisher 3, regardless of the presence or absence of intracerebral or intraventricular blood.

Until now, the NEUROSURGEON form (page 1, item A.2) had a "skip-out" associated with the Fisher 4 box to indicate the presence of intracerebral or intraventricular blood. The "skip-out" was to be completed only if Fisher 4 was checked. However, we observed a number of forms where a Fisher score of 2 or 3 was checked AND the skip-out was completed. This made us wonder whether the Fisher score might really have been a 4 instead of the marked 2 or 3. We have followed-up on all of these forms to clarify the intended score. If you have not heard from us by know on this, you won't. To get rid of this confusion, the "skip-out" is being eliminated and a reminder of scoring procedures has been added. On the NEUROSURGEON form, the new Fisher Scale will look like this:

2. SAH blood characteristics

- ☐ 1 No subarachnoid blood (Fisher 1)
- ☐ 2 Diffuse subarachnoid blood or thin layer with all vertical layers < 1 mm thick (Fisher 2)
- ☐ 3 Localized subarachnoid clot and/or vertical layers ≥ 1 mm thick (Fisher 3)
- ☐ 4 Diffuse (thin) or no subarachnoid blood, but with intraparenchymal or intraventricular clot (Fisher 4)

Score 1 or 2 if patient has no or small amounts of subarachnoid blood.
Score 3 if patient has a large amount of subarachnoid blood, regardless of the presence or absence of intracerebral or intraventricular clots.
Score 4 ONLY if patient has no or small amounts of subarachnoid blood and either intracerebral or intraventricular clots.

When you receive the new version of this page of the NEUROSURGEON form, please remove the old page and replace it with this new page in your unused case report form books.

Revisiting SCREENING and ELIGIBILITY forms Use of "99"

Completing SCREENING and ELIGIBILITY forms on patients who are clearly not eligible for IHAST2 remains a stimulating topic. Although addressed in the July 2000 *Update* you may find the following recap helpful:

The bottom line is, *regardless of eligibility*, we want a SCREENING form completed on all patients who are having an open craniotomy. And we also want an ELIGIBILITY form completed on all patients who also have had an SAH.

If a patient (who requires screening, but is *clearly not* eligible for IHAST2) presents for surgery at a very inconvenient time (say 2:00 AM Saturday) it *is* acceptable for the Study Coordinator not to see this patient immediately preoperatively and to complete the SCREENING and ELIGILIBILITY forms later. This exception applies *only* if the patient CLEARLY is not eligible for IHAST2, at the time of surgery. Therefore, we ask that you invoke this 'exception to the rule' only for NON-eligible patients that present after regular hours. For example, if a patient is to remain intubated prior to surgery, is too obese, is pregnant, or has a pre-SAH Rankin Score of 2, 3, 4 or 5, one can be sure that these criteria will not change; and therefore, the patient will not be

eligible for IHAST within the next 24 hours.

When this situation occurs, it is acceptable to complete the SCREENING and ELIGIBILTY forms retrospectively - in other words, after the patient has had surgery. However, we respectfully ask you to be "on your honor" about this. Be sure you have confidence in the people who are giving you the information. Also, if the patient is considered ineligible on the basis of their pre-SAH Rankin score or current WFNS score, the person making those determinations needs to be Rankin- and/or WFNS-certified.

Again, as noted in the July 2000 ***Update***, when completing the SCREENING and ELIGIBILITY forms retrospectively, or after surgery, please provide *answers* that reflect the patient's status *at the time the eligibility determination was actually made* (*e.g*., 02:00 AM, whatever). In contrast, please complete the footer information of the forms [initials, certification number(s), and signature(s) of persons completing the form; and the form completion date], by providing answers that indicate when the information was *actually* recorded on the form, and who actually recorded it, even if it is hours or days after the patient had surgery.

Please continue to make extreme efforts to obtain patient data required to complete all items on the SCREENING and ELIGIBILITY forms, whether completed at the proper time or retrospectively. In the event that information is not obtained, (this should never happen), please leave the item blank. Use of "99" is reserved for a few specific items. For example, on the ELIGIBILITY form Section A, Item 7, you may use "99" for "Verbal Score" when a patient is intubated. Only if this is necessary should the "Total GCS" and "Total WFNS" also be marked "99". If, on the other hand, you do not know the GCS score, because nobody evaluated the patient preoperatively (this should never happen either), the items should be left blank. If you need to leave an item blank (never, right?) please write in the margin that the data is not available. This *may* save a DER later.

Finally, please make an attempt to reconstruct a patient's Eligibility data if you learn about one retrospectively. Talk with the physician who cared for the patient to gather enough information to obtain scores.

Reporting Patient Deaths That Occur AFTER the 3-month Follow-up

Formally, patient follow-up is complete when the 3-month evaluations are complete (3-month CONTACT FOLLOW-UP, 3-month OUTCOME FOLLOW-UP, 3-month NIH STROKE SCALE, and the Neuropsychology battery). However, it is quite possible that patients may die after the 3-month evaluation from events or complications that had their onset before the 3-month evaluation. If there is any possibility that a patient's death may be due to a trial-related intercurrent event, we need to know about it.

Therefore, we ask you to informally, but actively, "keep your eyes and ears open" with regard to the death of any randomized IHAST2 patient for at least six months after surgery. We ask that you give special attention to patients who, at the 3-month evaluation, are hospitalized or have Glasgow Outcome Scores of 3 or 4. If for any reason, you happen to learn of the death of any IHAST2 patient, please inform the CCC.

Documenting Patient Consent

A few participating centers have policies that disallow placement of Consent Documents for Research in the patient chart. If this is the case at your hospital, we ask that you write a short note in the progress notes to ensure that your colleagues are aware that your patient is participating in IHAST2. Notation of patient participation is not only important for safe patient care, but will also help ensure that the patient is not enrolled in conflicting clinical studies.

Although Consent Documents are placed in the patient charts at Wake Forest University Baptist Medical Center, Charlotte Miller, IHAST2 Study Coordinator, also writes the following documentation in her patients' charts. This is a nice example of what we are looking for. Thanks Charlotte!

> ***This patient has been enrolled in the IHAST2 study examining intraoperative hypothermia for aneurysm surgery trial. The nature of this study has been explained to the patient and/or patient's family. The risks and benefits have been explained as well as the study procedures. Informed consent has been read by patient and/or family and signed. A copy of the consent has been given to the patient's family and placed on the chart.***