BIOS

Brain Injury OutcomeS (BIOS)
Division of Brain Injury Outcomes

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OVERVIEW

The Johns Hopkins Brian Injury OutcomeS (BIOS) Division is a clinical trial coordinating center (data management center, imaging reading center, and enrollment center) within the Johns Hopkins School of Medicine, Department of Neurology. Its focus is to provide multicenter management to clinical trials evaluating therapeutic, preventive and diagnostic interventions. Led by Dr. Daniel F. Hanley, BIOS has unique expertise in the coordination and management of trials investigating rare neurologic disorders, acute neurologic ICU conditions, rehabilitation, and functional outcomes. Since the 1990s, BIOS has coordinated international, federally-funded and industry-sponsored trials across a wide range of conditions for investigators within the JHU departments of Neurology, Neurosurgery, Anesthesia-Critical Care Medicine, Hematology, Neuroradiology, and for investigators at other academic centers around the U.S.

BIO has managed trials for stroke, neurological critical care, infectious disease, cardiovascular disease, cardiac arrest, and neuromuscular disorders as well as other brain and stroke-related disciplines. BIOS has coordinated trials testing drugs and devices to treat stroke, both ischemic and hemorrhagic, brain infections, muscular dystrophy, sickle cell disease, and brain trauma within the Johns Hopkins University, around the nation, in Canada and Israel, and throughout the European Union.

BIOS maintains a high level of research activity and has received substantial funding dollars from a variety of studies sponsored by the FDA Office of Orphan Products Development (rare diseases), NHBLI SBIR and DOD mechanisms, NINDS, NIAID, Department of Veterans Affairs, Washington State, the American Academy of Neurology, the American Heart Association, the Doris Duke Foundation, Genentech and several pharmaceutical organizations, and device companies, such as the EKOS Corporation and Infinite Biomedical Technologies via small business and Defense contracting.

Previous NIH trials include BIOS studies of acute viral encephalitis – “Adult HSE trials” (funded by National Institute of Allergy and Infectious Diseases [NIAID]); viral meningitis – “West Nile Virus trials” (NIAID) and acute hemispheric stroke – “Induced-Hypertension trial” (NINDS). Active trials with international coordination responsibilities include: intraventricular hemorrhage – “CLEAR III trial” (NINDS and prior FDA orphan drug program); ATACH (NINDS) and parenchymal hemorrhage “MISTIE trial” (NINDS). In addition, the group has pioneered the translation of laboratory-based, diagnostic and therapeutic measurements for the treatment of brain injury from global ischemia after cardiac arrest -- “CARES trial” (National Heart Lung and Blood Institute [NHLBI]). Currently, BIOS focuses on providing multicenter coordinating infrastructure to neurological clinical trials evaluating therapeutic, preventive and diagnostic interventions for stroke, and more recently, pediatric hematologic disease (sickle cell and silent stroke).

In each clinical area, BIOS has developed novel standardized clinical protocols and clinical assessment tools, using investigator consensus methods. BIOS has pioneered the use of surrogate measures from brain images to assess disease state and severity in different types of brain injury and is developing unique statistical methods to assess brain disease severity and the impact of neurologic treatments on clinical and surrogate measures of brain injury. And, tools from “first of a kind” BIOS trials have been adopted in subsequent trials by others. BIOS offers quality-controlled collection and validation routines for detailed neurological data and has extensive experience designing precise, unambiguous point-of-care tools designed to report and analyze:

- Injury, recovery and outcomes
- Surgical and ICU protocols and performance
- Medical event tracking
- Timeline analyses comparing physiologic measurements to dosing and adverse events, and performance within timeframes (door to CT, door to drug, stroke to ED, cardiac arrest times, and cardiac arrest to first neurostatus evaluations)

REGULATORY

All trials follow regulations published in the Code of Federal Regulations 21 CFR 312 defining the procedures and requirements governing the use of investigational new drugs and the monitoring of serious and unanticipated adverse events and are registered with Clinicaltrials.gov. BIOS is approved for multi-trial, multisite management by the JHU IRB and is likewise recognized as a coordinating center by the Western IRB (WIRB) and other IRBs. In collaboration with one of three satellite Surgical Centers (University of Chicago, I. Awad; U. Cincinnati, M. Zuccarello; and UCLA, P. Vespa) BIOS performs standardized treatment and performance metrics, depending on trial assignments. The Center for Drug Evaluation and Research (CDER, FDA) monitors many treatment protocols under IND 8523. Experience includes grant preparation, quarterly and annual reports, and activities for local and regional IRBs, Health Canada, MRA and other European agencies, FDA, NIH, CDER and pharmaceutical ISTs.

DATA MANAGEMENT

BIOS currently works with the Biostatistics Department at the Johns Hopkins School of Public Health. It also collaborates with data centers at the University of Alabama and the Medical University of South Carolina, and has worked with the University of Iowa data management center as a site. BIOS uses advanced electronic tracking methods and assessment algorithms to increase trial efficiency, and to facilitate patient recruitment and retention; it has on three previous occasions (American Brain Injury Consortium, UCLA, and the University of Glasgow) constructed data interchange interfaces to external data management systems.

GOOD CLINICAL PRACTICE

BIOS has GCP processes in place in the form of standard operational procedures (SOPs) and PWGs (Protocol Working Guidelines) to manage work flow and issues related to quality control, imaging, safety reporting, data entry, training and certification, financial planning, and the operational requirements for records maintenance, data security, filing and storage of study records. This experience demonstrates the center's ability to develop solid outcomes-based approaches across multiple acute disease processes employing functional outcomes and quality of life measures. BIOS has developed study handbooks, SOPs, and manuals of operations and procedures, as well as evaluation tools for neuropsychological outcome, brain hemorrhage outcome, stroke outcome and cardiac arrest outcome. It has implemented, tested and validated, via internal and external monitoring, multicenter brain CT and MRI data collection, storage and central reading efforts in numerous multicenter trials. The center has validated paper and customized web-based data collection systems with onsite monitoring and external review and has substantial experience with FDA CDER, FDA (IND) new drug application, FDA orphan products processes and approvals. BIOS has managed multicenter IRB approval processes, including additional regulatory experience with European Union regulatory and ethical requirements and has practical experience in augmenting study activities with additional sites for NIAID, NINDS and FDA-sponsored studies. BIOS is also experienced in EFIC (Exception from Informed Consent) studies, which are used for emergency research trials. Two such studies, RAMPART, a seizure trial, and ProTECT, a traumatic brain injury trial, are part of the NIH funded NETT (Neurologic Emergency Treatment Trials). The start-up work for these trials included collaborating with the IRB, to conduct community consultation and public disclosures regarding the purpose and scope of the trials.

BIOS utilizes public-private partnerships including inter-university center collaborations, materials agreements with pharmaceutical companies, international drug distributors, CROs, software developers, foundations, and device companies. Since organizing as a research center in the late 1990's, the team has developed a consortium of nearly 100 international, clinical sites, many of which, for more than a decade, have participated in multiple trials. With recruitment accountability learned from FDA and NINDS sponsored trials, BIOS has built outstanding capabilities to assess, measure, and meet recruitment requirements. BIOS has provided consistent training for methodologies and protocol practices and user-friendly processes for regulatory approvals and contract negotiations. BIOS and its enrolling centers have had an outstanding track record of center and site personnel retention. Likewise it has a cadre of familiar support services across trials, such as investigational drug pharmacists, site regulatory specialists, monitors, drug distributors, and a long-standing relationship with the JHU Office of Research Administration and the JHU CTSA.

MODEL TRAINING PROGRAMS

BIOS is a recognized leader in training medical and non-medical personnel in emergency neurological protocols, critical care protocols, ICU protocols, and functional outcomes. BIOS demands a rigorous, ongoing training program for all clinical site participants throughout the lifespan of each trial. It has a substantial up-to-date library of targeted training tools for acute and chronic status assessments required by clinical trials including but not limited to: surgical techniques, drug administration, imaging-dosing decision-making, the NIH Stroke Scale, Glasgow Coma Score, Glasgow Outcome Scale (GOS), extended GOS, Stroke Impact Scale, and neuropsychological testing, as well as a training library of data forms for capture of physiologic and interventional data.

The use of wide-ranging web capabilities enables BIOS to connect to consortia sites, which has exponentially improved the utilization of trial-specific web-based training. The BIOS experience is that web utilization has become a front-and-center feature of our trial management style—in discussions with coordinators and investigators about protocol, protocol variances, performance, goals and burdens. Every opportunity is a training opportunity, and every training opportunity is a sequence reinforced through repetitious FAQ-newsletter-live broadcast-website posting-self test. Presently, our web-based training includes site training, retraining and testing/validation of the training status of each investigative team. Our training utilizes both mandatory group training sessions and individual site team-building education. Key elements of training are always followed with a test to demonstrate competency and protocol mastery. A repository of trial instruction modules, hosted by our CRO partner -- Emissary International -- http://www.Emissary.com, allows individualized or multisite coordinator and investigator training and training of new personnel. New training modules are broadcast multiple times each month and then posted to each trial's website for future reference and training: http://BrainInjuryOutcomes.com/studies

The modules are video format or slide-show format with written notes or narrated text. Most of our modules are used at the secondary level as well for trial initiations and in-servicing. Not only is the training well-used with measured results, this efficiency greatly reduces coordinating center travel and provides the economical use of personnel time to trouble-shoot the critically important site problems. In addition half-day and full-day Webinars allow us to perform intensive "refresher" continuing education for the original protocol and for ongoing, experience-based protocol modifications rapidly. This effectively enhances protocol uniformity throughout an entire study. We use the same Emissary College to train new coordinators or investigators when site personnel change in mid study.

Traditional training methods are also available. BIOS is expert in organizing and hosting investigator meetings in the U.S. and abroad, and site managers and monitors are also available when site visits are needed.

ELECTRONIC TRIAL MANAGEMENT

BIOS is a paperless management group that has pioneered the conduct of all aspects of a trial in the electronic domain. This allows all team members simultaneous access to regulatory, contract and primary medical trial data for validation cross-check, timely data collection, and early quality monitoring. The audit capability of these electronic processes allow for economies in staffing, simplification of monitoring, straightforward dissemination of project management accomplishments and problems, and the development of virtual work groups to more rapidly review safety and protocol problems, adjudicate endpoints, and provide complete and up-to-date site performance assessments. As described above, in each area, these economies translate into greater site communication and investigator education. Specific electronic innovations include: remote monitoring using electronic medical record repositories, development of a fully electronic CT and MRI image reading center for multisite trials (including the training and support of study coordinator based DICOM image transfer), real-time image and surgical procedure adjudication of trial eligibility, and site-specific electronic quality assessments.

ON-CALL ENROLLMENT CENTER

BIOS functions 24/7 for site randomizations and enrollment decision-making. Central enrollment monitoring is critical when subjects are infrequent, as in rare disorders and new consortia. When performance processes are based on unique patient, image, and diagnostic data, correct screening decisions, enrollment by strata/group assignments should be based on technical reading of clinical history, images and diagnostic testing. BIOS has minimized this variable and increased enrollment by developing a study enrollment and protocol compliance monitoring capability that works in real time with digitally transmitted data to assure compliance and quality at this most critical study stage.

CENTRALIZED DATA EVALUATIONS

The BIOS CT/MRI reading center has developed innovative, accurate methods for the qualitative and quantitative volumetric analysis of brain lesions. It has successfully combined image and data management systems to produce meaningfully designed reports of neurological outcomes, neurosurgical performance, drug delivery, infection tracking, new brain bleeding events, and neurological adverse event (AE) tracking.

PROJECT DELIVERY

BIOS personnel have significant experience collaborating with NIH staff, meeting on multiple occasions to discuss grant program development and completion specifics. BIOS has forged strong working relationships with NIH/NINDS, the FDA Office of Orphan Products Development, and CDER personnel that facilitate IND, grant, and contract approvals.

BIOS has demonstrated its capacity to complete project goals and recruitment, as well as safety and dose finding tasks. With staffing capable of "role flexibility," we have identified and mitigated recruitment problems, improved protocol compliance and diminished novel unanticipated safety issues. We have demonstrated the ability to standardize protocols across enrollment centers by educating sites unfamiliar with a protocol to perform quality, detailed collection of study data and parallel clinical course and "standard of care" concurrent therapy data. This process is made possible with the use of innovative data collection and clinical care "standard operating procedures."

Representative Multicenter Trials Managed

Managed Multicenter Trials	CLEAR A	CLEAR B	ITM	MISTIE-ICES	CLEAR III	CARES	SLEUTH
1.Intervention	0.3 mg rt-PA vs. 1.0 mg rt-PA for IVH resolution q12h	1.0 mg rt-PA for IVH resolution q8h	None	Minimally invasive surgery plus rt-PA vs. medical management for ICH resolution [ICES Tier: Endoscopic ICH removal vs. medical management for ICH resolution]	1.0 mg rt-PA vs. Placebo for IVH resolution q8h	Observational study	rt-PA plus ultrasound for ICH and IVH resolution (device: EKOS NeuroWave™ Infusion Catheter)
2. Funding	FDA Office of Orphan Products	FDA Office of Orphan Products	Genentech, Inc.	NIH/NINDS	NIH/NINDS	NIH/NHLBI	Life Science Discovery Fund, Seattle Neuroscience Institute EKOS Corporation, Bothell, WA
3. IND Sponsor	Daniel F. Hanley	Daniel F. Hanley	Daniel F. Hanley	Daniel F. Hanley	Daniel F. Hanley	Infinite Biomedical Technologies (IDE)	Daniel F. Hanley
4. Drug Center	JHU Investigational Drug Services	JHU Investigational Drug Services	N/A	JHU Investigational Drug Services	JHU Investigational Drug Services	N/A	JHU Investigational Drug Services
5. Data Center	JHU BIOS	JHU BIOS	JHU BIOS	JHU BIOS	JHU BIOS	JHU BIOS	JHU BIOS
6. No. Sites	15 US, CA	34 Global	23 Global	26 Global	65 Global	5 US	2 US
7. Patient #	16	36	N/A	110	500	88	9
8. F/U Length	30 days	180 days	N/A	365 days	365 days	90 days	30 days
9. Award	10/30/2003	12/1/2004	10/1/2008	3/1/2005	7/1/2009	4/1/2007	4/1/2008
10. 1st SC	1 month	12 mo. pre-award	4 months	4 months	3 months	3 mo. pre-award	N/A
11. Last SC	2 months	Grp 1: 1 mo. Grp 2: 24 mo. Grp 3: 37 mo.	9 months	Grp 1: 4 mo.	Grp 1: 2 mo. Grp 2: 1 mo. Grp 3: 3 mo. Grp 4: 1 mo. Grp 5: 5 mo.	1 months	N/A
12. CC IRB	4 mo. pre-award	12 mo. pre-award	4 months	7 mo. pre-award	Grp 1: 5 mo. Grp 2: 8 mo. Grp 3: 9 mo. Grp 4: 6 mo. Grp 5: 7 mo.	3 months	2 mo. pre-award
13. 1st Site IRB	2 months	12 mo. pre-award	1 month	Grp 1: 7 mo. pre-award	1 mo. pre-award	7 months	4 months
14. Last IRB	14 months	Grp 1: 1 mo. Grp 2: 24 mo. Grp 3: 37 mo.	8 months	Grp 1: 5 mo.	Grp 1: 7 mo. Grp 2: 7 mo. Grp 3: 1 mo. Grp 4: 1 mo. Grp 5: 1 mo.	8 months	4 months
15. 1st Screen	2 months	8 months	1 month	10 months	1 month	6 months	4 months
16. 1st Enroll	2.5 months	10 months	N/A	11 months	2 months	7 months	4 months
17. Recruit Rate	13.5/year	15.5/year	1,000 screened/year	23/year	69/year	20/year	9/year
18. LTFU	0/16	1/36	N/A	3/current	0/current	1/88	1/9
19. LPV to Lock	1 month	2 months	N/A	Ongoing	Ongoing	3 months	1 month