

International Initiative for Traumatic Brain Injury Research

Sixth Conference

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Acronym List

ACS	American College of Surgeons
ADAPT	Approaches and Decisions in Acute Pediatric TBI
BIDS	Brain Imaging Data Structure
BOOST	Brain Oxygen Optimization in Severe TBI
BTF	Brain Trauma Foundation
BTOM	Brain Tissue O ₂ Monitors
CALIPER	Canadian Laboratory Initiative on Paediatric Reference Intervals
CDEs	Common Data Elements
CENTER	Collaborative European Neurotrauma Effectiveness Research
CER	comparative effectiveness research
CIHR	Canadian Institutes of Health Research
COAs	clinical outcome assessment
CREACTIVE	Collaborative Research on Acute TBI in Intensive Care Medicine in Europe
CT	computed tomography
DoD	Department of Defense
DTI	diffusion tensor imaging
ENIGMA	Enhancing Neuroimaging Genetics Through Meta-analysis
FAIR	Findable, Accessible, Interoperable over multiple platforms, Reusable, and attributed
FDA	Food and Drug Administration
FITBIR	Federal Interagency TBI Research
GCS	Glasgow Coma Scale
GNOS	Global Neurotrauma Outcomes Study
GOSE	Glasgow Outcome Scale
GWAS	genome wide association studies
HEMOTION	Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization
ICMJE	International Committee of Medical Journal Editors
ICP	intracranial pressure
ICU	intensive care unit
IHEC	International Human Epigenomic Consortium
InTBIR	International Initiative for Traumatic Brain Injury
IRDiRC	International Rare Diseases Research Consortium
LSR	living systematic review
MRI	magnetic resonance imaging
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OBI	Ontario Brain Institute
RFP	Request for Proposals
SCAT5	Sport Concussion Assessment Tool 5
SIREN	Strategies to Innovate Emergency Care Clinical Trials Network
SCI	spinal cord injury
TBI	traumatic brain injury
TED	TBI Endpoints Development

Introduction

The sixth conference of the International Initiative for Traumatic Brain Injury Research (InTBIR) was convened to review progress toward achieving the goal of improving outcomes and lessening the global burden of traumatic brain injury (TBI) by 2020. InTBIR was founded in 2012 by funding agencies from the EU, Canada and the United States. This year's meeting was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) and the U.S. Department of Defense (DoD). The 102 participants included leaders in TBI research and funders from Europe, Canada, and the United States. Presentations, which included frank discussions of successes as well as challenges, were organized into six sessions and are summarized below. The full agenda is included in Appendix A.

Welcome and Opening Statements

In his opening remarks, Dr. Walter Koroshetz reminded attendees of the historic nature of the international cooperation represented by InTBIR, spurred by a joint recognition by NIH and the European Commission that prospective collection of large amounts of high-quality data on TBI represents the most efficient mechanism to carry out comparative effectiveness research (CER) aimed at developing best practices in care. LTC David Johnston focused his comments on the impact of TBI on the military. He stressed that the paradigm for TBI diagnostics, therapeutics, and interventions needs to change to accommodate casualties who remain in the field for long time periods. Dr. Tom Mikkelsen described Ontario's Brain Institute's (OBI) approach to research, with Ontario serving as a "community laboratory" for health care innovation.

Session 1: InTBIR Work Group Progress Reports and Deliverables

Dashboard of InTBIR Data

Data Management Working Group: Dr. Mona Hicks on behalf of Dr. Jeff Grethe

The Data Management Work Group is responsible for the InTBIR data dictionary, data curation, quality control, platforms, and archives. Focusing on the platforms and archives, Dr. Hicks described the group's efforts to bring together data across all the studies. Currently 16 InTBIR clinical studies are collecting data from 321 sites around the world, and curation of these extremely large amounts of data represents a challenging task facing InTBIR.

To enable data sharing, the group endorses the FAIR principles, which dictate that data should be Findable, Accessible, Interoperable over multiple platforms, Reusable, and attributed. Multiple data platforms are available for use by InTBIR, including the OBI Brain-CODE, the NIH- and DoD-supported Federal Interagency TBI Research (FITBIR), the European Human Brain Project's platform, and the One Mind Portal. As a step forward, dashboards of metadata were created for individual and combined InTBIR studies and will be posted on the website once permission has been received from the investigators.

The metadata dashboard of the combined InTBIR studies demonstrated that currently more than 15,000 subjects are enrolled, that all age groups are well represented, and that the gender distribution mirrors the distribution seen in the general population. When available, GCS scores and time since injury of the study participants would enhance the metadata dashboards.

Catalog of Biospecimens

Biomarkers Work Group: Dr. Ramon Diaz-Arrastia

InTBIR has the world's best and most comprehensive collection of biological fluids related to TBI. TRACK-TBI and the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) have samples from patients admitted to the intensive care unit (ICU), floor, or emergency departments at days 1, 3, 5; 2 weeks; and 6 months. Sub-acute and chronic stage samples will be particularly valuable, because they are underrepresented in the current knowledge base. Collaborative Research on Acute TBI in Intensive Care Medicine in Europe (CREACTIVE) has ICU samples over the same time periods. The Canadian TBI Research and Clinical Network (CanTBI) samples, which are mostly ICU, are from days 1, 2, 4 and weeks 1, 2, 4.

Ongoing projects by members of this group include the following:

- CREATIVE and colleagues at Imperial College and University College received an ERA-NEURON Award to study samples collected in the ICU.
- TRACK-TBI received a grant supplement from NINDS to analyze biomarkers.
- TRACK-TBI collaborates with Abbott to test its initial 1,500 samples for five biomarkers over five time points, representing the largest study of these biomarkers to date. Publications showing the value of this analysis should appear within the next few months.
- TRACK-TBI collaborates with Quanterix, which has developed ultrasensitive detection methods for Tau, NF-L, and other biomarkers.
- In collaboration with the CALIPER network, CanTBI obtained pediatric normative data on serum Tau and NF-L in about 300 samples in the 0- to 18-year age range, showing that Tau is elevated in healthy children early in life. These researchers are now obtaining samples for a more comprehensive lifespan study.
- Another InTBIR collaboration is studying 5,000 patient samples to determine the correlation of autoantibodies with disease progression.

TRACK-TBI samples are available to the wider research community. Because the supply of biological samples is exhaustible, policies exist for identifying and prioritizing the most scientifically valuable efforts. The discussion highlighted the need for a uniform InTBIR policy for working with industry and other academic partners. Not all studies have attracted partners in industry. The Abbott collaboration was made possible because TRACK-TBI obtained funding from DoD to establish a biospecimen repository capable of meeting Food and Drug Administration (FDA) requirements, and Abbott received these samples blinded.

Catalog of Neuroimages

Neuroimaging Work Group: Drs. Pratik Mukherjee and Stephen Strother

The only way to achieve high image quality while maintaining generalizability is to standardize magnetic resonance imaging (MRI) pulse sequence acquisition. The TRACK-TBI imaging group standardized three-dimensional T1- and T2-weighted images at high resolution across the three major vendor platforms, as well as diffusion tensor imaging (DTI) and functional MRI. To standardize MRI pulse sequences across multicenter studies, the group is cataloging the parameters used by each study. Challenges to standardization are ongoing and include vendor differentiation, innovation of technology, and naming conventions. Dr. Mukherjee noted that the name of the DTI phantom that was used to standardize the scanners is not itself standard, highlighting the need to standardize terminology.

Data naming and metadata structure play crucial roles in ensuring that data adhere to the FAIR principles mentioned above. Naming conventions impact the first two requirements (findable and accessible), while the metadata structure impacts interoperability and reusability. To be FAIR, a neuroimaging database should contain a globally unique identifier for each participant. CENTER-TBI and the FITBIR bioinformatics platform follow this convention, but Brain-CODE does not. Russell Poldrack's Brain Imaging Data Structure (BIDS) may be able to solve some of the metadata problems for neuroimaging encountered by InTBIR.

In addition to the quality assurance issues that stem from small differences between MRI scanners and sites, there are other quality control issues. Technicians may run the wrong sequence or use the wrong scanner, so there must be processes to catch these errors. Visual inspection of the data is crucial. Finally, all of the data enter a processing pipeline, and it is unclear how to move forward with this stage. Should processing pipelines be standardized before researchers submit their data, or should data be submitted via diverse pipelines and compared afterward? Dr. Strother suggested that InTBIR collaborate with funding agencies to address gaps identified within the TBI neuroimaging research community. Participants noted the need for constant updating of data-processing protocols, along with funds to support such an effort.

InTBIR Data Analytics

Data Analytics Work Group: Dr. Steve Wisniewski

The Data Analytics Work Group sent a survey to all InTBIR principal investigators to determine whether six common CER outcome questions were part of their original study proposals and/or are addressable in their studies. The committee will review the responses, identify common CER questions, and bring together investigators with the aim of enabling analyses that could not be done in a single study alone.

Data will not be available to the larger research community until the original study has been completed and published. However, data related to questions not addressed by the original study could be shared earlier. Study design may dictate the best use of combined data; for example, two underpowered studies might benefit from pooling and analyzing their data together, whereas a pair of high-powered studies might be handled differently. The goal is to enable people to analyze data across studies through a grassroots approach. A series of papers on analytic methods has been drafted and reviewed, and the finalized papers will be re-submitted in December for publication.

InTBIR Policies (a): Data Sharing

Policies Work Group: Dr. Joanne Fleming

As of July 2018, all manuscripts submitted to International Committee of Medical Journal Editors (ICMJE) journals will be required to contain a data sharing statement. Given their plans to publish jointly, InTBIR investigators should therefore take prompt action to produce a data sharing agreement. InTBIR's data sharing environment must be secure for the participants, protect ownership, and clearly assign authorship credit. Consequently, there is a need for interlinked policies regarding data sharing, informed consent, and publication. The Policies Work Group has produced preliminary drafts of all three policies and has invited all InTBIR participants to contribute to their development.

Also needed is an agreed-upon data sharing platform. The work group recommended development of a federated database to permit data sharing at the macro levels of the Human Brain Project in Europe, FITBIR in the United States, and OBI's Brain-CODE in Canada. A protocol will determine which data to share within InTBIR and the timing of data access and will address sharing at various levels, from the individual study to the general scientific community. In the future, it would be helpful to have a uniform informed consent for InTBIR and other international consortia that includes language to permit cross-border data sharing, as well as minimum requirements for data encryption and protection standards to ensure that data are exchanged in a secure network.

Discussion

FITBIR has a single site that stores information about each individual study, including the data format, but the data themselves remain on individual servers. Similarly, for InTBIR as a whole, some data may not be fully shared in raw form, but these data could still be made accessible for the purpose of analysis. Raw data that remain behind firewalls will need to be standardized at some level to make this type of analysis possible.

InTBIR Policies (b): Publications

Policies Work Group: Dr. Isabelle Gagnon

The Policies Work Group has written a draft Publication and Authorship Guideline for all scientific output produced jointly by InTBIR members. Credit for primary authorship should be based on appropriate effort as defined in ICMJE's published guidelines. This includes meeting all four of the following criteria: make a substantial contribution to the work's design, conception, acquisition, analysis, or interpretation; draft or critically revise the manuscript; approve the manuscript; and accept accountability for all aspects of the work. Group members who do not meet all four criteria will be considered contributors and will be listed in alphabetical order at the end of the manuscript. Alternatively, they may be acknowledged as a group in the author list, such as "InTBIR Participants and Investigators." It was noted that there is no uniform procedure among journals for dealing with manuscripts with more than 100 authors. This policy requires formation of an InTBIR Publication Board, perhaps composed of the principal investigators, that will review manuscripts prior to publication.

Finally, this Work Group aims to develop a data sharing statement that would be included in all InTBIR publications, as well as a data access policy. The data access policy should protect data confidentiality and follow data security protections and all applicable laws—a process that will be complicated by the involvement of multiple jurisdictions with varied approaches to medical ethics. This project will be ongoing, because policies will require regular monitoring and updating.

Session 2: The Good, The Bad, and the Reality: 2017

MRI Biomarker Letter of Support from the Food and Drug Administration (FDA)

Dr. Geoff Manley on behalf of TRACK-TBI and TED investigators

Dr. Manley described recent work of the DoD-funded TBI Endpoints Development (TED) collaborative, whose goal is to improve clinical trial design to inform and accelerate FDA approval of diagnostic tools and therapeutic agents for TBI. The first step of this process requires development of a broad range of validated biomarkers and clinical outcome assessments (COAs) that are more sensitive and specific than those now available. To reach patients, these biomarkers and COAs must pass through a regulatory pathway, via the FDA in the United States or the European Medicines Agency in Europe.

In Stage 1, the TED team seeks to identify and validate biomarkers and COAs that extend beyond the GCS and Extended Glasgow Outcome Scale (GOSE). TED has developed Clinical Data Interchange Standards Consortium (CDISC) standards based on the Common Data Elements (CDEs) employed in InTBIR studies, to provide the FDA with the standard measures it requires to evaluate clinical trials and bring new treatments to patients.

In March 2016, FDA held its first public workshop for TBI, focused on biomarkers. Later that year, the FDA Center for Devices and Radiological Health issued a Recognition Letter of Research Importance to the TED initiative, indicating potential interest in assigning a clinical trial for TBI. The Office of Translational Sciences held a Critical Path Innovation Meeting to develop regulatory pathways for approving biomarkers in TBI. In April 2017, TED obtained a Letter of Support for Neuroimaging Biomarkers from the FDA Center for Drug Evaluation and Research, acknowledging the potential value of MRI as a biomarker for specific TBI-related pathoanatomic lesions and encouraging its use as a tool moving forward. A letter of support is currently in progress for blood-based biomarkers.

Challenges and Solutions in Data Curation: Experiences from CENTER- and TRACK-TBI

CENTER-TBI

Dr. Andrew Maas on behalf of the CENTER Collaborators

Dr. Maas described the complexities of curating massive amounts of complex data and making them usable. CENTER-TBI has data on more than 5,000 individuals with a target of 5,400 individuals. The EU registry has more than 20,000 participants, China more than 13,000, and India more than 2,500 and still enrolling. The complexity of these data is unparalleled, because they are derived from multiple centers in multiple countries with heterogeneous populations and containing different types of data. In CENTER-TBI alone, there are 2,641 unique data variables as well as additional elements (e.g., multiple time points and DICOM images) that multiply the complexity by a factor of 5,400, generating pentabytes of data.

The three streams of data curation—completeness, quality, and access—present their own challenges. Completeness of the CENTER-TBI data has improved, with follow-up data in survivors remaining steady at 65-70 percent. CENTER-TBI researchers have encountered numerous issues with data curation, for example, inappropriate numeric rounding or impossible dates and times. To address these issues, CENTER-TBI formed a data curation task force, which created a new workflow model and a curation SWAT team composed of three full-time investigators. Altogether, data curation efforts employ 7 to 10 full-time workers, none of whom was included in the original budget.

TRACK-TBI

Dr. Geoff Manley

TRACK-TBI has added new clinical sites and is set to enroll 3,000 subjects by the end of this year. Seventy-five investigators have obtained more than 4,000 computed tomography (CT) scans, 1,880 MRI scans, 42,000 biospecimen samples, and postmortem brains from patients who were phenotyped while alive. The data collected by TRACK-TBI researchers represent an entirely new level of complexity. Dr. Manley estimates that the effort to look at combined data has been underfunded by a factor of 10.

With One Mind and others, TRACK-TBI investigators have created excellent analytic pipelines for data curation, but significant problems remain. Imaging is complicated because standard volumetric programs do not work on brains with deformations. Researchers tried to use tranSMART to analyze genome/phenome associations, but they exceeded the data volume and “broke” the software. The data complexity may be understood as follows: More than 4 million data-containing fields were generated from 2,245 patients. These fields were machine-flagged with 50,000 errors, of which 5,000 remain unresolved. Some errors require painstaking manual review.

To generate less-complex data that can be handled by the current technology, TRACK-TBI researchers are looking at smaller, natural cohorts of roughly 1,100 to 1,500 subjects and cleaning the data as they go. These cohorts include a natural cohort for addressing CER questions, an MRI imaging Phase I cohort, and a biomarker Phase I cohort. This project has also informed understanding of GOSE and

validation of glial fibrillary acidic protein (GFAP) and Ubiquitin C-terminal hydrolase L1 (UCH-L1) biomarkers.

Tools from One Mind and other partners allow for storage of TRACK-TBI information in a form that is accessible to everyone. An idea board encourages collaboration. Before data can be released, investigators must submit a collaboration agreement that includes a research plan, consort diagrams, and analysis by statisticians. To achieve reproducibility, this agreement also requires deposition of the analytic plan and repatriation of the reference data set and metadata.

Data Curation Guidelines

Dr. Ari Ercole

Guidelines on achieving data quality exist for other fields, but the TBI field must navigate its own way through these complex observational data sets. Dr. Ercole provided the following advice for data curation:

- Form a multidisciplinary data curation team early on.
- Design appropriate data structures. Clinical data are a mix of cross-sectional data, longitudinal data, and repeated measures, and the representations of these data types differ.
- Think about data specification. CDEs are essential but not sufficient to ensure that all data will be homogeneous. It is important to specify permissible values, data type, and whether the field is mandatory and to use proper data ontology with a logical hierarchy.
- Shun free text.
- Specify everything. Consider internationalization, metadata, and units.
- Test and monitor data before the start. Define rules for dealing with missing data (i.e., the “test harness”), and manually check for inconsistent data.
- Have a robust mechanism for addressing problems. Some problems can be fixed with programming, others cannot be fixed but should be documented, and yet others will require resolution at the individual sites.
- Document activities on an ongoing basis.

Discussion

The discussion focused on strategies to improve data input on the front end. Six thousand rules are built into TRACK-TBI’s data entry software, and a data curation engine generates errors from the data, which drives new rules. At a programmatic level, the field should consider developing its own structured approach to data entry and curation, because no off-the-shelf application has been sufficient.

Data collectors should receive feedback about the quality of the data. To this end, the case report form should be designed with each site in mind. In addition, data sets should be available for early testing of the analytical tools by experts.

The data collected in longitudinal studies offer an unparalleled opportunity to conduct chronic-phase interventional trials. For example, TRACK-TBI has already seen enough chronic outcomes to power

studies on sleep disturbance and posttraumatic epilepsy. InTBIR researchers have noted improvements in the characterization of head injury in their clinics as a direct result of participation in this study.

Session 3: Informing Trials through Collaboration

Clinical Trials from Design to Interpretation

Managing Severe Traumatic Brain Injury without Intracranial Pressure Monitoring in Pediatric Populations

Dr. Nancy Temkin

Dr. Temkin and colleagues designed a Phase III multicenter randomized clinical trial, BEST-TRIP-Peds, to determine the effect of intracranial pressure (ICP) monitoring on outcomes for children with severe TBI, compared to standard treatment. This group performed a similar study, BEST-TRIP, in adults. Both studies are being conducted in Latin America. Dr. Temkin outlined the advantages and disadvantages of performing studies in low- and middle-income countries. Advantages include excellent basic ICU care with dedicated and resourceful staff; willingness to randomize a novel treatment; good data quality (with close oversight); a lack of competing studies; and the possibility of funding through the Fogarty International Center if the study can be done for under \$400,000 per year. Importantly, studies conducted in low- and middle-income countries, where the global burden of TBI is the greatest, enable what is likely to be a highly informative exchange and secondary analyses of data. Disadvantages include unfamiliarity with research at many of the sites; the need to obtain assurances for ethics committees; the need for instruction regarding informed consent as well as intensive training and oversight; language and cultural barriers; lack of timeliness; infrastructure issues; political instability; and fiscal issues.

Brain Oxygen Optimization in Severe TBI (BOOST) Phase III

Dr. Ramon Diaz-Arrastia

Dr. Diaz-Arrastia described the Phase III Brain Oxygen Optimization in Severe TBI (BOOST-3) study, which tests the effect of monitoring brain tissue oxygen levels on outcomes. Although the association of low oxygen with poor outcomes in severe TBI is well known, the use of Brain Tissue O₂ Monitors (BTOM) is rare because their efficacy has not been demonstrated. Researchers completed a Phase II trial of BTOM in the neurological ICUs of 10 U.S. trauma centers. They found that treatment based on a combination of BTOM and ICP reduced the amount of time that the brain experienced hypoxia relative to ICP alone and was consistent with a better outcome, although this study was insufficiently powered to achieve clinical significance. NINDS has approved funding for BOOST-3, with 45 planned sites and a target enrollment of 1,094, which is sufficient to detect a 10 percent improvement in outcome.

Recently, DoD invited this group to submit an application to collect biomarkers from participants in BOOST. Bio-BOOST proposes to collect blood from 300 participants twice daily over 5 days and again at days 7 and 14. Blood will be assayed for GFAP, UCHL-1, Tau, and NF-L. The goals are to confirm the relationship between tissue hypoxia and neurodegeneration and to assess the efficacy of treatments for hypoxia in preventing neurodegeneration.

HEMOglobin Transfusion Threshold in Traumatic Brain Injury Optimization (HEMOTION)

Dr. Alexis Turgeon

In critical care, anemia is frequent and has been consistently associated with unfavorable outcomes and death. Two large randomized controlled trials in critically ill patients (TRICC and TRIPICU) showed that a restrictive transfusion strategy was comparable to a liberal transfusion strategy. However, these trials were not designed to study the neurocritically ill populations, from both a sample size and outcome measures point of view. The HEMOTION trial was motivated by an absence of evidence on which red blood cell transfusion strategies to adopt in critically ill adult patients with TBI. It started with a multicenter retrospective study, in collaboration with the Canadian TBI Research Consortium (CTRC) and the Canadian Critical Care Trials Group (CCCTG). The primary hypothesis of the HEMOTION trial is that for critically ill adult patients with TBI and anemia, liberal transfusion will lead to improved long-term functional outcomes over a restrictive transfusion strategy. This 712-patient multicenter trial is funded by the Canadian Institutes of Health Research (CIHR) and is part of the program of the Canada Research Chair in Critical Care Neurology and Trauma. The trial is designed to look at 6 months outcome measures and the first patient was enrolled in September 2017.

Approaches and Decisions in Acute Pediatric TBI (ADAPT) Trial

Dr. Michael Bell

The ADAPT trial enrolled 1,000 children from 34 U.S. and 17 international sites to better evaluate the effect of interventions on the outcomes of children with severe TBI. This study was completed ahead of time, and researchers are now analyzing the data and beginning to publish their results, which have the potential to change current guidelines. ADAPT has documented tremendous variation in acute phase care. Practitioners administer more than 30 different concentrations of saline alone. Some children are not fed for 7 days, while others receive full caloric intake on the first day. Dr. Bell discussed preliminary findings on the effectiveness of intracranial hypertension strategies. This study also demonstrates that international data can be collected and shared, given appropriate approvals.

Session 4: Living Guidelines for Global TBI

Development of Quality Indicators for TBI

Dr. Hester Lingsma

Dr. Lingsma leads work on CER for the CENTER-TBI study. She noted that research is only the first step toward improving patient outcomes; it must be followed by synthesis, guidelines, and improvements in care. Based on a literature review, there seems to be tremendous variation in adherence to guidelines in the TBI field. Because no quality indicators (measurable elements of the quality of care) exist for TBI, Dr. Lingsma and colleagues are conducting a Delphi study to develop quality indicators through a consensus process.

Challenge of International Guideline Development

Dr. Franco Servadei

The worldwide distribution of neurosurgeons and ICUs shows tremendous variation by region. Epidemiology also varies, with a dramatic increase in TBIs due to traffic accidents in low-income countries and falls as a more frequent cause of TBI in high-income countries. TBI cases in high-income countries represent only 18 percent of total TBI cases but are the subject of 89 percent of published papers. Consequently, the guidelines for treatment of TBI do not address the patient profiles and resources that are common in the regions that experience the majority of TBIs.

In September, Dr. Servadei and colleagues launched the National Institute for Health Research Global Health Research Group on Neurotrauma. With the aim of assessing the feasibility of context-specific guidelines, they are conducting the Global Neurotrauma Outcomes Study (GNOS). The first element of this study, GNOS-1, will collect 30-day snapshots that describe the management and outcomes of patients undergoing emergency cranial surgery after a TBI. Any hospital in the world performing this surgery can participate. Guidelines will be stratified to reflect site-specific capacities. Dr. Servadei advised against letting the perfect be the enemy of the good: a 2 percent reduction in mortality from TBI would equate to hundreds of thousands of lives saved each year.

Opportunities to Collaborate with Global Organizations for Living Guidelines Development

American College of Surgeons

Dr. David Hoyt, Executive Director, American College of Surgeons (ACS)

The ACS has implemented continuous quality improvement programs in 2,800 hospitals. It employs a payer-blind, population disease model that incorporates four elements: research-based standards, appropriate infrastructure, rigorous data collection, and external, peer-reviewed verification. The ACS first published “Resources for Optimal Care of the Injured Patient,” which provides guidelines and processes for trauma centers, in 1976, and has continually published updates. By using the principles required to develop a high reliability organization and data to inform performance, hospitals achieved an 82 percent decrease in complications and a 66 percent decrease in mortality. Guidelines are most effective in leading to practice change by physicians when care is inconsistent and positive outliers can be shown to correlate with better outcomes.

Brain Trauma Foundation (BTF)

Dr. Annette Totten

Dr. Totten is working to update three BTF guidelines: Acute Management of Severe TBI in adults (complete); Management of Pediatric TBI (near complete); and Pre-hospital Management of TBI (in progress). “Guidelines” have three components: literature identification and synthesis, evidence-based recommendations, and protocols/algorithms. The TBI field has made progress toward developing the first two components, but little toward the third; current evidence-based recommendations do not offer an algorithm. Dr. Totten and colleagues will write algorithms for their guidelines in separate, companion documents. Future directions will require adapting the guidelines to trends in evidence-based medicine and creating the infrastructure needed to maintain living guidelines and systematic

reviews. It was noted that one-time funding models and standard publishing procedures and formats present obstacles to the maintenance of living guidelines.

International Consensus on Sport Concussion

Dr. Kathryn Schneider

The goal of the 5th International Consensus Conference on Sport Concussion was to generate a simple, clear message and tools to equip health care practitioners to manage sport-related concussions. A modified Delphi Method was used to develop the consensus questions. Through five rounds of deliberations involving a scientific committee, a two-day conference with more than 400 participants, and an expert panel, the group achieved consensus on 12 questions and developed Concussion Recognition Tool 5, Sport Concussion Assessment Tool 5 (SCAT5), and Child SCAT5. Twelve review articles were published in two special editions of the British Journal of Sports Medicine in June 2017. The statement has been translated into the Canadian Guideline on Concussion in Sport (July 2017). The next step is implementation, ideally on an international scale.

Guidelines for Diagnosing and Managing Pediatric Concussions

Dr. Roger Zemek

Adapting Graham and Harrison's ADAPT method, the Ontario Neurotrauma Foundation developed guidelines for mild TBI and concussion for use by the general non-academic practitioner. The ONF has both adult (>18 years) and pediatric versions. In addition, there are separate versions of the guidelines for health care professionals, schools/community centers, and parents/caregivers. The guidelines are presented in a common language implementing a "when, how, how, why" format with multiple tool kits. The guidelines are available online in an interactive and responsive flowchart format (<http://onf.org/documents/guidelines-diagnosing-and-managing-pediatric-concussion>). Some of the evidence used to develop these guidelines was derived from the 5P study, which was part of the InTBIR initiative. The ONF guideline team is currently exploring how to effectively transition from a 4-year cycle to a living guideline.

TBI Living Systematic Reviews

Dr. Alexis Turgeon

A systematic review is performed to obtain the best level of evidence for developing guidelines for clinical care. The review should follow a structured approach, including development and registration of a protocol and should ensure its replicability. To better guide clinical practice in a timely manner, systematic reviews should be living, that is, continuously updated to incorporate new evidence as it becomes available.

A living systematic review (LSR) requires explicit methods for when and how it is updated, continuous surveillance for new articles, rapid incorporation of new data, and use of standard methodologies. In May 2017, a Cochrane LSR methods workshop was held during the Cochrane Canada symposium to develop methods guidelines for LSRs. To conduct LSR, systematic searches should be ongoing or frequent, and if new evidence is discovered, then the analyses, findings, and conclusions should be updated accordingly. Electronic publication formats that are easy to update should be favored. Current

formats include MAGIC app, WikiRecs, and BMJ RapidRecs. LSR maintenance is time-consuming and human resource intensive. Data mining software to assist with the search strategy is in development. Living systematic reviews and guidelines are part of the program of the Canada Research Chair in Critical Care Neurology and Trauma and the CENTER-TBI initiatives. InTBIR researchers will help identify questions of interest and work on guideline development using LSRs.

Living Systematic Reviews

Dr. Andrew Maas

The 2016 guidelines for management of severe TBI have lower clinical appeal than the 1996 guidelines, owing to an overall downgrading of evidence that caused some recommendations in the older document to be omitted from the newer one. Preferring the term “practice recommendations” to “guidelines,” Dr. Maas envisions LSRs forming a continuous base of living evidence. By adding consensus expert opinion where data are lacking (“medicine-based evidence”) and tailoring to local settings, LSRs can be used to develop practice recommendations. CENTER-TBI has piloted three LSRs in TBI that have served as proof of concept for LSRs in what Dr. Maas refers to as the “new evidence ecosystem.”

Discussion

Participants noted that practice recommendations must clearly differentiate between evidence-based medicine and medicine-based evidence, and research to move from the latter to the former is essential because practice may not be optimal. A registry of LSRs relevant to TBI would be welcomed. In addition, funding will be needed to support the continuous updating and dissemination of LSRs and practice recommendations. As the pendulum swings back from all-evidence to “practice-based evidence,” additional considerations arise, such as patient-centeredness, cost/benefit, and feasibility. These considerations should be explicitly incorporated into the grade framework, but review authors are frequently prohibited from addressing cost concerns, and guideline panels vary in their emphasis on cost and patient values.

Session 5: Reducing the Global Burden of TBI by 2020

Insights and Opportunities from Other International Collaborations

International Rare Diseases Research Consortium (IRDiRC)

Dr. Adam Hartman

IRDiRC was founded in 2011 to unite patient advocacy groups, researchers, and public and private funders in support of research on rare diseases. The issue faced by IRDiRC of greatest relevance to InTBIR is data sharing. Linking a genetic variant with a disease requires finding several unrelated individuals who share both the genetic variant and phenotype. This effort has been aided by Matchmaker Exchange, a collaboration among several international organizations that puts rare mutations on a bulletin board to find a match; the IRDiRC Automatable Discovery and Access Task Force, which has standardized ways to represent consent and other conditions of clinical data use; and the International Consortium of Human Phenotype Terminologies, which standardizes data describing

signs and symptoms for automated searching. The IRDiRC Privacy-Preserving Record Linkage Task Force develops guidelines on ethical, legal, and technical requirements of participant identifiers, which can present a major challenge when personal health information is shared across borders.

Subsets of individuals with TBI who share a particular targetable mechanism can be conceptualized as endophenotypes that are fairly rare and become, in essence, rare diseases of their own. IRDiRC is valuable for these cases because it seeks to incentivize the development of orphan drugs; half the drugs approved last year by FDA were for rare diseases. IRDiRC has a large consortium assembly, governor's commission, diagnostics commission, therapeutics commission, and funder's commission, with no shared funding. InTBIR was modeled after IRDiRC, albeit without a central infrastructure.

Wings for Life

Dr. Jan Schwab

Wings for Life supports translational research and clinical testing for spinal cord injury (SCI), which tends to be high-risk and high-reward and has been underfunded compared to other neurological conditions. Since its founding in 2004, Wings for Life has funded more than 300 projects with 272 publications. A major source of support is the Wings for Life World Run, which brings together more than 100,000 runners worldwide each year to raise SCI awareness and funding.

In the SCI field, linking basic science discovery to clinical progress is a significant challenge. Preclinical research offers limited predictive value for clinical testing. Results are undermined by bias. Neuro-regeneration studies could not be reproduced, and analysis of studies testing interventions found that missing data (unpublished studies that produced negative results) led to wildly inaccurate effect sizes. To address this, researchers developed a data sharing community for SCI research using the FAIR guidelines. The field of SCI is still characterized by a small number of randomized clinical trials. TBI is a very prevalent comorbidity of SCI, and collaborations among researchers in these fields should be encouraged.

Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) Consortium

Dr. Emily Dennis

The ENIGMA Consortium was developed to enable the use of genome wide association studies (GWAS) to study how the brain is impacted by genetic variants. GWAS requires tens of thousands of subjects, so ENIGMA brings together 900+ researchers at 340 institutions in 37 countries. Each site does its own processing and site-level analysis using a set of harmonized protocols for image processing and QC agreed on by the group, amounting to massively distributed computing. There is no single data repository. Raw genetics and imaging data are rarely shared, but summary statistics are sent to central sites or teams for meta-analysis. ENIGMA has enabled researchers to perform cross-disorder analysis—for example, data from 13,504 patients and 21,146 controls were used to compare subcortical volume across disorders. There are collaborations between TBI and other disorders. The Stroke Recovery Work Group has focused on semi-automated processing of damaged brains, which is relevant to TBI.

Three subgroups of the ENIGMA Brain Injury Work Group address military brain injury, pediatric moderate-to-severe TBI, and sports concussion. Dr. Dennis presented preliminary results from the

military brain injury subgroup, in which pooled data from four sites obtained a significant effect size, which only one site would have obtained on its own. During the discussion, participants recommended formation of a collaboration between the InTBIR Neuroimaging Work Group and the ENIGMA Brain Injury Work Group.

International Human Epigenomic Consortium (IHEC)

Dr. Eric Marcotte

IHEC grew out of the Human Genome Project with the goal of generating reference maps of human epigenomes for key cellular states relevant to health and disease. Although it was built on the model that one partner would provide centralized data access and analysis, that never happened, and data was produced faster than anticipated. To address this issue, the Canadian Institutes of Health Research funded data centres, leveraged additional resources, and developed a mechanism for data centralization. A functioning IHEC data portal makes all the data appear as though it were in one place, although it is scattered around the world. IHEC has controlled access to the raw genetic data, but the hundreds of terabytes of transformed data are public.

IHEC coordinated a release of papers consisting of 41 publications in *Cell* and other high-impact journals. Cell Press built a custom portal for this collection that integrated with the IHEC portal. The marker paper lists the co-chairs as first author and last author, and “The IHEC consortium” (240 members) as the middle author, and is encoded so that PubMed has all the names but only two people must sign off on the manuscript. IHEC also negotiated open access for all the *Cell* papers at no cost. The ability to do this may vary with the journal. It may be time for funders, journals, and PubMed to work together to find new ways to recognize authors and contributors.

5 Years On: Communicating InTBIR’s Current Successes and the “Big Picture” Looking Ahead

European Commission

Dr. Stephane Hogan

Within the European Union, CREATIVE and CENTER-TBI contribute to InTBIR. The European Parliament has embraced InTBIR as the model for its global initiative on epilepsy research. Dr. Hogan recommended that InTBIR strengthen infrastructure, deliver pilots, and fully implement its data sharing strategy. In addition, InTBIR should consider widening its scope by integrating other institutions and/or countries as well as related diseases, such as epilepsy. Starting in 2018, the European Commission will fund a platform titled “Coordinating European brain research and developing global initiatives,” which could include, for example, cross-country data sharing. Priorities are being assigned for 2021. It will be essential to explain to leaders of the member states what this research delivers to their citizens.

Canadian Institutes of Health Research (CIHR)

Dr. Eric Marcotte

CIHR has a broad mandate to fund extramural research through its 13 institutes. Research on TBI is a major funded activity of the Institute of Neurosciences, Mental Health, and Addiction. A key national health priority is a pan-Canadian concussion strategy, which has driven development of a mobile app and video on concussion (Parachute Canada). CIHR expects its major TBI funding focus in the coming years to be in the concussion space. CIHR's focus with respect to the current InTBIR is to resolve issues related to data. In a similar case, CIHR helped solve a data-sharing crisis in the IHEC consortium. In the absence of dedicated funding, the IHEC research groups leveraged their resources in a creative way to build a data portal. As a result, funders became supportive of efforts that enhanced the portal's activities. In a similar vein, if InTBIR could demonstrate that it has found a partial solution for data sharing, then it might be able to free up additional funds.

One Mind for Research

Gen. Peter Chiarelli

With an interest in TBI and posttraumatic stress disorder and an unrelenting patient focus, One Mind emphasizes data quality and data sharing, big science, and multi-institutional collaboration. It de-emphasizes the primacy of peer-reviewed journal articles in favor of successful coordination with the FDA to generate better diagnostics, treatments, and cures.

Noting that problems with data curation, data sharing, and funding were discussed at the third InTBIR conference, Gen. Chiarelli asserted that the larger issue is a dysfunctional research system. Most people, including donors, believe that a direct line exists from bench science to translational science to bedside application. In reality, it may take a decade for medical professionals to accept new approaches if dissemination is poor. For example, the BrainScope One system—which cost more than \$20 million to develop—was approved by the FDA 1.5 years ago to diagnose concussion on the battlefield, but not one has been deployed for that purpose. Researchers need to stress the importance of data curation, storage, and analysis to producing breakthroughs. They also need to talk more about what does not work, in addition to what works.

Department of Defense (DoD)

Lt. Col. David Johnston

From the DoD perspective, two scenarios are likely to dominate in the future: small teams dispersed in remote locations and a dense urban environment during war or humanitarian disaster. The DoD plans to target its continued investment in the TBI field to deliverables and focused, hypothesis-driven research. Researchers need to better communicate their work to national leaders who are not scientists. When speaking with decision makers, Lt. Col. Johnston is expected to show a tangible goal, such as a device that can save lives in the battlefield, along with indications that progress toward achieving that goal is being made.

Every researcher must be responsible for quality control of their own data, which should be an explicit requirement in future Requests for Proposals (RFPs). Although the DoD supports linking data to enable changes to clinical practice guidelines based on the research, convincing decision makers to pay for data curation can be difficult. Regarding deliverables, InTBIR could help the entire community by developing a new classification scheme for TBI, which could be published as a consensus statement.

This statement would enable the government to modify its RFPs to request studies associated with particular pathophysiologies. For example, as pulse sequences for MRI are refined to look at different aspects of the injury, a better classification scheme might enable identification of pulse sequences that differentiate among various types of TBI.

Ontario Brain Institute (OBI)

Dr. Elizabeth Theriault

Upcoming funding opportunities for TBI in Canada include a federal Network of Centres of Excellence as well as a Canadian Open Neuroscience Platform competition funded by Brain Canada, with OBI and Brain-CODE as key players. OBI applied for renewed funding 2018-2024 and included a new program in concussion, the CONNECT Integrated Discovery Program (IDP), that spans preclinical to acute, post-acute, and long-term disease, including CTE.

OBI built the Brain-CODE informatics platform based on open-source data capture tools. Brain-CODE has a deeply phenotyped dataset of patients with neurological diseases and disorders collected from more than 40 research institutions in Ontario, British Columbia, Alberta, and Quebec, with data-sharing across the five IDPs. To facilitate comparisons across diseases, core demographic and clinical CDEs are collected across all IDPs, including standardized assessments across the life-span of quality of life, medical and psychiatric co-morbidities, as well as clinical outcome measures of depression, anxiety and sleep. Researchers have access to automated quality assurance/quality control pipelines. An extensive subject registry and ethics tracking are used to filter data query requests from investigators. The Brain-CODE database has enabled integration of several diseases by analysis over multiple modalities, including neuroimaging, clinical, genomics, and proteomics data. Brain-CODE is negotiating data sharing agreements with a variety of research networks and is a member of the NIH eRA Commons, which provides additional opportunities for collaboration and federation.

National Institutes of Health (NIH)

Dr. Walter Koroshetz

In fiscal year 2016, the NIH TBI portfolio was more than \$100 million, and 12 percent of grants were funded. Of these, 47 percent were for basic disease research, 20 percent for clinical research, 19 percent for clinical trials, and 14 percent for CER. Commercial entities will build on the science and make the products.

Data from all TBI studies are compiled in the FITBIR database, with tremendous effort applied to quality control. The Neurological Emergencies Treatment Trials network has served as a useful tool to conduct acute TBI trials. NINDS and the National Heart, Lung, and Blood Institute have formed the even more powerful Strategies to Innovate Emergency Care Clinical Trials Network (SIREN), which DoD is poised to join. The first new trial under SIREN will test hyperbaric oxygen treatment for brain injury in acute TBI. Additional NIH activities relevant to TBI research include the BRAIN 2025 initiative, which is building a brain circuit diagram, so that in 5-10 years it may be possible to map the affected cells in a patient with TBI. Other NIH efforts include a new program to move biomarkers from discovery to validation to industry, and NIH's intramural program is following TBI patients, as well as studying

pediatric concussion and CTE. NIH also hosted a workshop to focus on TBI issues specific to women, held December 2018.

Discussion

Despite the opportunities afforded by big data, inadequate funding for data curation and analysis remains a major barrier to success. InTBIR researchers have assembled the beginning of a rich and very deeply phenotyped database that represents years of effort and considerable amounts of money, and now they need the resources to interrogate it. In addition, as a large, long-term project, the Living Guidelines will also require significant funding. DoD and NIH representatives noted that their funding for data curation will run through FITBIR. In Europe, it is more difficult to earmark money and garner long-term commitments.

Session 6: Smart Goals and Milestones for 2018

Reflections from InTBIR Scientific Advisory Board

Leaders from TRACK-TBI and CENTER-TBI were asked to discuss their productivity to date and what they need to move forward.

CENTER-TBI

Dr. Andrew Maas

CENTER-TBI has three pillars. The first pillar, provider profiling across the 20 European countries, has already led to five publications in high-impact journals, with three more submitted. The second pillar is an observational study. The protocol has been published, but results will not be published until all data have been collected and curated. The third pillar is optimization of existing evidence through reviews. Researchers have published three LSRs and five traditional systematic reviews, as well as four general review articles in *Lancet Neurology*. An entire commissioned issue of *Lancet Neurology* is forthcoming. As of mid-October 2017, CENTER-TBI has produced 42 publications.

TRACK-TBI

Dr. Geoff Manley

TRACK-TBI was formed to overcome the problem of insufficiently powered sample sizes. Researchers have collected data on 2,500 of 3,000 targeted subjects. They have carved out cohorts (e.g., those with MRI data) to enable analysis of subsets before all data are collected. They have also written papers on lessons learned, including best practices for measuring outcomes and standardization of diffusion weighted imaging.

The TRACK-TBI pilot study is still generating results from its data collection, which ended 4-5 years ago: 30-40 papers have been produced from 600 subjects. Researchers are writing foundational papers, including a recently accepted study validating the feasibility of using a test battery to phenotype the functional deficit. More papers on biomarkers, Phase I MRI, and pediatric TBI are forthcoming. As the data from TRACK-TBI are cleaned up, the pace of publications will increase rapidly over the next several years.

Post-Breakout Session Reports from the Work Groups

Policies Work Group

Co-Chairs: Drs. Joanne Fleming and Isabelle Gagnon

Informed Consent Policy

The Policies breakout group discussed several topics, most notably separate consent to agree to sharing data with industry. Patients may be less likely to give consent to industry, although this may be a problem that can be addressed with careful wording. Draft language should be broadly circulated to representatives from each country for feedback and detailed recommendations.

Publication and Authorship Guidelines

Discussion of the Publication and Authorship Guidelines included the parameters for InTBIR studies that must comply with the publication policy. For example, is a secondary analysis of TRACK-TBI data an InTBIR study and therefore subject to the policy? Once in place, a policy becomes a governance issue that must be managed by a publication committee. In addition, authorship will depend on who is really contributing data to a specific analysis, so the composition of “InTBIR group” needs to be flexible. Funding partners rely on publications as a sign of productivity, but credit should be assigned in a meaningful way. Perhaps InTBIR authorship should be limited to publications that include methods and not data analysis. These issues require further consideration and broad input. Importantly, publications carrying the InTBIR logo serve as a legacy of the groundbreaking work of the InTBIR Initiative in the field of TBI.

Data Sharing Policy

It has become clear that data will not be pooled at a single shared location. Therefore, InTBIR must design a policy for accessing and analyzing data that lives behind firewalls at various federated sites. This effort will depend on harmonizing the data behind the firewalls and therefore overlaps with data analytics, in which case the focus of the policy will be less on data sharing itself and more on how to send the data and in what form.

Data Management Work Group

Co-Chairs: Drs. Lindsay Wilson and Tony Fabio

The Data Curation subgroup surveyed InTBIR studies to determine their data curation processes and protocols. None of the projects has a study manual specifically covering data curation. Given the enormous burden of data curation for many InTBIR projects, in terms of both volume and complexity of data, the breakout group identified the following priorities:

- Follow up on the Data Dashboard work to visualize summary data from projects.
- Collate data management manuals and protocols from InTBIR studies and DoD projects and make them available for sharing.
- Describe a framework for TBI data management and curation, producing a publication on the management of complex datasets in the context of TBI.
- Hold a consensus conference on data curation/harmonization, perhaps in the spring of 2018.

- Develop guidelines for TBI data curation, perhaps along the same lines as Consolidated Standards of Reporting Trials (CONSORT), as a long-term goal.

Data Analytics Work Group

Co-chairs: Drs. Steve Wisniewski and Hester Lingsma (presented by Dr. Ewout Steyerberg)

The Data Analytics Work Group plans to complete a series of methods papers for a supplement in the *Journal of Neurotrauma* in spring 2018. In addition, it will develop two overarching CER questions, one for pediatrics and one for adults. Data will be analyzed in a two-stage approach, first analyzing each study locally and then pooling the results into a meta-analysis. This can be done within a year and should satisfy the purpose of sharing knowledge while circumventing legal and technical aspects of sharing data. There is no or only a trivial statistical penalty for doing a two-stage approach.

Biomarkers Work Group

Chair: Dr. Ramon Diaz-Arrastia

The Biomarkers Work Group developed a series of “shovel-ready” projects that will move the field forward, can be done over the next 2-3 years with material and data that have already been collected, and require international collaboration. The first is the Genetic Association in Neurotrauma Initiative—a \$5 million project to perform GWAS on about 13,000 subjects with DNA and high-quality phenotypic data available. Patients span the spectrum from concussion through severe TBI. TBI needs a GWAS study, which should be high priority and may require multiple funding sources. An NIH biorepository could potentially house the samples, and there may be opportunities to collaborate with intramural investigators.

The second project would develop rigorous population-based normative standards throughout the lifespan. Dr. Cheryl Wellington has data from a pediatric cohort along with permission to examine a large lifespan cohort through age 79, which would require about 5,700 samples and 4-6 biomarkers. The third project would create a pool of biological samples to use as a calibration standard for investigators developing novel assays. The fourth project would create a registry of all biomarker studies done across InTBIR, enabling researchers to identify which biomarkers work best for which purposes. The fifth project would create an infrastructure for sharing biomarkers data.

Neuroimaging Work Group

Co-chairs: Drs. Stephen Strother and Pratik Mukherjee

On the data acquisition side, one deliverable in progress is creation of an inventory of MRI imaging as performed by the major TBI studies, including details of the sequence parameters being acquired. Once this work is completed and the data are cleaned, researchers will be able to apply the same data analysis methods to each of these studies to assess how the variability in sequence parameters across studies affects the precision of the various imaging biomarkers of interest. This analysis should indicate how data from each modality may be combined across studies and inform best practices for future studies. Challenges arise from the constant innovation in technology. Another challenge is making these data interoperable, to enable comparison across countries and to study diverse clinical applications.

Regarding analytics (the processing pipeline), this work group would like to partner with ENIGMA, which has a fledgling TBI group and plans to move its data into GWAS. InTBIR should get these scripts, though finding a high-performance computing environment to run them may be a challenge. Canada might serve as a neutral third party for data analysis, so that European data need not go to the United States and vice versa.

Closing Remarks

In closing remarks, Dr. Koroshetz expressed his desire to see InTBIR supported by a structure, leadership, and processes that would make it even more productive. There is great potential for international collaboration and funding. For example, an R24 grant might support creation of a publicly available resource of GWAS results on 13,000 samples. Intramural researchers can contribute significant resources and expertise to this effort. Lt. Col. Johnston mentioned the overlapping interests in TBI among diverse sectors, including defense, sports, industry, humanitarian assistance, and disaster relief. DoD's requirements are particularly acute and would favor innovations that help to diagnose and stabilize soldiers in far forward environments. Researchers need to communicate success to the public, policy makers, and funders in a way that includes the human dimension.

Appendix A: Agenda

Monday, October 30

7:30 Registration

8:20 Welcome and Opening Statements (10 min each)

- Dr. Walter Koroshetz, Director, NINDS Col Mike Davis, Director, DoD/JPC-6
- Dr. Tom Mikkelsen, President, Ontario Brain Institute

Session 1: 2017 InTBIR Work Group Progress Reports and Deliverables

8:50 Moderator: Dr. Steve Wisniewski; Coordinator: Dr. Elizabeth Theriault
(10 min presentations & 5 min Q&A)

9:00 Dashboard of InTBIR Data – Co-Chairs: Drs. Tony Fabio and Jeff Grethe

9:15 Catalog of Biospecimens – Chair: Dr. Ramon Diaz-Arrastia

9:30 Catalog of Neuroimages – Co-Chairs: Drs. Pratik Mukherjee and Stephen Strother

9:45 InTBIR Data Analytics – Co-Chairs: Drs. Hester Lingsma and Steve Wisniewski

10:00 Break

10:15 InTBIR Policies (a) – Co-Chairs: Drs. Joanne Fleming and Isabelle Gagnon

10:30 InTBIR Policies (b) - Group Authorship and Academic Credits (panel discussion)

Session 2: The Good, The Bad, and the Reality: 2017

10:45 Moderators: Drs. Andrew Maas & Geoff Manley; Coordinator: Dr. Mona Hicks

11:00 MRI Biomarker Letter of Support from FDA – Dr. Geoff Manley

11:15 Challenges and Solutions in Data Curation: Experiences from CENTER- and TRACK-TBI
(10 min presentations & 15 min Q&A)

- Center-TBI – Dr. Andrew Maas
- TRACK-TBI – Dr. Geoff Manley
- Data Curation Guidelines – Dr. Ari Ercole

12:00 Lunch (on your own with option to buy lunch boxes)

Session 3: Informing Trials through Collaboration

13:00 Moderator: Dr. Jamie Hutchinson; Coordinator: Dr. Patrick Bellgowan

13:15 Clinical Trials from Design to Interpretation (20 min presentations & 25 min discussion)

- Managing Severe Traumatic Brain Injury (TBI) Without Intracranial Pressure Monitoring (ICP) in Pediatric Populations – Dr. Nancy Temkin
 - Brain Oxygen Optimization in Severe TBI Phase III (BOOST III) – Dr. Ramon Diaz-Arrastia
 - HEMoglobin Transfusion Threshold in Traumatic Brain Injury Optimization (HEMOTION) – Dr. Alexis Turgeon
 - Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT) – Dr. Michael Bell
- Discussion Points: Potential for international collaboration within trials, potential for

patient stratification, potential hurdles, advantages and disadvantages of international participation in clinical trials.

15:00 Break

Session 4: Living Guidelines for Global TBI

15:10 Moderators: Drs. David Menon and Roger Zemek, Coordinators: Drs. Mark Goldammer and Stephane Hogan

15:15 Lecture 1: Development of Quality Indicators for TBI – Dr. Hester Lingsma

15:45 Lecture 2: Challenge of International Guideline Development – Dr. Franco Servadei

16:15 Opportunities to Collaborate with Global Organizations for Living Guidelines Development (60 min panel discussion & 15 min open Q&A)

- American College of Surgeons – Dr. David Hoyt
- Brain Trauma Foundation – Dr. Annette Totten
- International Consensus on Sport Concussion – Dr. Kathryn Schneider
- TBI Living Reviews – Dr. Alexis Turgeon
- Living Systematic Reviews – Dr. Andrew Maas
- LABIC Guidelines Process – Dr. Randy Chesnut

17:30 Adjourn

18:00 No host “happy hour” at Marriott Hotel

Tuesday, October 31st

8:00 Welcome Back – Goals for Day 2

Session 5: Reducing the Global Burden of TBI

8:10 Moderator: Dr. Guido Bertolini; Coordinator: Dr. Eric Marcotte

8:15 Insights and Opportunities from Other International Collaborations (40 min panel discussion; 20 min Q&A)

- International Rare Disease Consortium – Dr. Adam Hartman
- Wings for Life – Dr. Jan Schwab
- ENIGMA – Dr. Emily Dennis
- IHEC – Dr. Eric Marcotte

9:15 Break

9:45 5 Years On: Communicating InTBIR’s Current Successes and the “Big Picture” Looking Ahead: “how can each organization contribute their unique resources to coordinate and advance the InTBIR mission?” (~10 min summaries from each funding organization followed by 60 min open discussion)

- European Commission – Dr. Stephane Hogan
- Canadian Institutes of Health Research – Dr. Eric Marcotte
- One Mind for Research – General Peter Chiarelli
- Department of Defense – Dr. Alicia Crowder
- Ontario Brain Institute – Dr. Elizabeth Theriault

- National Institutes of Health – Dr. Walter Koroshetz
- 11:45 Lunch (on your own with option to buy lunch boxes)
- ad hoc InTBIR Scientific Steering Committee Meeting
 - ad hoc InTBIR Scientific Advisory Board Meeting

Session 6: SMART Goals and Milestones for 2018

- 12:50 Moderator: Dr. Kent Bassett-Spiers; Coordinators: Drs. Alicia Crowder and Carol Taylor-Burds
- 13:00 Reflections from InTBIR Scientific Advisory Board (30 min panel discussion)
- 13:30 Work Group Breakout Sessions (75 min discussions)
- Reflections and discussions about current challenges and opportunities, and creation of SMART goals for 2018 (ISAB and ISSC members are invited to join workgroup breakouts)
- 14:45 Break
- 15:00 Reports from the Working Groups (10 min presentations with 5 min Q&A)
- Policies – Co-Chairs: Drs. Joanne Fleming and Isabelle Gagnon
 - Data Management – Co-Chairs: Drs. Lindsay Wilson and Tony Fabio
 - Data Analytics – Co-Chairs: Drs. Steve Wisniewski and Hester Lingsma
 - Biomarkers – Chair: Dr. Ramon Diaz-Arrastia
 - Neuroimaging – Co-Chairs: Drs. Stephen Strother and Pratik Mukherjee
- 16:15 InTBIR Closing Statements and Adjournment: Dr. Walter Koroshetz and Col Mike Davis
- 16:30 InTBIR Executive Committee Meeting (90 min closed meeting)