

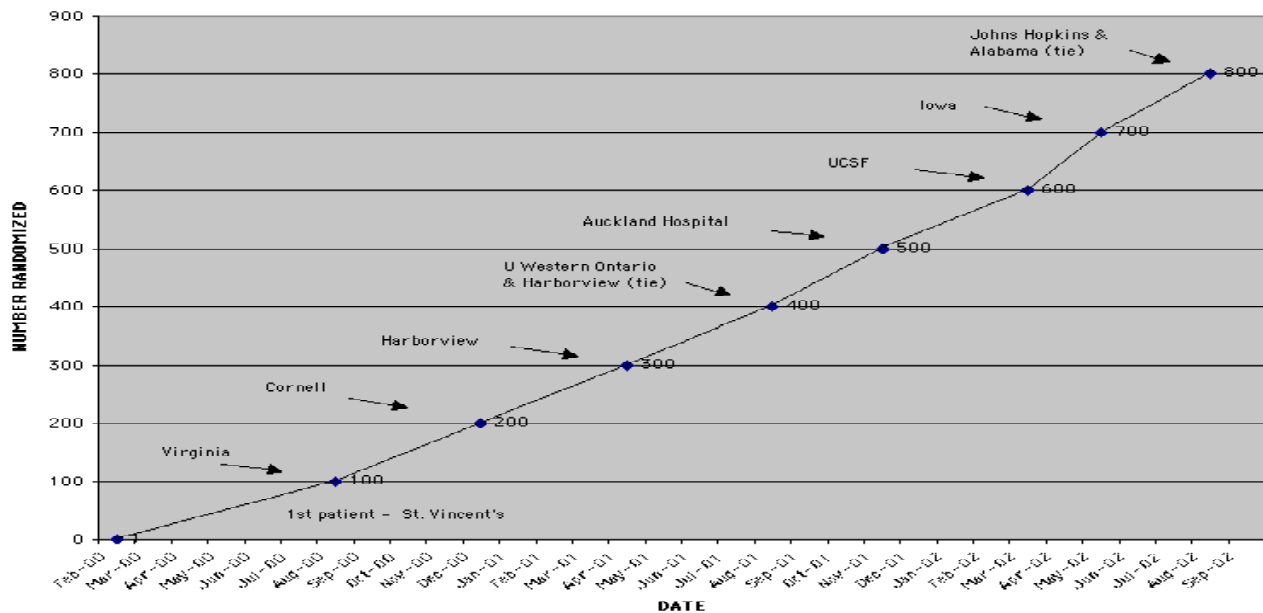
IHAST2 Update

September 2002, Volume 3, No. 2



800th Patient Enrolled!

IHAST2 ACCRUAL



Congratulations to the IHAST2 teams at Johns Hopkins and the University of Alabama! On August 26th they enrolled patients nearly simultaneously and thus enrolled the 800th patient into IHAST2!

Our thanks to Dr. Marek Mirski, Dr. Rafael Tamargo, Ms. Susan Rice and Ms. Karen Lane and their IHAST2 team at Johns Hopkins! Also our thanks to Dr. Susan Black, Dr. Winfield Fisher, Ms. Diana Wilhite and Ms. Cheryl Hall and their IHAST2 team at the University of Alabama!

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)

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New Centers

IHAST2 welcomes **five** new centers to our ranks!

Austin & Repatriation Medical Centre in Australia completed their “practice” patients and began patient enrollment in March, 2002. Dean Cowie MD, (Anaesthesia PI); Gavin Fabinyi MB, BS, FRACS, (Neurosurgery Co-PI); and Stephanie Poustie BN (Coordinator) put their team together and completed all paperwork, certification, and all the other tasks in record time (five months!). They have enrolled three “real” patients to date.

Methodist Hospital, University of Tennessee, Memphis began patient enrollment in June, 2002. Their team consists of Allen Sills, Jr. MD, (Neurosurgery PI); Fred Steinman MD, (Anesthesia Co-PI); and Pam Sutton RN and Allen Redmond BSN (Coordinators). They have enrolled two “real” patients thus far.

The University of Alabama at Birmingham also began patient enrollment in June, 2002 and have enrolled three “real” patients. The team is headed by Susan Black MD, (Anesthesia PI); Winfield Fisher III, MD, (Neurosurgery Co-PI); and Diana Wilhite RN and Cheryl Hall LPN (Coordinators).

After interminable delays regarding their Polar Air unit (through which they worked diligently), Derriford Hospital in the United Kingdom began patient enrollment in July, 2002. J. Robert Sneyd MD, (Anaesthesia PI); Louis Pobereskin BS, MD, (Neurosurgery Co-PI); and Susan Salsbury BSc, MSc (Coordinator) have led their team in enrolling three “real” patients.

Our final center to come on board is the Royal Adelaide Hospital in Australia. Guy Ludbrook MBBS, PhD, (Anaesthesia PI); Peter Reilly MD, (Neurosurgery Co-PI); and Ian Banks MD and Jo-anne Petito (Coordinators) completed the **LAST** “practice” patient for IHAST2 and were authorized to begin randomization on August 21, 2002.

Good luck and thanks to all the new centers!

Interim Analysis

On August 19th, we met in San Francisco with the DSMB for our biannual meeting - and to perform the second (and last) of our preplanned interim analyses. This analysis was based on complete follow-up data from approximately 655 randomized patients.

As noted in our recent email to everyone, the DSMB concluded that we should continue until we complete the enrollment and follow-up of the originally planned total of 1000 patients.

What does this mean? I think it is important that people don't over interpret this action or try to “guess” about the actual trial results. Ethical considerations require that a trial be halted when a) the primary hypothesis has already been proven (i.e. efficacy is proven), b) it is clear that enrolling more patients will not result in a significant difference (i.e. it is futile to continue) or c) there is evidence that one treatment is resulting in an excess number of serious adverse events.

Specific statistical criteria for each of these were established before the trial was started (stopping rules). The recommendation to continue means simply that none of these three criteria have been met.

It is also important to remember that no one at the CCC (Mike Todd, Brad Hindman, Julie Weeks, Linda Moss, Alice McAllister or Janan Winn) knows anything about the data presented to the DSMB. Dr. Todd and Dr. Hindman were asked to leave the room when discussion of outcome results began. Only a limited number of people in the Data Management Center know anything about A vs B differences (Bill Clarke, Jim Torner and Michelle Wichman) - and even they don't all know which group is normothermic and which is hypothermic. Dr. Hal Adams (Patient Safety Monitor) is aware of the rates of adverse events in Groups A and B - but does not have any outcome information. Results were also presented to the DSMB as "A vs B", not as hypothermia vs normothermia.

Keep up the great work! As of today (September 4th), over 800 patients have been randomized. We are still on track to enroll our final patient sometime in April or May 2002, with follow-up completed in late summer.

Notice of Grant Award = Money

Dr. Todd expects to receive this year's official "Notice of Grant Award" from NINDS on or about September 4, 2002. This award extends from June 1, 2002 through May 31, 2003. Because IHAST2 has been waiting for the notice of award since June 1st (and therefore could not pay you), many of you (your centers) will receive a very large payment in the near future. As soon as we receive the Award Notice, a subcontract amendment with a retroactive start date of June 1, 2002 (to cover payments for patient data received since June 1st) will be sent to your center. In addition, the PI and Study Coordinator can expect a communication from the CCC indicating when, and to whom, the subcontract amendment has been sent. We strongly urge you to contact this person to confirm that your subcontract will be processed

in a timely manner. This subcontract amendment will need to be 1) signed by your institution and 2) received back at the University of Iowa before we can send you your long awaited (and very much overdue!) payment. We will do everything within our power to get money sent to you as fast as possible!

Study Completion

Enrollment of the 1000th patient does not mean that IHAST2 is done. A great deal of work will remain. First, outcome data on the last patients will need to be collected, and all of the inevitable DERs completed. Second, final audits will need to be completed. The DMC will then finalize the contents of the database - and only then will we be able to start our analysis. If we are lucky, we may be able to start our analysis sometime in the Fall of 2003.

Many of you have done a great deal of work on this project - and we believe that it is only fair to provide all IHAST2 investigators with access to the database and to permit those investigators to write and publish papers based on the analyses. The key is to insure that this process doesn't become chaotic; it isn't hard to imagine a flood of trivial or poorly considered questions, or important questions arriving simultaneously from 3 or 4 separate people/groups, or data being provided to someone who fails to ever actually write a promised manuscript (even when others have expressed interest in the same subject).

To avoid this, a formal set of procedures will be established. We will discuss these in greater detail at the October investigators' meeting. In brief:

- a) Two or three "primary outcome" manuscripts will be written by members of the CCC and DMC (although all IHAST2 investigators will be credited). These will be announced as soon as possible.
- b) A Web site will be established where participating investigators will be able to formally submit requests for data analysis.

This will involve some work. Remember, DMC personnel have only so much time to run requested analyses - so they can't spend time on trivial questions. This means those making the request will be required to "do their homework", (i.e. review the literature, formulate a clear hypothesis and define as much as possible exactly which data are required to evaluate the hypothesis). In essence, these will be miniature "grant applications". We are also going to discourage asking questions based only on curiosity - the goal of any query should be a publication.

- c) The 4 primary investigators at Iowa (Mike Todd, Brad Hindman, Bill Clarke, and Jim Torner) will form the primary coordinating group. A publications committee made up of roughly 6 or 8 local PIs/Co-PIs/Advisory Committee members will function as a kind of editorial board. When a request for data is submitted via the Web, it will be assigned to one of the four above-mentioned individuals who will serve as "editor-in-chief". The request will then be sent to 2-4 of the members of the publications committee who will then review it for quality/importance, etc. If the proposal is accepted, a formal request will be sent to the DMC for data. If there are problems with the request, the "editor" will try to work with the individual who submitted the question to better formulate the question. If similar questions arrive from more than one person, the Iowa group will try to organize these people into a small cooperative working group.
- d) Once data are provided to an investigator, it is critical that preparation of any manuscript proceed with due haste. We reserve the right to "withdraw" permission to publish if there is undo delay between data analysis and submission of a final manuscript.
- e) All manuscripts resulting from IHAST2 data will be submitted to the Iowa oversight group and may also be reviewed by members of the publications committee. Our goal is to help, not obstruct - but we also want to be sure

than anything carrying the IHAST2 name be something we can all be proud of.

2002 IHAST2 Annual Meeting

The 2002 IHAST2 Annual Meeting is closer than you think! The Investigators' meeting will be held in Orlando, Florida on Saturday, October 12, 2002 in conjunction with the ASA. The meeting will be at the **Rosen Centre Hotel in Salons 5 & 6**. A continental breakfast will be available beginning at 7:30 AM and the meeting will start at 8:00 AM.

Topics on the agenda include closeout plans, what the next year will hold and data analysis plans. There will also be presentations by Dr. Guy Clifton from the University of Texas regarding Hypothermia & Trauma, Dr. Jon Zaroff (PI) from the University of California San Francisco regarding MIDS (Myocardial Injury/Dysfunction Sub Study), and Dr. Brad Hindman regarding other hypothermia trials.

After lunch (poolside) those investigators involved or interested in CFAAST (Cognitive Function After Aneurysm Surgery Trial), are invited to reconvene for a start-up meeting conducted by Dr. Satwant Samra (PI) from the University of Michigan.

If you have not already done so, please let us know by **September 13th** (we'll need a head count for breakfast and lunch). You can register using the following link.

https://dmchost.public-health.uiowa.edu/registration/reg_dinner.aspx

(You will need your certification number to register). If you have any questions about the Annual Meeting, please contact the Clinical Coordinating Center at ihast2@uiowa.edu or 319-356-0461.

Come join us fellow IHASTEES!!!

***Date of
Hospital Discharge***
DAILY POST-OP SCREEN form, Page 3

Some medical centers participating in IHAST2 have associated inpatient rehabilitation units on site. In these medical centers, IHAST2 patients who require inpatient rehabilitation services often are transferred from Neurosurgical services and admitted by Rehabilitation services while remaining within the same physical facility. What should be recorded as the date of discharge? Is it the date the patient leaves the acute care (neurosurgical) hospital, or is it the date they finally leave the associated rehabilitation unit? We have thought about this, and for consistency in several of the IHAST2 outcome measures, we have arrived at the following answer:

Whenever a patient is discharged (or “transferred”) from acute care to the rehab unit (even if within the same hospital) this is to be considered the official “Date of Discharge” on the DAILY POST-OP SCREEN, Page 3, Item 1. In addition, the discharge NIHSS would be obtained on the day the patient is discharged (transferred) to the rehabilitation service.

If you have been recording the date that the patient is discharged from rehab as the “Date of Discharge”, please contact us and we will help you revise the necessary case report forms. Thanks!

***Physician Support in
Scheduling 3-month
Follow-up Exams***

Coordinators are doing an excellent job of scheduling 3-month patient follow-ups! Physician support is essential to aid coordinators in facilitating 3-month follow-up appointments. Clinic scheduling personnel are

key to the success of patients returning within the desired time frame for their 3-month follow-up. Physicians can promote successful scheduling coordination by making scheduling personnel aware that they support their coordinators’ efforts to schedule patient visits.

***Data Edit Reports
Decrease***

Congratulations to all IHAST2 centers for the decrease in the number of data edit reports (DERs) over time! Data Management Center (DMC) reports reflect a drop from 35 percent (January - June 2000) to 13 percent (January - June 2002) in the number of case report forms producing at least one DER question. This is very impressive from a data standpoint. In many studies, the data edits increase as more patients are enrolled. However, for IHAST2, more data is submitted to the DMC but less data corrections have been generated. Study coordinators' experience, knowledge and efforts to obtain accurate data is largely responsible for this drop. So “hats off” to all of you!

A few reminders to help sustain the downward trend of DERs :

- Always remember to review the ANESTHESIOLOGIST and NEUROSURGEON forms before submitting them to the DMC.
- Read over the NIHSS form directions carefully before submitting them to the DMC. Please do not hesitate to contact the CCC or the DMC regarding any questions related to the IHAST2 study.
- Encourage neuropsychology examiners to include how much time it took the patient to complete the Complex Figure Test.
- Take an extra moment to review dates in header and footer areas of forms for accuracy prior to submitting forms. A common mistake is to write a certification number in the blank for the patient ID number.

Keep up the excellent work!

NIHSS Supplemental Motor Exam Form

One of the many things we are trying to capture in our data collection efforts are instances when IHAST2 patients develop focal motor deficits. Because the design of the original NIH stroke scale tests voluntary movement only in response to *verbal* command (*not* in response to pain or other noxious stimuli), an additional page, the Supplemental Motor Exam, was added on to the NIHSS for the IHAST2 study. The point of the Supplemental Motor Exam is to test for movement in response to a *noxious* stimulus (items 12 and 13) when patients cannot make a *voluntary* movement in response to a *verbal* command (items 5 and 6) because they are obtunded. Although the addition of the Supplemental Motor Exam was needed, it has problems. The wording may seem to contradict the rest of the NIHSS form, and for some people it is confusing and even irritating ☹. Hopefully the following will help you understand this additional page and even (eventually) appreciate it ☺.

Please consider completing the “Supplemental Motor Exam of Obtunded/Stuporous/Comatose Patients” whenever a patient scores a “4” (No Movement) to any one of the voluntary motor items (5a, 5b, 6a, or 6b) on the main NIHSS. If your patient is *perfectly* alert and is otherwise responsive to verbal commands, then completing page 5 is *not* necessary. On the other hand, if your patient is not very alert and/or is not consistently responding to verbal commands, then please do complete the Supplemental Motor Exam.

When completing the Supplemental Motor Exam page, you must answer all questions (12a, 12b, 13a, and 13b). As usual, no blanks allowed. However, if when you scored motor items 5a, 5b, 6a, and 6b, you already observed purposeful movement in any of the extremities (“0”, “1”, “2”, or “3” - but not a “4”) then you should

automatically assign a score of “0” to the corresponding limb in item 12a, 12b, 13a or 13b. You will still need to test the extremity (or extremities) that previously scored a “4” (No Movement) in response to your verbal command. If, in response to the *noxious* stimulus, the patient makes a *voluntary* response, please indicate this on the form. If, instead, there is a decorticate/decerebrate response, or no response, then please indicate this on the form.

Finally, if when all is said and done, the patient demonstrates bilateral purposeful movement in either the upper or lower extremities (either in response to verbal [items 5 and 6] or noxious [items 12 & 13] stimuli), then the skip out box must be completed. This provides the answer that IHAST2 needs--whether limb asymmetry is present.