Summary Report
3rd International Initiative for Traumatic Brain Injury Research (InTBIR) Meeting
"Sowing the Seeds for Synergy"
San Francisco, CA
June 28 - 29, 2014

Background

The International Initiative for Traumatic Brain Injury Research (InTBIR) is a unique consortium of funding agencies from the European Union, Canada and the United States that supports collaborative international research to reduce the global burden of traumatic brain injury (TBI) by 2020. InTBIR has invested over $90M USD in TBI research since 2012 to examine how patient characteristics, injury characteristics, and treatments influence clinically meaningful outcomes. To facilitate collaboration across the studies, the InTBIR consortium hosts an annual meeting. The first meeting was held in Brussels in November 2011 where the focus was on practical considerations for developing and linking research initiatives across the consortium. The second meeting was held in Vancouver, Canada in October 2013 to present an overview of the newly funded projects and introduce the teams of investigators. The focus of the third InTBIR meeting in San Francisco in June 2014 was on ways to promote synergy. A series of sessions during this meeting provided a forum for discussing ways to acquire, share, and analyze the TBI research data across the spectrum of age, injury severity, and time (acute to chronic), requisite steps for enabling synergy across projects. The following is a summary of the meeting, the agenda and a list of participants.

3rd InTBIR Meeting San Francisco, June 2014

The meeting began with a review of the recommendations from the previous InTBIR meeting followed by 'flash presentations' from the EU, Canadian and American principle investigators that described progress to date, challenges and use of common data elements (CDEs). Overall, the progress during the 8 months since the Vancouver meeting was very impressive, both in terms of scientific progress and interactions among teams. The collaboration between CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in TBI and TRACK-TBI: Transforming Research and Clinical Knowledge in Traumatic Brain Injury was especially notable, with approximately 95% concordance of data elements between these two major studies. This is a tremendous accomplishment and highly responsive to the goals of the InTBIR consortium. In addition, good progress has been made in response to the International Scientific Advisory Board's (ISAB) recommendations from the previous meeting, including the development of a website for InTBIR (http://intbir.nih.gov/ and http://ec.europa.eu/research/health/medical-research/brain-research/international-initiative_en.html) and encouraging the use of Common Data Elements (CDEs) wherever possible. CDE resources are described on the InTBIR website under the "Resources" heading.

The second session consisted of a panel discussion on biomarkers, where the goal was to provide examples of progress and gaps in developing standard protocols, the use of CDEs in the collection of patient data and resources for fluid biomarker research that will meet industry and

regulatory standards and lead to the development of clinically useful TBI biomarkers by 2020. Some promising data were presented, but also data demonstrating great variability in results across biomarker studies (i.e., S100beta). The issues raised were important and it was recommended that an InTBIR Biomarker Subcommittee be formed to address them. In addition, it was recommended that the subcommittee review the TBI biomarker research landscape and publish these findings in a relevant journal. The review article would be informative across international studies and constitute an early deliverable from the InTBIR consortium.

The third session, dedicated to policies for sharing research data, provided an overview of The Alzheimer's Disease Neuroimaging Initiative (ADNI 2), given its potential to inform and guide the InTBIR consortium. ADNI 2 is in the second phase of an extensive public-private research partnership tasked with identifying biomarkers to detect Alzheimer's disease (AD). The landmark study has gathered and analyzed thousands of brain scans, genetic profiles and biomarkers in blood and cerebrospinal fluid, and *provides an open-source database for investigators around the world.* Additional presentations provided examples of other best practices in data sharing including the Rare Diseases Consortium and the International Human Epigenome Consortium, as well as an update on Federal interagency Traumatic Brain Injury Research Informatics System (FITBIR) data sharing policies. The pros and cons of "controlled" versus "open" data sharing were also debated, with excellent points made on both sides of the issue. One interesting suggestion was to focus on the questions that can best be answered by sharing data, rather than on the data sharing policies *per se*. In other words, give people a reason for sharing their data. Another suggestion was to create a library of case report forms (CRFs) and post them on the InTBIR website to facilitate standardization across projects. (Standard operating procedures would also be needed along with the Case Report Forms). With this background information in hand, the establishment of a subcommittee that includes representatives from the funding agencies, ISAB, and PIs to develop a data sharing policy for InTBIR within the coming year was recommended.

The fourth session consisted of a panel discussion on neuroimaging where the goal was to provide examples of progress and gaps in developing standard protocols, data elements and resources for neuroimaging studies that will lead to the development of clinically useful tools by 2020. The TRACK-TBI group proposes to use the ADNI protocol for structural MRI, with some minor modifications. They are also undertaking steps to calibrate the MRI scanners across centers and manufacturers using Diffusion Tensor Imaging phantoms, something which has not been done before to this extent. The calibration study has the potential to significantly advance the field beyond the InTBIR projects, and could be another early deliverable for InTBIR. The formation of a subcommittee was also recommended for the neuroimaging experts.

The fifth and final session of the first day was a panel discussion on progress and issues related to federating the numerous InTBIR project databases to achieve the goal of a high quality, granular TBI database with 10,000 children and adults by 2020. The moderator and panelists represented experts from One Mind for Research, FITBIR, the International Neuroinformatics Coordinating Facility (INCF), and Quesgen. These key public and private organizations are already in communication and working collegially to address common goals and issues and

trying to build off of each other's projects rather than create something *de novo*. As the databases are still under development for most of the InTBIR projects, direct steps toward federation have not been undertaken. However, essential requirements for federation were identified and include: consent forms that allow for the use of the data for other research questions; defined data sharing policies; and use of common data elements whenever possible or well-defined unique data elements. It was also mentioned that high quality, raw data is where the most value lies because the analytical tools keep evolving. Nevertheless, some of the informatics systems will include analytical tools and making these accessible to the entire InTBIR projects would be a valuable resource.

The first session of the second day (Session VI) was devoted to satellite and related projects in other countries, with the objective of learning more about these studies and how they relate to ongoing InTBIR projects. The highly impressive research that was presented demonstrated the even greater potential for InTBIR to reduce the global impact of TBI through these potential collaborations with funding agencies in India, China and Australia. The general discussion revealed enthusiasm for expanding membership to other groups both public and private (e.g., One Mind, General Electric, Departments of Defense) that are willing to join InTBIR and adopt the mission, goals and protocols. A draft version of an InTBIR policy for adding new members is underway and should be further developed and reviewed for approval by the founding members in the coming year.

Session VII included presentations about some existing and potential InTBIR subprojects to stimulate ideas and momentum for additional collaborations. The TRACK-TBI and CENTER-TBI projects have been working diligently to coordinate their efforts, and in the process have identified some previously unrealized discrepancies in how the Glasgow Outcome Scale – Extended (GOS-E) is administered. This is an important discovery in itself and while it might be viewed as an issue, is actually an example of a discovery that should be seen as a success. The Canadian projects on pediatric TBI are all using the same case report forms (CRFs), which is highly impressive and will undoubtedly lead to knowledge unattainable by single studies. Ways to better integrate all the InTBIR pediatric studies with the adult studies would be valuable and should be encouraged. The InTBIR Quantitative Methods subcommittee is an excellent example of a collaboration focused on a timely and critical topic for the success of InTBIR. General principles should be drafted in this area, in order to set up the baseline for the whole consortium. A series of topics have been identified for collaborative manuscripts and will be another early deliverable for InTBIR. Four, exciting novel projects that could be advanced through InTBIR collaborations were also mentioned. To enable these collaborations, the formation of subcommittees is highly recommended, and breakout sessions for them should be incorporated into the next InTBIR meeting, which is tentatively planned for the latter half of 2015 in the EU.

Outcomes and Recommendations

The final session of the meeting provided a chance for the ISAB and the InTBIR funding agencies to give their reflections on the meeting and their recommendations for further progress, which included:

- There was uniform acknowledgement of the substantial progress made over the past 8 months. This is a new approach toward better interventions that is based on identifying causal factors from a prospective, observational study. The high level of work being done by the InTBIR investigators is impressive and ahead of other brain-related disease areas in many ways. There appear to be no major problems.
- The ISAB suggested that current goals and longer-term vision for InTBIR should be better articulated and communicated to all the relevant stakeholders, including the broader scientific community, private foundations, industry, and patients and their families. Adding a public site to the InTBIR website is one specific suggestion for enhanced communication. Successes need to be tracked and highlighted as part of this enhanced communication.
- The funding agencies recommended the formation of several subcommittees to enhance the mission of InTBIR, including for biomarkers, neuroimaging, data sharing and informatics. The sub-committee on data sharing should develop an InTBIR data-sharing policy.
- A recommendation from the ISAB was to designate a secretariat for InTBIR that organizes and coordinates ad hoc working groups and subcommittees, maintains the website, facilitates policy development and other activities that go beyond individual studies should be considered. (Note that currently the role of secretariat rotates among the funding agencies' programmatic staff and has been managed through monthly teleconferences and emails.)
- Implementation of the findings is essential to the success of InTBIR. To that end, the funding agencies recommend that the FDA and European and Canadian regulatory agencies should be invited to future meetings and encouraged to participate in other activities, as appropriate.
- The ISAB requested that their role be clarified in order to enhance their contributions to InTBIR.
- Another recommendation from the funding agencies was that individual studies should *cross-walk* their data elements with the *TBI Common Data Elements* and report back to InTBIR on the percent of common and the percent of unique data elements. This would provide an overview of the similarities and differences across the studies and essential for sharing data in the future.
- Individual studies will most likely find associations – and the funding agencies recommended that these could be corroborated by others. Investigators should therefore explore opportunities to identify similar findings across their studies. This is another example of an exceptional opportunity for InTBIR to accelerate knowledge on TBI.
- With respect to expectations for new members: the funding agencies reported that a draft version of a policy for adding new members is underway and should be further developed and reviewed for approval by the founding members in the coming year.

Agenda

Day 1

8:15 – 8:45 **Welcome**

Walter Koroshetz, Deputy Director, NIH/NINDS
Catherine Berens, Health Directorate, European Commission, DG Research and Innovation
Anthony Phillips, Scientific Director CIHR-INMHA

8:45 – 10:00 **Session I: Project Hot Topics: The Good, the Bad, and the Collaborative**

(Flash presentations, 5 min presentations using 4 slides. The goal is to report on progress, issues, and collaborative efforts since the October, 2013, Vancouver meeting)

- ISAB Recommendations from 2013 InTBIR Meeting – Sam Weiss (Moderator)
- TRACK-TBI – Geoff Manley
- CENTER-TBI – Andrew Maas
- TBI-Prognosis– Alexis Turgeon
- ADAPT – Mike Bell
- CREACTIVE – Guido Bertolini
- Managing severe TBI without ICP monitoring - guidelines development and testing – Randy Chesnut

10:00 – 10:15 Break

- Improving the diagnosis and treatment of mTBI in children and youth: the power of common data - Isabelle Gagnon
- Neurocare – Nick Reed
- Predicting and preventing post-concussive problems in pediatrics study – Roger Zemek
- Concussion Prevention in Youth Ice Hockey - A program of research in primary , secondary and tertiary prevention – Carol Emery
- Post-Concussive Syndrome in youth: GABAergic effects of melatonin – Karen Barlow

11:15 – 12:15 **Session II: Fluid Biomarkers – Protocols and Resources for InTBIR**

(30 min moderated panel discussion followed by 30 min open discussion. The goal is to provide examples of progress and gaps in developing standard protocols, data elements and resources for fluid biomarker research that will meet industry and regulatory standards and lead to the development of clinically useful TBI biomarkers by 2020)

- Moderator: Marie-Noelle Castel
- Panel members: Ramon Diaz-Arrastia, Jamie Hutchison, Alexis Turgeon, and Andreas Jeromin

12:15 – 13:15 Lunch

13:15 -14:15 **Session III: Neuroimaging - Protocols and Resources for InTBIR**

(*30 min moderated panel discussion followed by 30 min open discussion. The goal is to provide examples of progress and gaps in developing standard protocols, data elements and resources for neuroimaging studies that will lead to the development of clinically useful neuroimaging surrogate markers by 2020)*

- Moderator: Mike Weiner
- Panel members: Pratik Mukherjee, Pim Pullens and Ravi Menon

14:15 – 15:15 **Session IV: Resources for Sharing and Analyzing Data**

(*30 min moderated panel discussion followed by 30 min open discussion. The goal is to provide examples of progress and issues in developing and federating InTBIR research databases so that by 2020 we have high quality, standardized data on more than 10,000 children and adults with TBI and advanced analytical tools available to all of the projects)*

Moderator: Stephen Johnson

Panel members: Alison Garcia, Jeannette Soderberg and Mike Jarrett

15:15 – 15:45 Break

15:45 – 17:30 **Session V: Policies for Sharing Research Data**

(10 min presentations to provide examples of data sharing policies and procedures, followed by a friendly 30 minute debate about what might work best to advance the goals of InTBIR and a 30 min open discussion. The goal is identify a strategy and next steps for developing a fair and practical data sharing policy that meets international regulatory requirements and will advance the goals of InTBIR)

Moderator – Ravi Menon

- International Rare Disease Consortium Data Sharing Policy – Catherine Berens (10 min)
- FITBIR Data Sharing Policy – Mona Hicks (10 min)
- International Human Epigenomics Consortia Data Sharing Policy – Anthony Philips (10 min)
- Overview of the Alzheimer's Disease Neuroimaging Initiative – Mike Weiner (10 min)
- Pros and Cons of Open Access vs. Controlled Access – Mike Weiner and Randy Chesnut (30 min debate)
- Moderated discussion to inform the development of an InTBIR policy (30 min)

17:00 Day 1 Meeting Adjourns

Day 2

10:00 – 11:30 **Session VI: Satellite and other Related Projects**

(*10 min presentations and 5 min discussion, followed by a 15 min moderated discussion at the end. The goal is to learn of related projects and obtain input about how to expand the membership of InTBIR*)

Moderator – Walter Koroshetz

- Center TBI and China – Guoyi Gao

- Center TBI and Australia – Jamie Cooper
- Center TBI and India – Deepak Gupta
- Chronic Effects of Neurotrauma Consortium – Ramon Diaz-Arrastia
- Considerations for expanding membership – Elizabeth Theriault
- Moderated discussion (15 min)

11:30 – 12:30 **<u>Session VII – Development of Joint Projects</u>**

(30 min moderated panel discussion followed by 30 min open discussion. The goal is to provide examples of coordinated projects and to identify priorities and strategies for additional collaborations)

- Moderator – Sam Weiss
- Panel members: David Menon, Geoff Manley, Steve Wisniewski, Isabelle Gagnon

12:30 – 13:30 Lunch *(ISAB convenes to prepare summary reflections)*

13:30 – 14:30 **<u>Session VIII: Where do we go from here?</u>**

Moderator –Kent Basset-Spiers

- Reflections from the ISAB – TBN *(30 min)*
- Reflections from the InTBIR Members *(10 min each)*
  - **Catherine Berens,** Health Directorate, European Commission, DG Research and Innovation
  - **Anthony Phillips,** Scientific Director CIHR-INMHA
  - **Walter Koroshetz,** Deputy Director, NIH/NINDS

14:30 **Meeting adjourns**

14:45 – 16:00 **InTBIR Members Forum** *(closed session)*

PARTICIPANT LIST

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