Medical Device Connectivity Challenges Outline the Technical Requirements and Standards For Promoting Big Data Research and Personalized Medicine in Neurocritical Care

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ABSTRACT Brain injuries are complicated medical problems and their management requires data from disparate sources to extract actionable information. In neurocritical care, interoperability is lacking despite the perceived benefits. Several efforts have been underway, but none have been widely adopted, underscoring the difficulty of achieving this goal. We have identified the current pain points of data collection and integration based on the experience with two large multi-site clinical studies: Transforming Research And Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) in the United States and Collaborative European Neuro Trauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) in Europe. The variability of measurements across sites remains a barrier to uniform data collection. We found a need for annotation standards and for a standardized archive format for high-resolution data. Overall, the hidden cost for successful data collection was initially underestimated. Although the use of bedside data integration solutions, such as the Moberg's Component Neuromonitoring System (Moberg Research, Inc., Ambler, PA, USA) or ICM+ software (Cambridge Enterprise, Cambridge, UK), facilitated the homogenous collection of synchronized data, there remain issues that need to be addressed by the neurocritical care community. To this end, we have organized a Working Group on Neurocritical Care Informatics, whose next step is to create an overarching informatics framework that takes advantage of the collected information to answer scientific questions and to accelerate the translation of trial results to actions benefitting military medicine.

INTRODUCTION

Neurocritical care is the medical discipline that deals with complex neurosurgical, neurological, and systemic complications in critically ill patients who suffered acquired brain injuries, such as traumatic brain injury (TBI). In the United States alone, TBI accounts for 2.2 million emergency department visits each year, with 280,000 hospitalizations and 50,000 deaths.[1] The cost for brain-injured patients is approximately $76 billion yearly[1] and highest when patients have poor outcomes that require prolonged rehabilitation. In the military, over 350,000 soldiers have been affected by TBI since 2000,[2] and this number is likely underreported due to the difficulty in diagnosing mild head injury.

Emergency and critical care in the initial hours and days after brain injury can make a significant difference in patient outcome and overall health care costs; optimizing management in this therapeutic window is therefore of high importance. To this end, neurocritical care largely focuses on both preventative measures and careful neuromonitoring aimed at intercepting and treating impending secondary brain injury to improve neurologic outcomes.[3] Despite this therapeutic intent, the past 30 yr have not yielded a single successful therapeutic trial for TBI,[4] most likely due to the patient-specific nature of these brain injuries. Although there is some evidence of promise in many of the attempted approaches, their effect size is drastically reduced by the lack of homogeneity within the clinical groups of interest. A much more sophisticated stratification of TBI patients would allow targeting specific subgroups for which given approaches might be effective. Researchers and key opinion leaders have come to the realization that detailed and potentially quantifiable phenotyping of patient information is necessary to improve the stratification and, thus, the management of these patients.[4–6] Several multi-site research studies (Transforming Research And Clinical Knowledge in Traumatic Brain Injury [TRACK-TBI], Collaborative European Neuro Trauma Effectiveness Research in Traumatic Brain Injury [CENTER-TBI], Development and Validation of Spreading Depolarization Monitoring for TBI Management [SDII], BOOST3, The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy [EpiBioS4Rx], and others) are ongoing or pending as part of funded multi-center research to characterize the multifaceted and highly dynamic nature of brain function post-injury. These studies aim at gaining a better understanding of the neurophysiological underpinnings of the injured brain and, in order to do so, a diverse and extensive data set is recorded for each patient, including medical history, laboratory results,

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genomic testing, neuroimaging, and in many circumstances high-resolution temporal data. High-resolution temporal data allow to uncover relations between different physiological variables that would otherwise go unnoticed if using only the low-resolution data available through standard electronic medical records. An example is given by the relation between intracranial pressure and arterial blood pressure: by recording and analyzing how these variables change within seconds, valuable information is obtained about the brain's ability to autoregulate.

Multi-modality monitoring (MMM) offers dynamic context-specific information heretofore scarce or unavailable in large-scale research: measures of duration and severity capable of quantifying neurologic metrics accrued over time (e.g., intracranial pressure), information regarding early treatment response (e.g., seizures), and correlative information about the impact of bedside care strategies (e.g., sedation interruption).[7] Parameters recorded during MMM include those traditionally collected in medical intensive care units (electrocardiography [ECG] and telemetry), arterial blood pressure (ABP), respiratory and ventilator parameters, and temperature, supplemented by an often large number of neurophysiologic parameters more specific to brain injury, ranging from electroencephalography (EEG), intracranial pressure (ICP), brain oxygenation, and cerebral blood flow to brain metabolic markers.[8–11] For some of the monitored parameters, their overall trend over time is sufficient to obtain relevant insight about the patient's status: for example, the patient's temperature can be measured at discrete intervals. Other variables, like scalp and depth electroencephalography, ECG, ABP, and ICP among others, contain complex waveforms distributed over a wide range of frequencies (up to hundreds of hertz), and which afford useful physiological information when recorded, stored, and analyzed at the highest available resolution.

Data collection and integration in large multi-center research studies, however, have historically proven to be a more difficult and expensive task than anticipated. Multi-modality monitoring data and other contextual clinical information are provided by a variety of sources and their formats can vary widely between different sites, for example, because of different source devices, different electronic medical records, or different therapeutic protocols. Poor medical device connectivity is the first barrier to the creation of consolidated patient data records, where all data sources are integrated. A recent survey of the status of medical device connectivity in neurocritical care found that device communication protocols are often proprietary, poorly designed, and undocumented.[12] However, seamless data collection would reduce the often overlooked costs of creating *ad hoc* infrastructures for each clinical study. The purpose of this manuscript is to identify the major pain points of data collection and management as experienced during large neurocritical care observational and interventional clinical trials, in order to raise awareness both in the scientific/clinical community and in the funding agencies.

METHODS

We examined the pipeline of data collection and integration in clinical studies in two currently underway studies of traumatic brain injury: TRACK-TBI in the United States[13] and CENTER-TBI in Europe.[14] They are multi-site longitudinal studies that will collect comprehensive data from a total of over 8,000 patients spanning the continuum of brain injury severity, with the objective of refining patient stratification and, therefore, improving targeted management. The collected data includes genomic, imaging, physiological, and phenotypic information, as well as pre- and post- psychometric testing. Collection of high-resolution data is being performed using Moberg's Component Neuromonitoring System (CNS Monitor) (Moberg Research, Inc., Ambler, PA) at 7 of the 11 sites participating in TRACK-TBI (Fig. 1) and at 11 of the 21 CENTER-TBI sites and using the ICM+ software (Cambridge Enterprise, Cambridge, UK) at 12 of 21 CENTER-TBI sites (including three sites using a combination of both solutions) (Fig. 2). The CNS Monitor is an FDA-cleared medical device that connects to vital sign monitors and other monitors present in a neurocritical care unit to synchronize, store, analyze, and display multiple parameters. Data capture from external monitors is achieved through direct connection (through cable) or via the hospital network. Continuous EEG data are collected via an amplifier connected directly to the product. Data can be exported at the end of the monitoring session for each patient or incrementally archived to a central server if the CNS Monitor is connected to the hospital network. Additionally, the CNS Monitor allows to review and further analyze the collected data in real time or prospectively.

Our group was directly involved in the setup and support of the data collection at each of the participating sites. Each site presented unique challenges in terms of data connectivity, therefore limiting our ability to perform a systematic analysis. However, we prospectively categorized the recognized challenges in broader groups. These groups represent the major pain points of data collection, management, and sharing in multi-center trials that focus on the collection of high-resolution data in neurocritical care.

RESULTS

By working closely with the investigators in both studies, we have identified challenges that have either hindered the progress of the trials or that have required a considerable amount of resources; we also outline the benefits of enhanced interoperability for these trials. Overall, the main barriers encountered in the data collection and management phases of the studies stem mostly from poor connectivity between data sources and from the overall lack of standardization. Seven main obstacles were identified.

1. The electronic medical record system versions in practice did not enable collection of full-resolution waveforms from data sources in neurocritical care units.

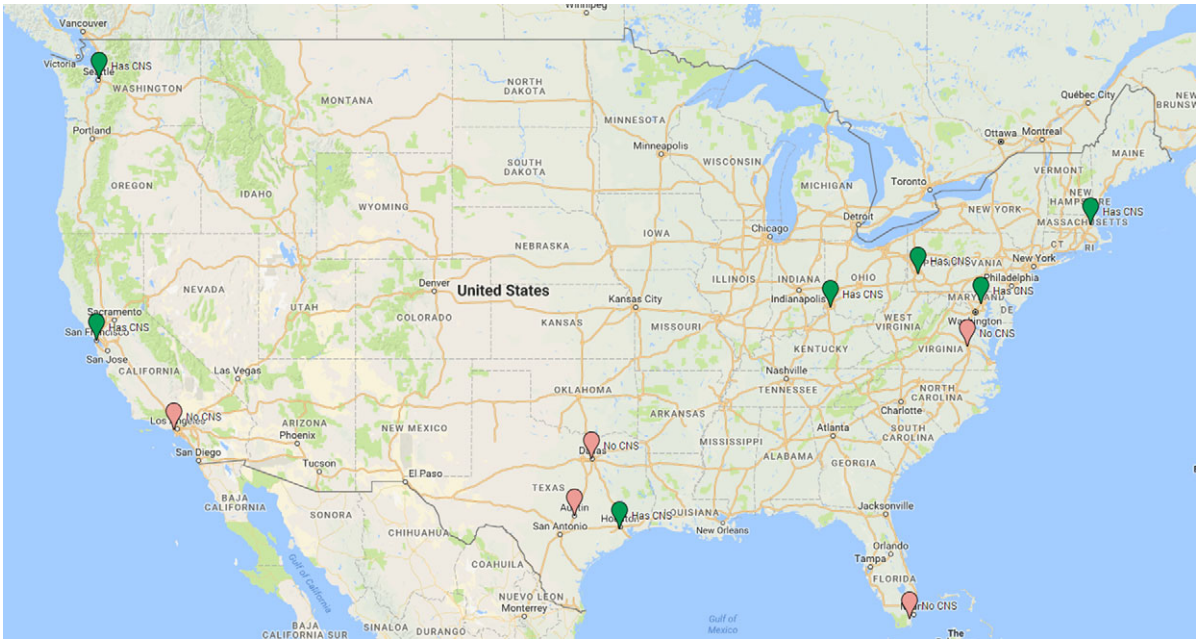

FIGURE 1. Locations participating in the TRACK-TBI study for the collection of high-resolution data. Locations using the Moberg CNS Monitor are marked in green.

Collection of waveform resolution data necessitated the use of systems configured in parallel to the electronic health record, such as the Moberg CNS monitor (Moberg Research, Inc., Ambler, PA, USA), the BedMaster software platform (Excel Medical, Inc., Jupiter, FL, USA), or the ICM+ software (Cambridge, UK), which allow collection, time synchronization and integration of complete sets (i.e. high- and low-resolution data) available from multiple devices. However, when done on a case-by-case basis without full integration into the existing electronic health record, complexity was increased by requiring manual downloading and parsing of data elements, as well as decoding to a common data format. This task was usually performed by research associates, who needed to be trained and supervised by data scientists and/or software engineers that devised institution-specific solutions and procedures. A further challenge was that many of the medical devices could only serve one data collection system at a time, which meant that, with the electronic record system installed, access to the high-resolution data might be blocked.

2. Variability and availability of measurements and labels from devices across sites was a barrier to uniform data collection.

Depending on the source devices available at each research site, different sets of measurements were collected. These were generally recorded at variable resolutions based on the source devices (e.g., ICP can be recorded as a mean trend available at intervals of 1 s or 5 s or at full waveform resolution with the sampling frequency of 100 Hz or more). Some of the burden of managing site-to-site variability was lessened by using data integration platforms (such as the Moberg CNS Monitor, BedMaster platform, or the ICM+ software) designed following plug-and-play principles, therefore minimizing study start-up efforts.

The variability of source devices across sites was further compounded with the lack of a comprehensive, standardized nomenclature for data in neurocritical care; therefore, data streams that effectively measure the same physiological parameter can be recorded with different labels in different clinical sites.

3. No standard or clinical data elements were available for the annotation of contextual clinical events.

Records of clinically relevant events were high-value contextual data intended to be included as part of the patient data record for prospective and context-specific analyses. However, no standard terminology existed to label clinical events (e.g., administration of a specific dose of a given drug, nursing procedures, or clinical observations), introducing variability between records collected by different teams. This was addressed for CENTER-TBI, at least to some extent, by providing a multiple-choice bedside annotation tool offering a concise list of standard, predefined, relevant to the project events, but this solution was limited to one data collection platform without clear ability to be translated to other neurocritical care projects or for combining data from projects using different systems.

4. Data transfer was hindered where systems were not networked, requiring intensive resources and manual processes for delivering data on encrypted hard drives.

Seamless data transfer from the point of data collection to a central repository was recognized to be a key to ensure the availability of data to all researchers, so that it could be effectively used to answer scientific questions. However, unless the data collection and management system was used in routine

FIGURE 2. Locations participating in the CENTER-TBI study for the collection of high-resolution data. Locations using the Moberg CNS Monitor are marked in green; locations using the ICM+ software are marked in blue; locations using a combination of both solutions are marked in purple.

care, the systems were not connected to the hospital network due to the significant information technology overhead required: the connection of a new device to the hospital network requires that the local IT Department can allocate resources to the investigation of the new device from the cybersecurity perspective, that network ports are available and working in the rooms where the device will be used, that storage space is allocated in a centralized server for the data download, and that IT personnel is available to resolve potential support issues. This is an expensive and lengthy (3–12 mo) process, often incompatible with the timeline of a funded research study. Therefore, wherever data collection and integration systems were not connected to the hospital network, it necessitated manual data archiving and upload. This step could be performed either using external data storage devices or by transferring the data to an intermediate platform (e.g., a laptop) that would then provide a secure data transfer function to the central repository once connected to the network. Besides adding a step to the already cumbersome process of data acquisition, it increased the chances of data corruption or loss. In particular, when hard drives were chosen as the intermediate step in the data transfer, they necessitated an additional layer of encryption to prevent possible mishandling of protected health information.

5. The lack of a sharable archive format for high-resolution data has delayed data aggregation.

There is currently no standardized archive format for high-resolution data in neurocritical care, so every data aggregation solution creates a different custom format for the patient data record. However, existence of a standardized archive format would promote the development of tools for data management and analysis. A good example of the benefits of a standardized archive format is that offered by EEG: since the adoption of the EDF/EDF+ file format is widespread, data repositories and analysis software have been designed to support them, independently of the EEG platform used for data acquisition. In order to satisfy the requirements of CENTER-TBI project, a new format was created based on an open-source HDF5 framework for archiving ICU monitoring data.[15] The format has been successfully used to archive data from nearly 200 patients from 20 centers so far. The work within CENTER-TBI could be treated as a proof of concept and a foundation of future efforts to create a standard format for neurocritical care ICU data archiving and exchange. Other file formats such as Multiscale Electrophysiology Format, version 3 (MEF3),[16] have been developed to offer an open-source data format that is intuitive to read and resistant to corruption by virtue of being hierarchical and is capable of encoding high-resolution, multichannel data from physiologic monitors and EEG by virtue of being highly compressible.

6. The cost (time and resources) for successful data collection was often underestimated.

Because of the current status of medical device connectivity in neurocritical care and lack of standardized data formats, custom informatics infrastructures were created from the ground-up for each clinical study. This required significant infrastructure and effort that were beyond the funded budgets of the clinical trial. Tasks could be classified as development of interfaces to devices and/or electronic medical records as appropriate, outlining of standard operating procedures for the handling of data, annotation by trained personnel dedicated to the annotation, curation, harmonization, and synchronization by staff staging data for hosting a central repository, database maintenance and indexing, and development of a process for data queries.

7. Harmonization of neuromonitoring data across domains with clinical, imaging, biomarker, and outcome data required significant IT resources.

In addition to the high-resolution data collected in neurocritical care (e.g., EEG, intracranial pressure, and brain perfusion), information was of interest from the continuum of care before and after intensive monitoring. Data recorded on case report forms were available but lacked the detail of annotations or time stamping of medications often present in the electronic health record. There has not been the budgetary flexibility for developing a framework for harmonizing MMM physiologic

data with disparate discrete data sources, such as imaging or imaging, surgical, pathology, or neurophysiology reports, analysis of serum biomarker data, or short- and long-term outcome measures.

DISCUSSION AND CONCLUSION

Currently, there is no seamless, unified, data pathway for the collection, transfer, analysis, and archiving of high-resolution physiological data recorded in neurocritical care. Data of interest include EEG, ICP, and blood pressure waveforms, and other data not found at an adequately high resolution in the electronic medical record. Recording these data is becoming highly significant not only in clinical trials but also in the precision management of patients with brain injuries. For example, analyses of patterns hidden within the full-resolution waveforms of intracranial pressure have been shown to reveal information about the state of cerebral volume compensation and cerebral hemodynamics,[17] which in turn offer means of establishing individual, and dynamic, targets for personalized acute medicine.[18,19]

However, interoperability of both medical devices and data is largely lacking in neurocritical care, despite the perceived benefits to patient care and to data collection and management in multi-center research. This report focuses on our experience with device connectivity and informatics in the context of two large multi-site studies.

Overall, a seamless, harmonized path for data collection and analysis would boost the success of large studies, which require data from a variety of disparate sources. The added costs of creating of *ad hoc* informatics infrastructures to overcome poor interoperability would be minimized and the resources now dedicated to that could be re-directed to other scientifically and clinically relevant tasks. Additionally, improved medical device connectivity and interoperability with the electronic medical record systems would enable the creation of more complete data sets without a duplication of efforts. Last but not least, standards to guide measurement nomenclature, annotation terminology, and archive format are recognized as a high priority and would facilitate the collection, curation, and sharing of comprehensive and rich data sets.

Although the use of the Moberg CNS Monitor, BedMaster, and ICM+ software platforms has successfully facilitated the uniform collection of synchronized data across sites, there remain issues that need to be addressed primarily by the neurocritical care community. Several efforts have been underway for the past decade to create a standardized, integrated architecture for medical information communication. None have been widely adopted, underscoring the difficulty of achieving this goal. Different medical disciplines have different needs and developing an all-encompassing architecture has proven to be an arduous process. In addition, neurocritical care is still underrepresented in the groups designated with the task of developing new medical information communication standards and its needs have largely gone overlooked. In order to overcome this, neurocritical care organizations should lobby with medical device manufacturers for the adoption of available standards instead of the creation of proprietary formats. In addition, researchers planning new clinical trials should carefully map the envisioned flow of data from the patient all the way to the data repository and to the data scientists analyzing the collected data. Procedures for data handling should be designed ahead of the proposal submission, as it is done for biological samples.

We have approached this problem with a "bottom-up" needs assessment by focusing on requirements for neurocritical care data integration, encoding, synchronization, transfer, storage, and analysis that can be solved with an integrated informatics platform, rather than starting "top-down" by developing an all-encompassing standard. Our premise is that this approach will translate lifesaving technology to critical care within military medicine faster than waiting for standards to be developed. To this end, the Working Group on Neurocritical Care Informatics (www.SmartNeuroICU.org) was established in 2015 to gather clinical leaders, researchers, and medical device manufacturers to facilitate the advancement of the field. The first achievement was the release of Recommendations for Medical Device Connectivity, where best practices in the design of device communication protocols are outlined. The next goal is the release of recommendations aimed at investigators planning clinical trials and funding agencies, in order to raise awareness about the core importance of proper planning for the collection and management of high-resolution data in neurocritical care. The overarching goal is the creation of a conceptual informatics framework that promotes efficient clinical trials and collaborative research. This framework will facilitate the identification of required resources and site-specific requirements for physiological data collection in future multi-center clinical trials. Uniformity of data in the continuum of care, from combat to hospital to rehabilitation, will be achieved through standardized nomenclature and data annotation and it will be valuable in remote monitoring of physiology and telehealth for troops in forward care facilities. Optimized data archiving will promote data sharing and will pave the way for the development of additional data analysis and visualization tools. Overall, this framework will accelerate discovery in the field of brain injury, to the benefit of both military personnel and civilians, and it will provide a platform for precision management.

PRESENTATION

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