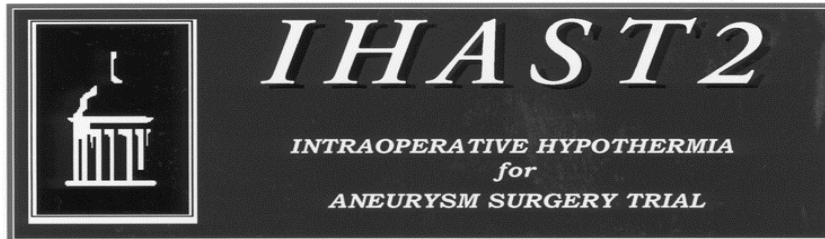
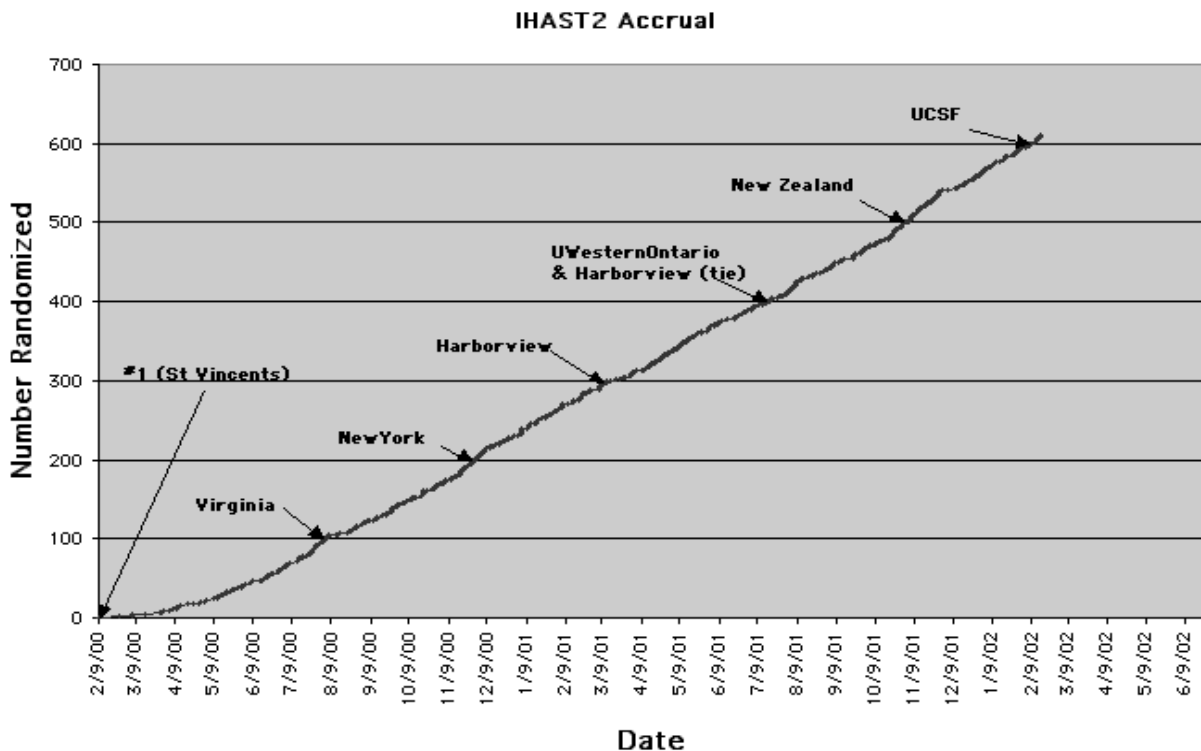


IHAST2 Update

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600th Patient Enrolled!



Congratulations to the University of California, San Francisco for enrolling the **600th** patient into IHAST2!

The 600th patient was enrolled and randomized on February 8, 2002, almost exactly two years after the first patient was randomized in IHAST2 (February 9, 2000). Our thanks to Dr. Larry Litt, Dr. Michael Lawton, Ms. Lisa Hannegan and their entire IHAST2 team!

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**Enrollment of WFNS
Grade II and III
Patients**

In New Orleans, we discussed our concern that there was a growing tendency of centers to enroll only WFNS Grade I patients. This concern remains - and is shared by the PSMB. IHAST was predicated on enrolling a mixture of WFNS Grade I, II and III patients - and our sample size calculations were based on this mixture. If we have too few Grade II and III patients, then our overall fraction of good outcomes will increase (since Grade I patients tend to do better over the long haul) - and it becomes impossible to draw meaningful and statistically valid conclusions.

We understand that enrolling WFNS II and III Grade patients is harder than enrolling Grade I patients. They are often confused and consent must be obtained from family members (who are sometimes hard to find). In addition, many centers opt for interventional radiology procedures in poorer grade patients. Nevertheless, please do your best. It REALLY is important that every effort be made to enroll as many eligible WFNS Grade II and III patients as humanly possible.

**Temperature
Management**

A major topic of conversation in October dealt with problems in temperature management. We were worried about an apparent increase in the number of hypothermic patients who were not reaching target - and normothermic patients were being allowed to drift below 36°C. This discussion, which included a lot of great suggestions for how to better reach target temperatures, was followed by a detailed letter on this issue in November.

While it is too early to have statistically meaningful data, a review of more recent cases suggests that the situation has improved. There are (and will always be) a few situations where things don't go as planned, in spite of best efforts. However, it's clear that the increased effort being made by anesthesiologists is resulting in a much greater fraction of patients reaching target. **THANK YOU AND KEEP UP THE GOOD WORK- THIS IS CRITICAL TO THE SUCCESS OF IHAST2!**

**2002 IHAST2
Annual Meeting**

The 2002 IHAST2 Annual Meeting will be held in Orlando, Florida on Saturday, October 12, 2002. Mark this date on your calendar and please plan to join us. More details to follow in the coming months.

Please File Your IHAST2 Updates

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)

Finances and Follow-up

I goofed. In the first year of enrollment, we quickly recognized that expenses being incurred to screen patients who were not subsequently enrolled were mounting up at some centers. At that time, we decided to begin paying centers \$50 for each screened patient - and told everyone that this was the case at the October 2000 Annual Meeting. However, after a great deal of trial and turmoil, we finally convinced NIH to increase the per-patient reimbursement rate from \$3000 to \$4500 (never again!!). In addition, they agreed to make this retroactive to June of 2000. Part of the justification we used to gain this increase was to cover the costs of screening, and once this supplement was received, we dropped the \$50/patient fee. Unfortunately, I never communicated this to the centers - and not unexpectedly, some of you have asked "what about the \$50". I like to think that you are now actually getting these funds - they are just 'hidden' in the increased per patient reimbursement. I'm sorry for the confusion.

By the way, there were delays in getting some centers paid. No excuses - we just ended up with too much work and not enough hours. Julie Weeks, working with our new accountant, John Stark, with the DMC and with the UI Grants Management office, has done a great job of improving this payment process. All supplementary payments back to June 2000 have gone out and the delay between receipt of the needed case report forms and the transfer of funds has been substantially reduced.

Another unexpected expense that some of you have encountered is related to either getting patients to return for 3-month follow-up visits, or in getting examiners to patients who can't/won't travel. A number of you have paid for airfares, hotels, meals, etc. for patients or examiners (depending on the direction of travel!). Like the \$50 screening fee, part of the justification for the

increased per patient reimbursement was to help you cover these expenses. In fact, we budgeted \$100 of each \$4500 patient fee for this purpose (assuming that you would need funds once in every 10 patients, giving you \$1000 to work with). However, we also realize that sometimes the costs of such "retrieval efforts" are more than expected. Therefore, we are willing to help. Just contact the office and we'll work things out (no trips to Bermuda in February!!!!)

Michael M. Todd, MD

Signatures and Certification Numbers

The signature and certification number located in the footer of a case report form indicates who completed the portion of the IHAST2 protocol needed to provide the data recorded on the form. If a Study Coordinator's signature appears on the bottom of an ANESTHESIOLOGIST or NEUROSURGEON form, we assume that the Coordinator completed those forms and has assumed responsibility for the case and the data. However, since the Coordinator is not supposed to be in the OR, this should not happen.

This means that the Anesthesiologist and the Neurosurgeon who complete a case, must sign their corresponding forms and take responsibility for the accuracy of the data on those forms. Their certification numbers - not the coordinator's - should be included. The Study Coordinator, or other certified IHAST2 personnel, may assist in completing these forms after completion of the case and may also initialize corrections but must not sign these forms.

In a similar vein, the Neurological Examiner who completes the 3-month exams must sign the 3-month OUTCOME FOLLOW-UP form and 3-month NIHSS form to indicate that they administered the exams. The Study Coordinator should never sign these case report forms

because they should not complete the 3-month neurological exams (except under very unusual circumstances). The Study Coordinator may complete the 3-month **CONTACT FOLLOW-UP** form and therefore sign this form.

NOTE: We are still seeing too many 3-month outcome exams being performed by Study Coordinators, rather than Neurologic Examiners. GOS is our primary outcome and Study Coordinators are often not strictly blinded or unbiased. There are unusual circumstances where this is unavoidable – but please contact the CCC before contemplating such an exam.

Coordinators: Speak with the attending neurosurgeons. One reason for coordinators doing 3-month exams is related to poor scheduling. The surgeon schedules a patient to return at 6-8 weeks after surgery – but no effort is made to reschedule for a later visit. Alternatively, a patient is scheduled to return when the Neurologic Examiner is not available. Some careful advanced planning – which most of you have already done – can eliminate a LOT of problems

You Too Can Help Prevent Misrandomizations

Yes, we have had several cases where the wrong envelope was opened! You can help prevent the wrong Randomization Envelope from being opened by giving only the **assigned** Randomization Envelope to the Anesthesiologist. After making the enrollment call, we recommend that the **UNASSIGNED** Randomization Envelope be pulled from the study packet before sending it into the operating room.

IHAST2 Comment Entry System

Additional comments relating to IHAST2 patients can be submitted via the IHAST2 Web site. The purpose of the IHAST2 Comment Entry System is to provide a method for submitting patient data that you feel is important but that is not requested on the Case Report Forms. Please note that the Comment Entry System is only for data submission and does not replace the email system. Communications that require timely notification and responses are best handled by email, fax, or telephone calls.

Auditing Changes

Most of the study centers have experienced an IHAST2 audit. However, we found that the process was quite cumbersome and laborious for both the study coordinator and the auditor. This experience demanded a more efficient auditing process (for both you and us). So we revamped the system making it more streamlined and therefore more user-friendly. The most noticeable change is that the process should minimize follow-up queries. Our goal is to complete the audit while at the study center. We have utilized this new process several times and found that it works very well with more useful information for the study. We think you will find future audits a lot less tedious!

When to Complete a Pre-op IE

The reason why we ask you to report Intercurrent Events (IEs) that have their onset before aneurysm surgery is so the patient's preoperative condition is adequately characterized. For example, if a patient has a

myocardial infarction or delayed ischemic neurologic deficit (DIND) before surgery, then any subsequent complications and/or adverse outcomes will be better interpreted by knowing that such events occurred.

Probably the best way to decide if a preoperative event needs to have an IE report completed is by use of the POST-ADMIT SCREEN. Item A.7 and items B.1-8 ask a series of questions regarding events and procedures that, when checked "Yes" will mean an IE form should probably be completed. If all of these items are "No" then, probably, no preoperative IE report is needed.

A common question has to do with preoperative hydrocephalus and/or brain swelling noted before aneurysm surgery. Does this warrant a preoperative IE report? Answer--it depends. (Sorry.) If the hydrocephalus or brain swelling does not appear to have any major clinical impact prior to surgery, then an IE report is not needed. In other words, if some mild hydrocephalus and/or brain swelling is noted, but the patient's level of consciousness is okay and/or they do not need a ventriculostomy prior to aneurysm surgery, then you do not need to file a separate IE report. The fact that there was some hydrocephalus and/or swelling will be captured on the NEUROSURGEON form (items A.3, and B.3). However, if the hydrocephalus (or brain swelling or intracranial pressure) is severe enough to warrant a ventriculostomy prior to aneurysm surgery, or to have resulted in a major impairment of consciousness, then a preoperative IE report should be completed.

Sometimes patients have some hydrocephalus (or brain swelling or high intracranial pressure) before aneurysm surgery AND they have it (usually more severe) afterwards. Should the IE onset be noted as preoperative or postoperative? Answer--it depends. If the severity of the preoperative hydrocephalus (or swelling or ICP) was not sufficient to warrant an IE report by itself, then we would generally recommend that the onset date/time for the IE report would correspond to when, postoperatively, the event did become

clinically meaningful. For example, the patient had mild asymptomatic hydrocephalus before aneurysm surgery, but on postoperative day ten (10) became drowsy, had marked hydrocephalus on the CT scan, and needed CSF drainage. In this case, we would recommend the date of onset for hydrocephalus to be postoperative day 10. On the other hand, if hydrocephalus (or swelling, ICP, or cerebral infarct, *etc.*) is clinically meaningful preoperatively (*i. e.*, requires a procedure or impairs neurologic status) and appears to be a continuing problem postoperatively, then we would recommend that the date of onset for the IE be preoperative. These situations are sometimes difficult so, when in doubt, please just give us a call--we'll work it out with you.

IE Reports for Transfusion

Please remember that transfusion of any blood product (red cells, fresh frozen plasma, cryoprecipitate, or platelets) requires completion of an IE form. There is ONE EXCEPTION. It is not necessary to complete an IE form for blood administered by the Anesthesiologist during the aneurysm surgery so long as there are NO other associated severe or indicator IEs. However, if a severe or indicator event occurs intraoperatively that results in blood product administration, then please add the appropriate transfusion code(s) (890, 891, 892) to the IE report.

Example#1: Surgery and anesthesia are totally normal and uncomplicated but the anesthesiologist gives some red blood cells in order to keep a high hemoglobin concentration. Does a separate IE form need to be completed to report the transfusion?--No.

Example#2: Surgery complicated by blood loss of more than 1000 ml (item 6 on ANESTHESIOLOGIST page 6) and red cells are given. Does an IE form need to be completed to report transfusion?--Yes. The primary IE code

would be 800 (Severe Hemorrhage, which is an INDICATOR event) and the related code would be 890 (red blood cell administration).

Example#3: Surgery complicated by significant hypotension (item 12 on ANESTHESIOLOGIST page 6, rated as severe) and anemia (item 23). Because of these problems, red blood cells are given. Does an IE form need to be completed to report transfusion?--Yes. The primary IE code would be 233 (HYPOtension-NOT intended, rated severe) and the related codes would be 820 (anemia) and 890 (red blood cell administration). Because the intraoperative hypotension was rated as severe, the associated transfusion needs to be reported.

Example#4: During surgery the patient receives vasopressor infusion to support the cerebral circulation (item 15 of ANESTHESIOLOGIST form page 6) but there is not excessive bleeding or meaningful hypotension, *etc.* During the case, the patient meets criteria for anemia (hematocrit $\leq 24\%$ or hemoglobin < 8 mg/dL) and receives red blood cells. The patient does well. Does a separate IE form need to be completed to report transfusion?--No. If none of these intraoperative events are considered to be severe or to have adversely affected the patient, then no IE report for the intraoperative transfusion is required.

Bair Hugger Blankets

For those centers that rely on Augustine Medical to provide Bair Hugger Blankets, there has been a small change in procedure for ordering. Please send your requests to the IHAST2 CCC rather than directly to Augustine. To request blankets please email us at: ihast2@uiowa.edu. Provide us with the following information: 1) Name to whom they should be shipped; 2) Mailing address and; 3) Number of blankets needed (10 or 20). Please allow at least two weeks to receive the blankets.

Technology Reaches *IHAST2!*

January 18th, 2002 we had our first-ever videoconference training session. We connected with 3 remote sites (UVA, Pittsburgh, & Johns Hopkins) and had people from two Centers (Alabama, Derriford) "in the studio" here at Iowa. Those attending by remote link included: Tracey Blount and Angel Morris from UVA, Lori Kirby from Pittsburgh, Susan Rice, Karen Lane, Melanie Prasad-Dehaney and Nital Subhas from Johns Hopkins. Study coordinators that came to Iowa were: Sue Salsbury from Derriford, Diana Wilhite and Cheryl Hall from Alabama.

We did experience a couple of glitches but forged ahead. This was a great opportunity to explore a new avenue for disseminating the IHAST2 protocol. Thanks to all the pioneering spirits that shared this experience with us!

IHAST3

On the afternoon of the investigators' meeting, we had a superb meeting to talk about future projects that the IHAST group should consider, whether funded or not - and not necessarily involving SAH. A lot great ideas were advanced. These included (but are not limited to):

- 1) a study of anesthetic protection
- 2) a study of long-term maintenance of normothermia in SAH patients
- 3) an assessment of laryngeal injury/dysfunction after anterior c-spine surgery
- 4) an assessment of the relative roles of hypocarbia vs. head-up posture for controlling brain bulk
- 5) the impact of N₂O on brain bulk (and maybe ICP)

- 6) an epidemiologic study of the utility of intraoperative EEG or EP monitoring during surgery (impact on outcome)
- 7) an evaluation of the utility of jugular venous catheters
- 8) an examination of the ability of mannitol with and without furosemide to reduce brain swelling
- 9) studies on fluid management, etc.

Some projects are moving forward. Brad Hindman already has a cardiovascular supplement to IHAST in place, and Satwant Samra and Greg Thompson at Michigan have submitted a supplementary grant to NIH to study long-term neuropsychologic outcome in SAH patients. At Iowa, we are currently in the earliest phases of evaluating the feasibility of a temperature maintenance trial (but have a long way to go). All of these ideas have promise - and I'd urge all of you to give serious thoughts to some or all of these. However, don't assume that "the guys at Iowa will take care of things".

PLEASE - we have something wonderful in the IHAST "consortium". Let's not let it simply go away at the end of IHAST2. This means, however, that others will need to take on some of the developmental responsibilities. We can provide an enormous amount of help - but we can't do it all. If anyone has any ideas related either to neuroanesthesia, neurosurgical issues related to intraoperative care, or anything else, please let us know. Valuable studies do not necessarily require millions in NIH funding, thousands of patients or complex measurements. Some great studies can be designed using the cooperative efforts of only 3-4 centers.