GO Grant Handbook

Transforming Traumatic Brain Injury Research and Clinical Care

March 22, 2010

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I. INTRODUCTION

I-A. STUDY SITES AND CONTACTS

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I-B. ABSTRACT

Transforming Traumatic Brain Injury Research and Clinical Care

A Multi-Center Study:
University of California, San Francisco/San Francisco General Hospital
Mount Sinai Department of Rehabilitation Medicine/MSMC
University Medical Center at Brackenridge Hospital
University of Pittsburgh Medical Center

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Traumatic Brain Injury (TBI) remains one of the greatest unmet needs in medicine and public health. Advances in basic science research in the past 20 years have created new opportunities for targeted therapies for TBI. However, these advances have failed to translate into a successful clinical trial or a new treatment for TBI.

With broad-agency support, a multidisciplinary group of thought leaders was brought together to draft a proposal for standardization of data collection across TBI studies with an emphasis on demographics, neuroimaging, outcome measures, biomarkers, and psychological health, referred to as the TBI Common Data Elements (TBI-CDE). The global aim of this proposal is to test and refine standards for data collection in TBI studies, suitable for use across the broad spectrum of TBI (Aim 1), and to explore novel approaches for TBI classification (Aim 2) and outcome after TBI (Aim 3), making use of emerging technology. In addition, we aim to develop a pilot set of performance indicators for assessment of the health care quality and effectiveness in TBI (Aim 4).

Testing and validating the TBI-CDE will be performed in a multicenter observational study with three TBI Centers (UCSF/SFGH, University of Pittsburgh Medical Center, University Medical Center at Brackenridge Hospital) and a TBI Rehabilitation Center (Mount Sinai Rehabilitation Center), each of which has multicenter TBI research experience and existing infrastructure to rapidly and successfully complete the study. We will create or expand existing data repositories for patient demographics, neuroimaging, plasma biomarkers and genomics, thereby providing researchers and clinicians with the infrastructure to develop the TBI field in a concerted multidisciplinary effort. For the first time, the development of TBI specific performance indicators will be explored. Taken in combination, the deliverables of this project have the potential to transform TBI research and clinical care.

I-C. RESEARCH PLAN

RESEARCH AREA

Traumatic Brain Injury (TBI) is a field in medicine with one of the greatest unmet needs in medicine and public health (Maas et al 2008). Not only is it a major cause of death and disability, incurring great personal suffering to victims and relatives, but it also leads to huge direct and indirect costs to society. In the US, the annual burden of TBI has been estimated at over $60 billion (Finkelstein 2006). Globally, the incidence is increasing and in the US, TBI resulting from blast injuries is being increasingly recognized in military personnel returning from Middle East conflicts. Basic science research has greatly advanced our knowledge of mechanisms involved in progressive damage after TBI, creating opportunities for medical intervention and targeted therapies. Advancing the clinical field forward, however, and improving the quality of health care delivery and treatment results across the field, has been substantially hampered by various factors. These include a lack of standardization in data collection, dispersion of research efforts and the use of insensitive and outdated approaches to classification of initial injury severity and outcome.

The global aim is to develop, test and refine standards for data collection in TBI studies, suitable for use across the broad spectrum of TBI, and to explore novel approaches for classification of the initial injury severity and outcome after TBI, making use of emerging technology. In addition, we aim to develop a pilot set of performance indicators for assessment of the quality of health care delivery in TBI.

We anticipate that this project has the potential to substantially advance and revolutionize clinical research in TBI. It will build bridges across disciplines, break down artificial constructs and barriers that have slowed progress and facilitate comparison and meta-analysis of individual patient data across studies. The standards and formats for data collection will be made available for general use in an open access format. The tools for classification will offer researchers and clinicians novel approaches for studying TBI. Repositories for neuro-imaging data, biomarkers and proteomics will facilitate the evolving field of these emerging technologies in TBI. Further, the development of a pilot set of performance indicators will offer clinicians and administrators the potential to assess and improve the quality of health care delivery in TBI. We will thus develop the infrastructure, implement networking and collaborative activities and offer new tools and repositories for advancing the field in a truly multidisciplinary approach. With reference to the huge socioeconomic costs involved from TBI, we consider this project highly relevant to public health in general.

OPPORTUNITY

Traditionally, research in TBI has been characterized by dispersion with little collaboration between researchers in the acute care setting (emergency medicine, neurosurgery, intensive care medicine) and in the post-acute care setting (rehab medicine, neuropsychology) and very little attention has been paid to health related quality of life in TBI patients. Artificial constructs, such as the differentiation of TBI into the crude categories of mild, moderate or severe injury according to the Glasgow Coma Scale, has led to researchers to focus mainly either on mild or on severe TBI. Relatively little research has been performed on the so-called ‘moderate’ patients and the concept that the severity of TBI lies on a continuum has been lost. Recent workshops co-organized by NIH along with NIDRR, VAMC, DVBIC, DCOE, and other stakeholders (Classification; October 2007 and the Common Data Elements Workshop for Research in Psychological Health and Traumatic Brain Injury; Washington March 2009) have established a broad acceptance for the necessity of multidisciplinary collaboration and standardised data collection in TBI. This broad acceptance, combined with increasing realization of the gaps in our scientific knowledge, misconceptions and fallacies in previous research and substantial advances in

emerging technology now present a unique opportunity for advancing TBI research. Initial steps have already been made to integrate research on psychological health and TBI, particularly in the fields of depression and PTSD, which may be of much greater importance in TBI than previously anticipated. We feel strongly that the created momentum should be grasped.

GAPS IN OUR SCIENTIFIC KNOWLEDGE OF THE TBI POPULATION INCLUDE:

- Lack of standardization in data collection for TBI:
  This has been a major factor complicating comparison of treatment results across studies and countries and in performing meta-analyses of individual patient data collected during different studies or trials. Difficulties involved in such a meta-analysis were for example illustrated in the IMPACT project (*International Mission on Prognosis and Clinical Trial Design in TBI; R01-042691*). These studies merged individual patient data from observational series and randomized clinical trials in TBI into a large registry, currently including prospectively collected data from over 12,000 patients with severe and moderate TBI (Marmarou et al 2007). The creation of this database was however a major undertaking, involving over 10 person years of work due to the widely differing structure of the study datasets and variability in coding. This experience has highlighted the necessity to standardise data collection in TBI, which would fit well within the ongoing efforts developed by NIH-NINDS to implement common data elements across different fields of research in neurological disorders. The development of standardized, TBI specific data elements can then be added as a dedicated 'spoke' to the 'hub' of these common data elements. The multidisciplinary initiative resulting from the NIH cosponsored workshop on Integrated Approach to Psychological Health and TBI has provided a draft proposal for standardization of coding of data elements for use in TBI studies. This draft requires further refinement, translation into a web based format and testing of the final beta-version in clinical practice. This can best be accomplished in a prospective observational study, with the added advantage of increasing acceptance in the field as investigators feel involved in the development process.

- Antiquated approaches to classification of TBI:
  Traditional approaches to the classification of TBI in clinical research include assessment of clinical severity by the Glasgow Coma Scale and assessment of structural damage by computerized tomography studies. According to the GCS, TBI is broadly categorized as severe (GCS 3-8), moderate (GCS 9-13) and mild (GCS 14-15). This artificial construct however, completely forgoes clinical reality that TBI severity lies across a continuum over the full spectrum of TBI, ranging from very mild with no measurable long term consequences to virtually unsurvivable injuries. Moreover, in modern practice classification of TBI by clinical severity is limited because accurate assessment of the GCS is often confounded by medical sedation, paralysis or intoxication. Assessment of structural damage by CT examinations is not influenced by these confounders, but the Marshall CT classification (Marshall et al 1991) as commonly used for TBI, is relatively crude and has limitations such as the broad differentiation between diffuse injuries and mass lesions, and the lack of specification of the type of mass lesion (eg. epidural versus subdural). Participants of the NIH-NINDS workshop on TBI classification (October 2007) concluded that there was great need for a new and improved, multidimensional classification system for use across the broad spectrum of TBI (Saatman et al 2008). It was suggested that emerging technologies (eg. biomarkers, proteomics and advanced MRI imaging), could offer new opportunities for developing novel approaches to the classification of TBI. Although various efforts are ongoing investigating these emerging technologies, none take a combined and comprehensive approach, or include large numbers, which are prerequisites for developing a multidimensional approach to classification across the injury spectrum.

- Unfocused and insensitive approaches to outcome classification:
  Outcome after TBI is by definition multidimensional including neurophysical disabilities, disturbances in mental functioning (eg. cognitive and executive functioning) and consequent problems in social re-integration. Most clinical studies in TBI have used the Glasgow Outcome Scale (GOS), assessed at 6 months post injury as primary endpoint. The GOS however, as a global outcome measure, is relatively insensitive and may not capture improvements in important domains such as cognitive function. In research, investigators have amplified the insensitivity of the GOS by the common practice of dichotomizing the GOS into two categories: unfavourable versus favourable. This has limited the field in the same way as the mild, moderate, severe TBI injury classification. Few TBI studies have used health related quality of life measures. Reasons are first the lack of availability of disease specific instruments and second the misconception that TBI patients may not be able to rate their own quality of life reliably. Comprehensive, disease specific instruments for assessment in subjects after TBI are now available and this can facilitate inclusion of quality of life measures in a multidimensional approach to classify outcome. We see a need to explore the feasibility of developing a multidimensional approach to outcome assessment and classification.

- Absence of disease specific performance indicators for assessing quality of health care delivery:
  Performance indicators (including measures of structure, process and outcome) have been developed and tested for many diseases, but not for TBI. Benchmarking is mainly limited to comparing crude mortality rates of specific hospitals against national norms. Standardized mortality rates (SMR) and calculation of the standardized mortality ratio (observed deaths/expected deaths) have not been developed specifically for TBI. In the epidemiological literature SMRs are generally adjusted for age and sex, and in intensive care medicine for baseline characteristics based on scoring systems such as APACHE II, TRISS or SAPS II/III. The applicability of these scores for the indication TBI is doubtful. Moreover, in TBI functional outcome is much more relevant than mortality. In TBI, little attention has been paid so far to performance indicators related to structure (eg. available neurosurgical facilities), process (eg. transfer procedures to a neurosurgical facility) and outcome (combining information on survival and functional outcome; other potential indicators). Recently, two groups of investigators have published validated prognostic models developed on large patient series, for use in severe and moderate TBI (Steyerberg et al 2008, MRC CRASH). Predictive models provide individualized risk estimates and thus can enable the setting of baselines for clinical audits and benchmarking by permitting analysis of observed/expected outcome. As the models have been developed not only for mortality but also for functional outcome as assessed by the GOS, we consider these models of great potential relevance for assessing the quality of health care delivery. The validity of the models however needs to be confirmed in a contemporary population of TBI. We aim to accomplish this and develop a pilot set of performance indicators in a prospective observational study.

POTENTIAL IMPACT

This project has the potential to revolutionize and substantially advance clinical research in TBI across the broad spectrum ranging from mild to severe injuries and across disciplines from emergency care medicine to rehabilitation medicine and outcome researchers. By setting new standards for data collection, by developing proposals for novel approaches to classification and benchmarking, and by creating the infrastructure for repositories, it will facilitate and advance both research and health care delivery. Although young adult males are predominantly at risk for TBI, none of us are immune and TBI can afflict all age groups from the very young (intentional and unintentional injuries) to the geriatric population. Recent data show a substantial increase of the incidence of TBI in the elderly. Comparison

of the age distribution of observational studies published over the last decades, shows a gradual increase in median age and percentage of patients over 50 years old (Table 1). These facts emphasize the relevance of TBI to all age groups. The epidemiology of TBI is thus changing: falls are a more frequent cause of injury in older patients and result in a different type of injury with more patients developing contusive brain injury. In contrast to the changing epidemiology, most of our population-based studies and concepts of TBI are based on earlier studies of patients that are not representative on the TBI population today. If we are to improve outcome in TBI, the proper population must be targeted. The primary aim of this project is to create the infrastructure and develop tools to facilitate future work to address these current limitations that are hampering the field. In this context we will include a focused small-scale population-based observational study that spans all ages and injury severity.

This study will provide an important and much needed contemporary picture of TBI epidemiology and treatment. There are no contemporary observational studies in TBI. Previous observational studies go back more than 15-20 years and these were instrumental in advancing the field; for example the Traumatic Coma Data Bank (TCDB: 1984-1987) introduced the Marshall CT Classification and highlighted the importance of hypotension and hypoxia as second insults. The later observation provided the foundation for the prevention of "secondary brain injury" that is the cornerstone of the acute treatment of TBI. From this project we therefore expect in addition to accomplishing the primary objectives, there will be many spin off results as in previous observational studies that could have the potential to re-focus TBI research and clinical care. Overall, we expect a major global impact of the proposed project, relevant to the entire population.

Table 1: Increasing age in TBI

TBI Study	Year of study	N	Median age	% > 50 yrs
Traumatic Coma Data Bank	1984 –1987	746	25	15
UK 4 Center study	1986 –1988	988	29	27
EBIC Core Data Survey	1995	847	38	33
Rotterdam cohort study (unpubl)	1999 – 2003	774	42	39
Austrian Severe TBI study	1999 – 2004	415	48	45

APPROACH

We propose to develop common data elements for use across the broad spectrum of TBI and to test the infrastructure for data collection in a pilot multicenter observational study.

We will create and implement repositories for neuroimaging studies, biomarkers, genomic and metabolomic studies, providing researchers and clinicians with the infrastructure to further develop the field in a concerted, multidisciplinary effort. The data collection will further be used to develop proposals for novel approaches towards the classification of TBI, a multidimensional assessment of outcome and towards the development of a pilot set of performance indicators for TBI, investigating the specific aims as outlined below.

It is not our goal to provide definitive results, but rather to develop the infrastructure and tools as well as specific proposals for classification and performance indicators. We do however consider a pilot observational study appropriate to accomplish the study objectives, outlined under the Specific Aims. Another option would be to research the objectives in the IMPACT database or by including data from ongoing studies in a central repository. However, we should recognize that an existing repository can never be used to validate the TBI Common Data Elements. Moreover, the IMPACT database predominantly consists of older studies, the results of which may not directly reflect contemporary approaches. Many of the older studies also suffer from restrictive inclusion/exclusion criteria that precludes the study of children and the elderly. Ongoing studies suffer many of the selection biases by focusing only on selected populations with specific enrolment criteria and thus limiting the ability to generalize any findings. We will however, during the current study, implement the infrastructure also for a repository on clinical data to which results from other studies can be added and used for verifying and further investigating findings in larger numbers.

We aim for a six-month data collection period with a limited three-month follow up and an extensive six-month follow up. We intend to enrol up to a total of 1,050 patients. Patient enrolment will occur in our three high-volume TBI Centers (UCSF, UPMC, UMCB) and a TBI Rehabilitation Center (Mount Sinai). These Centers have a long track record of multicenter TBI research experience and existing infrastructure to rapidly and successfully complete the study within the two-year time frame. We will include all patients admitted acutely with a history of head injury. The inclusion criteria follow the recently published American College of Emergency Physicians and the Centers for Disease Control and Prevention (CDC) Panel recommendations for neuroimaging and decision making in mild traumatic brain injury (Jagoda 2008). These criteria include head injury patients with loss of consciousness or posttraumatic amnesia along with one or more of the following present: headache, vomiting, age greater than 60 years, deficits in short-term memory, physical evidence of trauma above the clavicle, posttraumatic seizure, GCS less than 15, or focal neurologic deficit. These Guidelines are already in place at the participating Centers and are used to determine which patients will get a non-contrast CT scan as part of their initial evaluation. Thus, all 900 patients enrolled in the acute or early study group will have an admission CT to contribute to the TBI-CDE Neuroimaging Repository. Because we are seeking to collect a population-based sample of subjects across the spectrum of TBI, patients will not be excluded based on age, race, gender, ethnicity, substance abuse, or prior psychiatric history. We will also seek to enroll 150 patients who present late at the participating Centers with complaints following suspected TBI. It is anticipated that a majority of these patients will be enrolled in the outpatient and rehabilitation setting. A smaller group of 490 patients (early and late presentation) will be recruited to have an MRI scan within two weeks of injury and for collection and storage of plasma and DNA from a blood sample. This data will be contributed to the TBI-CDE Neuroimaging Repository and the TBI-CDE Biospecimen Repository, respectively. Informed consent will be obtained from all subjects or their proxy in case they are mentally incapacitated due to the injury, according to local regulations. Patients will also receive a small reimbursement to compensate for their time to participate in the MRI and the six- month outcome testing.

A web-based format for data entry and data management procedures will be developed at UCSF in collaboration with NIH-NINDS Common Data Elements effort. In order to support high quality data that will yield valid results, the TBI-CDE Data Core personnel will collaborate with the Center Co-PIs to create a training manual for all project staff that contains protocols for patient enrollment, data acquisition and web-based entry, biospecimen collection, handling, and tracking, and Federal and institution-specific human subjects protection regulations. The goal is to ensure that uniform practices are followed at each institution so that patient data, neuroimaging data, and biospecimen samples can be managed

securely and efficiently. Through database design and periodic interaction with the PI, Co-PIs, and project staff, the Data Core will serve as the central source for oversight of patient enrollment goals, data quality and study compliance.

All patient and biospecimen data will be entered into a single TBI-CDE Data Repository. The relational database application will be designed by QuesGen Systems, Inc. (Burlingame, CA). QuesGen is a Software-as-a-Service company which provides web-based data management for clinical research as hosted applications. Clinical data, tissue specimen information, and personnel training documents will be stored in the TBI-CDE project database. Through this web-based application, study personnel can collect, store, update, monitor and query research data efficiently and securely. The QuesGen application is designed with strong security protocols, audit functions for tracking database access and data modification, and roles-based permissions. Over the past five years QuesGen's subscription software has been used by a variety of investigators at UCSF and other academic research centers. QuesGen's security system is HIPAA compliant; Security protocols meet the high standards of UCSF's Enterprise Information Security Office (EIS) and have been verified through an EIS audit.

Statistical analysis will be coordinated in collaboration with the IMPACT study group under the direction of Dr. Andrew Maas (Consultant). Dr. Charles McCulloch and his staff from UCSF's Biostatistics, Research Ethics, and Design Program will perform the analyses and will review any additional results produced by project staff. We hope to preferentially involve young promising statistical investigators form this group, and will offer them the additional opportunity to participate in exchange programs with renowned TBI research centers, such as the IMPACT study group. Thus, we hope to get more young investigators with great potential involved in TBI research, which will undoubtedly benefit the field far beyond this project. Dr. Maas, the IMPACT study group, and Dr. Charles McCulloch will review all statistical information prior to publication.

Specific Aim #1: Standardization of data collection

We aim to:

- Finalize the beta version of the modular Case Report Form (CRF) with web-based data entry, including automated data checks for use in TBI with a structure consistent with the NINDS Common Data Elements project to create the TBI Common Data Elements (TBI-CDE)
- Test the TBI-CDE system in a prospective observational study and to use this experience to fine tune and improve the system
- Create repositories for data on neuroimaging studies (TBI-CDE Neuroimaging Repository) and TBI biospecimens (TBI-CDE Biospecimen Repository)
- To make the standardized formats for data collection in TBI widely available with open source access.

In the context of the NIH, NIDRR, VAMC, DVBIC, and DCOE interagency initiative towards an 'integrated approach to TBI and psychological health' we have developed a Case Report Form (CRF) containing all essential common data elements for TBI studies. This CRF is based on the consensus recommendations from the Common Data Elements workshop for Research and Psychological Health in TBI (March 2009). The data elements for TBI are grouped together in categories developed with the consensus of TBI experts and thought leaders from the fields of emergency medicine, neurosurgery, intensive care medicine, statistics, rehabilitation medicine, outcome research, neuroradiology and psychological health. The structure of the common data elements (CDE) for TBI are consistent with the CDE's developed by NIH-NINDS (www.commondatalements.org) for use across different fields of neurological

diseases. Criteria for the utility and validity of the data elements and the web-based TBI-CDE Data Repository will be the user friendliness, time for completion and general feedback from investigators. The functioning of the automated data checks for plausible values and consistency between variables will be assessed separately.

Blood samples will be collected and processed using the best practice guidelines recently adopted by the TBI Biospecimens and Biomarkers Working group (Common Data Elements Workshop for Research in Psychological Health and Traumatic Brain Injury; Washington March 2009). For acutely injured TBI patients, blood samples will be collected by the ED, OR, or ICU staff as part of standard blood specimen collection. Blood specimens will be sent to the clinical laboratory for separation of cells and plasma and storage until the Research Assistant retrieves them. Upon receipt of the initial specimen, the Research Assistant will barcode the specimen and transfer it to the TBI-CDE Biospecimen Repository for storage. It will be the responsibility of the Research Assistant to enter collection times and unique barcode identifiers in the database. Pilot genotypic analyses of DNA specimens will take place at UCSF to verify the integrity of the process and obtain genomic data for classification and outcome studies. We will determine the ApoE genotype in all 480 patients with baked biospecimens. Banyan Biomarkers will also conduct limited proteomic and analyses on the serum specimens in Year 2. These biomarkers will include S100beta and UCH-L1 and will be measured in all 480 patients.

CT and MR imaging studies performed in the context of this study at all centers will follow the scan acquisition parameters specified by the Neuroimaging Working Group CDE framework (March 2009). These include the admission CT, performed with the adult or pediatric CT protocol. Follow-up noncontrast 3T MR imaging would be performed within two weeks of presentation for further TBI classification. The 3T MR protocol would include all sequences in the CDE Tier 1 (basic) protocol, including T2 FLAIR, 3D T1 MP-RAGE, and GRE images, as well as the 3T DTI acquisition from the Tier 2 (advanced) protocol. Participating Centers will transfer the DICOM files of imaging studies for inclusion in a central TBI-CDE Neuroimaging Repository, which will be created in the context of this project.

Specific Aim #2: Classification of TBI: New approaches

We aim to:

- Determine associations between existing approaches to classification of TBI
- Investigate to what extent emerging technology (biomarkers, advanced neuroimaging, genotyping) may contribute towards improved classification
- Develop a multidimensional classification system for TBI.

This specific aim is a logical sequel to the NIH-NINDS workshop on TBI classification and response to the strong recommendation that a new multidimensional classification system for TBI should be developed (Saatman 2008). Current approaches include those by physical mechanism (eg. closed versus penetrating), by clinical severity (GCS), by pathoanatomic features (structural damage visualized by CT) and by pathophysiology (primary versus secondary). More recently, the concept of classification by baseline prognostic risk was launched. Each of these approaches has its own specific merit as well as limitations. Consensus exists that none of these approaches taken in isolation are adequate to appropriately characterize the injury pattern and injury severity in individual patients or across groups of patients. Remarkably, in the literature very little attention has been paid to the associations and interactions between different approaches to classification of TBI. We will therefore first investigate the associations and interactions between these existing approaches. This will be done by standard statistical approaches and by graphical modelling. We anticipate that this approach will yield insight into

the dependencies between the approaches but will not be sufficient for the development of a new multidimensional classification system. Except for the classification by prognosis, the approaches are relatively crude and we anticipate that emerging technologies (eg. TBI protein biomarkers, genotyping, and metabolomics profiling) as well as advanced neuroimaging can offer new opportunities for improving approaches to classification. Automated analysis of CT and MR images will yield quantitative volumetric measurements of pathoanatomically significant features such as subarachnoid/subdural/ epidural hemorrhages, basal cistern effacement, and midline shift (Yuh et al., J Neurotrauma 2008) for observer-independent reproducible TBI classification. In addition, FA values of selected functionally significant white matter tracts, will be measured using reproducible quantitative DTI tractography methods (Wakana et al., Neuroimage 2007). These tracts include the corpus callosum, cingulum bundle, anterior corona radiata, uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, arcuate fasciculus, and the inferior fronto-occipital fasciculus. We have experience in successfully performing multicenter DTI studies of TBI (Niogi et al., 2008a; Niogi et al., 2008b) and have recently characterized these white matter tracts in a prospective longitudinal 3T DTI study of mild TBI using the methods proposed above (Ng et al., Proc ISMRM 2009). The DTI data is expected to be especially useful in the classification of the milder spectrum of TBI, where gross pathoanatomic abnormalities would not be expected on CT or conventional MR imaging.

We plan to investigate the added value of these emerging techniques for purposes of classification. The added value will be analyzed and expressed as Nagelkerke's R2. Next we will attempt to develop a multidimensional classification system for TBI. To this purpose we will adopt two approaches: first, we will attempt to group patients in a sensible way, according to clinical insight and the results of specific aim 2a and 2b. Next, we will attempt an unbiased statistical approach to grouping patients with multilevel modelling. Much experience in the application of multilevel modelling techniques in the analysis of TBI, in particular relating to center and treatment effects, has been accumulated by the IMPACT study group lead by Dr. Maas (Consultant). We will collaborate with his group with the assistance Dr. Charles McCulloch and his staff in developing the most sensible and efficient approaches.

Specific Aim #3: Classification of Outcome through a multidimensional approach

We aim to:

- Investigate the relevance of different outcome measures to the standard and novel TBI classification groups identified in Specific Aim 2
- Explore development of a multidimensional approach to outcome assessment in TBI
- To characterize the relation between early standard and novel endpoints and multidimensional outcome.

Outcome assessment will be mandated during the prospective observational study at three and six months post injury. The three-month outcome measure will only include the Glasgow Outcome Scale – Extended (GOSE) and will serve primarily to track the patients to increase the percentage of patients for a more extensive follow up at six months. The outcome assessment is based on the consensus recommendations of the TBI Outcomes Working Group (Common Data Elements Workshop for Research in Psychological Health and Traumatic Brain Injury; Washington March 2009) and will address the various domains relevant to outcome after TBI. Global outcome will be assessed by the Glasgow Outcome Scale – Extended (GOSE). Functional impairment will be captured by the FIM. Neuropsychological tests will include the RAVLT, TMT, WAIS-III, RPQ, BSI-18, CHART-SF and SWLS. Health related quality of life will be recorded both by a generic measure (SF-36) and by a disease specific HRQoL scale for which we propose to use the recently developed and already validated QOLIBRI scale.

Additionally, in collaboration with psychological health researchers, we will screen for PTSD complaints using the PCL-C. Questionnaires for the disease-specific HRQoL assessment may be sent by mail and returned after self-rating by patients and caretakers. Global outcome, PTSD symptoms and post acute care treatment will be assessed either by telephone interview or on follow-up investigation in the outpatient department. Every attempt will be made to conduct the six-month follow-up during a personal interview following which neuropsychological tests will be performed. A central review of outcome assessment with the GOSE according to the structured interview will be performed for which we will develop a dedicated algorithm, and results compared to investigators scores.

The associations and interactions between the different domains of outcome will be assessed by ANOVA analysis and subsequently by structured equation modelling. In the next step, we will attempt to create a multidimensional tool for classification of outcome following TBI, selecting the most discriminating tests with multilevel modelling. This analysis will be repeated following stratification for initial injury severity and initial classification of TBI as determined in Specific Aim 2. We hypothesize that different aspects of outcome assessment may be more relevant for different types of injuries.

We will also examine if there is statistically significant correlation between the above-mentioned outcome measurements and biomarker and genomic results (from Specific Aim 2). Quantitative variables from admission CT and follow-up 3T MRI/DTI will be correlated with six-month outcome scores and neurocognitive results to examine whether these imaging variables can serve as prognostic tests, either in isolation or in combination with other clinical or biomarker data.

Specific Aim #4: Performance Indicators and Quality of Health Care Delivery

We aim to:

- Assess the applicability of previously developed prognostic models towards calculation of standardized mortality rates
- Explore structural (trauma organization, facilities), process –related (time frames, quality of treatment) and outcome related (mortality and functional outcome) indicators for TBI
- To develop methodology to assess the relative contribution of these indicators towards variation in outcome
- To generate pilot data to power a subsequent substantive study that robustly validates prognostic models and quantifies the impact of keys variables on outcome.

Most prior studies have targeted individual therapies for TBI treatment and these include numerous failed clinical trials for a wide range of neuroprotective treatments, including pharmacological agents and hypothermia. Yet, the most substantive clinical advances in TBI care have been made by taking observations from observational studies such as the Traumatic Coma Data Bank (TCDB) and ultimately developing standardized guidelines for care. Thus, although basic science understanding of mechanisms of TBI cellular injury have resulted in many rational, but ultimately unsuccessful, treatment trials, current TBI treatment advances have really been driven by clinical paradigms of integrating care into standardized treatment approaches involving multiple interventions delivered concurrently (e.g. ICP monitoring, while providing early nutritional support, while avoiding hypotension, while using deep venous thrombosis prophylaxis, etc.). Thus, despite its complexity, testing of TBI care probably lends itself most to an approach analogous to Clinical Effectiveness Research (CER) in which existing approaches to care are tested against each other. In fact, one of the clinical trials in TBI which has made the most impact on treatment of secondary brain insults tested the comparative efficacy of two

different clinically used approaches, cerebral perfusion pressure (CPP) directed therapy versus intracranial pressure (ICP) directed therapy (Robertson, Critical Care Medicine 1999).

Prior to the initiation of the prospective observational study, a survey will be conducted amongst the four participating centers to capture basic information on trauma systems, neurosurgical facilities, caseload and protocols for treatment approaches. The validity of identified process and structural performance indicators for assessing the quality of health care delivery will then be further determined on analysis of the prospectively collected data from each Center. We aim to develop a pilot set of performance indicators for TBI care. The proposed observational study is considered appropriate in order to eliminate 'surveillance system bias'. Multilevel modelling will be applied to determine the association of both process and structural indicators to outcome. For outcome we will consider mortality on discharge, mortality at six-months follow-up and functional outcome at six months assessed by the GOSE and, if successfully developed, the multidimensional approach to classification. These results will also validate the utility of the TBI-CDE and Data Repository for collecting standardized data for healthcare effectiveness research.

II. OVERVIEW

II-A. TIMELINE

I. Start-up (Six Months): September 30th, 2009 – March 31st, 2010

   A. UCSF collects IRB documentation; collects site contact information; prepares subcontracts.

   B. December and January Conference Calls.

   C. UCSF develops, implements, and tests web-based entry system.

   D. Investigators' Meeting March 22nd in San Francisco.

II. Enrollment (Six Months): April 1st, 2010 – September 30th, 2010

   A. All eligible participants receive:

      1. Emergency Department CT as part of clinical care

      2. Case Report Forms

   B. Subset of participants receive:

      1. Blood draw: Genomics and Proteomics

      2. Imaging: MRI

III. Follow-up (Nine months): July 1st, 2010 – March 31st, 2011 (Overlap with Enrollment Period)

   A. Subset of participants receive:

      1. 3-month follow-up GOSE/GOSE Peds via telephone

      2. 6-month follow-up GOSE/GOSE Peds/Neurocognitive Testing. Patients may have the option of returning measures by mail and/or completing them online.

IV. Completion (Five months): April 1st, 2011 – August 31st, 2011

   A. Data analyses

   B. Initial proposals for classification and performance indicators.

II-B. FLOWCHART OF DELIVERABLES

What	Timing	Sample Size	Details
CT as part of clinical care	Within 24 hours of presentation	All	• ED needs to follow CT guidelines
Case Report Form	Acute: due one month after patient discharge from acute care Rehab: due one month after admission to rehab	All	• Acute: Initial presentation to ED within 24 hours of TBI; initial CT completed as part of clinical care • Rehab: All patients transferred from acute hospital to rehab center; initial CT completed as part of clinical care
Biospecimens "Optional"	Within 24 hours of presentation	Subset	• Exclusions: refusal to consent
3T Research MRI "Optional"	Within 1 – 2 weeks of presentation	Subset: Target those who have consented to blood draw, then expand search.	• Exclusions: refusal to consent; < 8 years old; pregnant; fails screening • Radiologists share results with patients
Outcomes: Telephone call (GOSE) "Optional"	Three months after presentation	Subset: Target those who have consented to blood draw and/or MRI, then expand search.	• GOSE for patients 18+ • GOSE Pediatrics for patients < 18 years old • Training necessary
Outcomes: Neurocognitive Tests "Optional"	Six months after presentation	Subset: Target those who have consented to blood draw and/or MRI and/or three-month follow-up, then expand search.	• GOSE plus Outcome Measures for 18+ • GOSE Pediatrics for patients < 18 years old • Training necessary

III. COMPONENT ONE: (A) ENROLLMENT AND (B) CASE REPORT FORMS

III.A: ENROLLMENT WITHIN 24 HOURS OF PRESENTATION

III-A.1. INCLUSION/EXCLUSION

ACUTE SITES (UCSF, UPMC, UMCB):

INCLUSION
- Emergency Department within 24 hours of injury;
- Require a CT brain scan for a traumatic brain injury as part of clinical care.

EXCLUSION:
- Patients presenting at ED later than 24 hours post-injury;
- Patients presenting at ED who do not require a CT for clinical care;
- Patients in custody, incarcerated, or a danger to themselves or others (psych emergencies)

REHAB SITE (MOUNT SINAI):

INCLUSION
- All patients transferred from acute hospitals to rehabilitation center.

EXCLUSION:
- Patients not transferred from acute settings;
- Patients in custody, incarcerated, or a danger to themselves or others (psych emergencies).

III-A.2. CONSENT/ASSENT FORMS

- Following Enrollment and Case Report Forms, Components Two, Three, Four, and Five are "optional" and have their own additional inclusion/exclusion parameters, which will be discussed later in this Handbook.

- In theory, a subset of patients would consent to and participate in all five components.

- In reality, patients will be given the opportunity to pick and choose to consent only those Components that they are actually willing and able to do.

- So as not to bias this subset group up front, collect as many consents as possible for as many components of the study as possible. Patients will whittle themselves down into their respective subsets based on their willingness and ability to follow-up.

- Three Sample Consent/Assent Forms can be found in Appendix A.

III-B. CASE REPORT FORM (CRF) OVERVIEW

Data will be entered into a web-based data entry form and database developed by QuesGen Systems, Inc. (Burlingame, CA). Selection of variables for this data form was based on rrecommendations from the NIH interagency working group on demographics and clinical assessment and the IMPACT database developed by Dr. Maas, et.al.

The data entry form captures information encompassing all domains of this study:

- Site information
- Subject information
- Demographics
- Initial presentation
- Treatments
- Vital signs
- Medications
- Outcome
- Follow-up
- Patient management
    - Dates biospecimens drawn/sent
    - Dates CT sent to repository
    - Date MRI sent to repository
    - Date follow-up scheduled/testing complete

Patients will be consented for one or more of the study components:
Data
Biospecimen
MRI
Outcome Measures

There are four enrollment patient categories:
ED Only
Hospital admit with ICU
Hospital admit no ICU
Rehab patient

Following are views of the major sections of the web-based data entry form:

Site Information

Site Name	IRB Approval Date	IRB Expiration Date
UCSF		

Λ | Site | Personnel | Screening Log | Biospecimen Log

Subject Information

SubjectID	Patient Number	Last Name	First Name	Age	Sex	Site Name	Bio Collected	Bio Shipped	Adm CT Sent	MRI Compete	MRI Sent	3 M Follow Complete	6 M Follow Complete	PatientType
5	PI-0001	Curry	Hot	22	M	University of Pittsburgh								

Λ | Subject | Initial Pres | Hospital | CT | Rehab | 3 Month FU | 6 Month FU | Patient Mgmt

Initial Presentation

Presentation | ED | Injury | LOC PTA | Socio Adult | Med Hx | TBI Hx

Hospital

Admis-Discharge | Surgeries | Monitoring Dev | Complications | Concom Meds | Labs | Vitals | AIS ISS | TIL

Rehab

Admission | BIA | Neuro Assmt | Post Disch

3 month follow-up

GOSE Questionnaire | Neuro Assmt | Post Disch

6 month follow-up

GOSE Questionnaire | GOSE Form | Neuro Assmt | Post Disch | Outcomes

Patient Management Tab Contents

Site Name
UCSF University of Pittsburgh University Medical Center: Brackenridge Mount Sinai

Biospeciments
Date Bio Specimen Collected
Date Bio Specimen Shipped

Imaging
Date Admission CT Sent

Date MRI Completed
Date MRI Sent

Follow-up
Date 3 Month Follow Up Completed
Date 6 Month Follow Up Completed

Date CRF Complete

Date of final study contact

Status at final study contact
- Subject completed study
- Consent Withdrawn
- Lost to follow-up
- Dead
- Other

Bio Specimen Notes

Imaging Notes

Follow Up Notes

IV. COMPONENT TWO: BIOSPECIMENS/BLOOD DRAW

IV.A. INCLUSION/EXCLUSION

INCLUSION:
- Patients eligible to participate in the Project who consent to a blood draw.

EXCLUSION:
- Those who are not eligible to participate in the Project or who do not consent to a blood draw.

NOTES:

- Patients enrolled in more than one research study that involve blood draws cannot exceed the daily/weekly IRB blood draw limitations.

- Whenever possible, blood draw should be within 24 hours of presentation.

- Adults who are eligible will have an 8 ml blood draw for genetic and plasma marker analyses.

- Minors under the age of 18 will have the amount of blood drawn as allowed by each site's IRB.

- Blood sampling will take place by venipuncture, unless an arterial line is in place as part of clinical care. No more than two venipuncture attempts will take place.

- Processing will be done locally. Blood tubes and aliquots will be labeled, frozen, and transported via Federal Express to the UCSF DNA Bank at Mission Bay, where it will be banked. Genetic and protein testing will be performed to look for differences that may affect or predict recovery after traumatic brain injury.

- UCSF will cover shipping materials and costs.

- Initial analyses: As a test, UCSF will forward the first ten plasma aliquots from each site to Banyan Biomarkers (BB) without identifiers as to which samples belong to acute patients and which belong to rehab patients.

UCSF University of California San Francisco	**GO GRANT** **Transforming TBI Research and Clinical Care**	Effective Date: 04/01/2010 Version: DRAFT- Final
DRAFT Biospecimens and Biomarkers Protocol **Sample Collection, Processing, and Shipment**		

I. GENERAL INFORMATION

A. OBJECTIVE

1. This document describes the requirements for the collection, processing, and shipment of biospecimen samples from individual research sites to the UCSF DNA Bank at Mission Bay.
2. Adherence to this protocol will ensure that all samples are accounted for, and that their integrities are maintained, during the collection and transport process.

B. SCOPE

1. This Protocol applies to all biospecimen samples collected during the course of the GO Study, as well as all staff responsible for collecting, processing, and recording such samples.

C. RESPONSIBILITIES

1. All personnel involved in specimen handling will be trained and certified on the United States and International laws governing the handling and transport of blood-borne, bio-hazardous materials through their site's recognized local agency(s).
2. The Principal Investigator (PI) at each research site is responsible to ensure the proper handling of study samples.
3. Each research site is responsible for organizing and documenting sample shipments to the central processing and storage facility, UCSF DNA Bank at Mission Bay.
4. The UCSF DNA Bank at Mission Bay is responsible for receiving and documenting sample shipments, storing samples from all centers, providing DNA analyses, and transferring samples to other laboratories as requested.

D. ATTACHMENTS

1. Form 1: Site Specimen Log
2. Form 2: UCSF DNA Bank – Sample Processing Request Form
3. Form 3: Shipper's Declaration for Dangerous Goods (Example)
4. Table A: Indicative Examples of Category A Infectious Substances
5. Table B: Summary of Shipping Information
6. Diagram I: Shipping Labels (Example)

II. SUPPLIES

A. COLLECTION SUPPLIES

1. ☐ Biohazard bag
2. ☐ BD Vacutainer (x2) – 4.0ml, lavender top, plastic, contains 7.2mg K_2EDTA
3. ☐ Bio-Pen for labeling the 4.0ml BD Vacutainers
   a. Use Patient ID's provided by CRF upon enrollment, i.e. SF-0003
4. ☐ Site Specimen log in the format provided (Form 1)

B. PROCESSING SUPPLIES

1. ☐ 6 x 1.2ml externally-threaded cryovials for collection of plasma
2. ☐ 2 x 3.0ml externally-threaded cryovials for collection of aqueous blood mixture

3. ☐ Bio-Pen to label cryovials according to specimen type and aliquot number
   a. In the form of "Site ID + Patient Number/Aliquot Type + Aliquot Number "
   b. i.e. for UCSF, Patient #2, Plasma Aliquot #3: SF-0002/P3.
4. ☐ Transfer pipettes for blood and plasma
5. ☐ Centrifuge capable of 4000RPM
6. ☐ Appropriate cryovial storage rack to hold all cryovials
7. ☐ -80°C non-frost free freezer

C. PACKAGING SUPPLIES

1. The **PRIMARY CONTAINER** is the externally-threaded cryovial that holds biospecimen aliquots.
2. The **SECONDARY CONTAINER** is the 5"x5"x2" 81-slot cryovial case and the leak-proof, biohazard-labeled plastic bag, capable of withstanding pressures to 95kPa during air transport.
3. The **OUTER CONTAINER** is the 12"x12"x12" insulated bio-shipment box, which consists of an inner styrofoam box placed inside an outer cardboard box.
4. **DRY ICE**: 3kg per outer container
5. **UCSF DNA BANK FORM**, placed in separate plastic bag
6. **FEDEX LABEL** with the individual site's address in the "Sender" area and UCSF Mission Bay's address in the recipient area
7. **SHIPPING LABELS**
   i. UN 3373 (Category B) or 2814 (Category A)
   ii. Class 9 (dry ice)
   iii. Restricted to Cargo Aircraft Label
8. **If Category A Infectious Substance:** Fill out FedEx "Shipper's Declaration of Dangerous Goods" (refer to Table B)
   i. Label must have every section filled out according to guidelines

III. BIOSPECIMEN COLLECTION

A. GENERAL COLLECTION INFORMATION

1. Prepare collection kit prior to sample collection.
2. Follow Universal Precautions at all times.
3. Track the patient closely and obtain the blood draw ASAP (ideally within 24 hours).
4. **OPTION 1 (SEE BELOW): Patients who have not received a blood transfusion** will receive one blood draw for both DNA and Plasma.
5. **OPTION 2 (SEE BELOW): Patients who have received a blood transfusion** will receive two separate blood draws:
   a. The first draw to be collected ASAP for Plasma.
   b. The second draw to be collected between 24-72 hrs after time of final transfusion for DNA.

B. OPTION 1: PATIENTS WHO HAVE NOT RECEIVED A BLOOD TRANSFUSION

1. Blood will be collected in the Emergency Department (ED), Intensive Care Unit (ICU), or ward. **EXCEPTION:** Mount Sinai collects the sample upon patient presentation at Rehabilitation Center.

2. As soon as possible, draw 8ml blood using 2 BD Vacutainers (4.0ml lavender top tube with K_2EDTA additive), filling each to its maximum volume with whole blood.
3. Invert each sample 10 times to ensure complete mixing of whole blood and K_2EDTA. [An inversion is one complete turn of the wrist (180 degrees) and back]
4. Place the samples in the biohazard bag, fill out the specimen log, and transport the collection kit immediately back to the lab.

C. OPTION 2: PATIENTS WHO HAVE RECEIVED A BLOOD TRANSFUSION

1. Blood will be collected in the Emergency Department (ED), Intensive Care Unit (ICU), or ward. **EXCEPTION:** Mount Sinai collects the sample upon patient presentation.
2. First Blood Draw: for Plasma ONLY. Plasma is not affected by blood transfusions.
   a. As soon as possible, draw 8ml blood using 2 BD Vacutainers (4ml lavender top tube with K_2EDTA additive), filling each to their maximum volume possible with whole blood
   b. Invert each sample 10 times to ensure complete mixing of whole blood and K_2EDTA. [An inversion is one complete turn of the wrist (180 degrees) and back]
   c. Place the samples in the biohazard bag, fill out the appropriate fields on the specimen log, and transport the collection kit immediately back to the lab.
3. Second Blood Draw: for DNA ONLY. Genomics is affected by blood transfusions.
   a. Between 24-72 hours after final blood transfusion, draw 4ml blood using 1 BD Vacutainer (4.0ml lavender top tube with K_2EDTA additive), filling it to its maximum volume with whole blood.
   b. Invert the sample 10 times to ensure complete mixing of whole blood and K_2EDTA. [An inversion is one complete turn of the wrist (180 degrees) and back]
   c. Place the sample in the biohazard bag, fill out the specimen log, and transport the collection kit immediately back to the lab.

IV. BIOSPECIMEN PROCESSING

A. OPTION 1: PATIENTS WHO HAVE NOT RECEIVED A BLOOD TRANSFUSION, SINGLE BLOOD DRAW

1. Place **each** sample from the 4.0ml BD Vacutainer upright on ice for 5 minutes.
2. Spin the sample on centrifuge at 4000RPM at room temperature for 7 minutes to separate plasma from red blood cells.
3. Draw the top 1.5ml of the spun tube (this should be roughly 70% of the total plasma volume) into the 1.2ml cryovials, in volumes of 500ul per cryovial. A total of three (3) 1.2ml cryovials should be filled with plasma per 4.0ml BD Vacutainer.
   a. The remaining 30% of the plasma is left in the tube to provide a buffer during the aliquoting process, to ensure that no blood products are drawn into the plasma aliquots.
4. Transfer the remaining blood mixture into the 3.0ml cryovial.
5. Label all cryovials appropriately.
6. Fill out all appropriate fields on the specimen log.
7. Record whether specimen is known to contain any of the Category A Infectious Substances listed on Table A. If YES, record the specific substance(s). Otherwise, leave the field blank.

8. Store cryovials in storage rack grouped by patient study ID.
9. Place storage rack in -80°C non-frost free freezer. (Frost free freezers go through freeze cycles which damage the sample.)

B. OPTION 2: PATIENTS WHO HAVE RECEIVED A BLOOD TRANSFUSION, TWO BLOOD DRAWS

1. Processing First Blood Draw for Plasma (obtain ASAP, ideally within 24 hours):
   a. Place each sample from the 4.0ml BD Vacutainer upright on ice for 5 minutes.
   b. Spin the sample on centrifuge at 4000 RPM at room temperature for 7 minutes to separate plasma from red blood cells.
   c. Draw the top 1.5ml of the spun tube (this should be roughly 70% of the total plasma volume) into the 1.2ml cryovials, in volumes of 500ul per cryovial. A total of three (3) 1.2ml cryovials should be filled with plasma per 4.0ml BD Vacutainer.
      i. The remaining 30% of the plasma is left in the tube to provide a buffer during the aliquoting process, to ensure that no blood products are drawn into the plasma aliquots.
   d. Discard the remaining aqueous blood mixture.
   e. Label all plasma cryovials appropriately.
   f. Fill out all appropriate fields on the specimen log.
   g. Store plasma cryovials on the same storage rack grouped by patient ID.
   h. Be careful to minimize the open-close times of the freezer.
2. Processing Second Blood Draw for DNA (obtain between 24-72 hours post blood transfusion):
   a. Transfer the 4ml sample from the BD Vacutainer to two separate 3.0ml cryovials, with 2ml per cryovial.
   b. Label all cryovials appropriately.
   c. Fill out all appropriate fields on the specimen log.
   d. Store cryovials on the same storage rack grouped by patient ID, next to the 1.2ml cryovials containing previously aliquoted plasma samples.
   e. Be careful to minimize the open-close times of the freezer.
   f. Do not take the storage rack out of the freezer when placing the new 3ml cryovials containing whole blood.

V. BIOSPECIMEN PACKAGING

A. GENERAL COLLECTION INFORMATION

1. Potentially hazardous biological materials must be triple packaged to withstand leakage, shocks, temperature and pressure changes that occur during handling and transportation.
2. Due to the fact that dry ice sublimates immediately upon contact with ambient temperatures, do not initiate biospecimen packaging procedures until all the following conditions have been met:
   a. The adequate number of patient specimens has been collected.
   b. The packaging and shipping materials have been gathered and are at hand.
   c. The shipper (FedEx) has been contacted for pickup.

B. THE PRIMARY CONTAINER is the cryovial that holds the aliquoted biological material.

1. Make sure the cryovial itself is properly and tightly sealed.
2. Verify that proper labeling has been completed.

C. THE SECONDARY CONTAINER is the 81-cryovial cardboard case and the leak-proof, biohazard-labeled plastic bag, capable of withstanding pressure change to 95kPa during air transport.

1. **Important: If a patient's biospecimen is known to contain any of the infectious substances listed on Table A, set them aside and package them separately.**

Packaging Plasma

1. Fill the 81-slot cryovial case with the maximum number of 1.2ml cryovials (ONLY plasma) without splitting up samples from the same patient. DO NOT split up cryovials from the same patient to different cryovial boxes.
2. Line the inside bottom of the plastic bag with one piece of absorbent material.
3. Place the cryovial box inside the plastic bag and seal tightly.

Packaging Blood Products

1. Place up to thirty (30) 3.0ml cryovials (blood products) inside ONE (1) plastic bag, separate from the 81-slot cryovial box.
2. Wrap the cryovials on all sides using 2 pieces of absorbent material. This is to ensure no cryovials will come in direct contact with the dry ice in the outer container.

C. THE OUTER CONTAINER is the insulated bio-shipment box, which will contain up to FOUR (4) 81-slot cryovial cases (inside plastic bags), the plastic bags that each contains up to THIRTY (30) 3.0ml cryovials corresponding with the same patients, as well as dry ice.

1. Important: If a patient's biospecimen is known to contain any of the infectious substances listed on Table A, follow the "Category A" Infectious Substance directions at the end of the section. If not, follow the "Category B" label directions.

"Category B" Infectious Substance Label

1. Affix the UN 3373 label on the outside of the bio-shipment box to designate it as a Category B Infectious Substance – Diagnostic Specimen.
2. Affix the Class 9 label on the outside of the bio-shipment box to designate it as containing dry ice.
3. Fill out the FedEx label completely, with the sender and recipient's full name and address, and affix it to the outside of the box.
4. Fill out the UCSF DNA Bank Form, which includes all containers, and place it in a separately sealed leak-proof plastic bag inside the box.
5. Place enough dry ice to completely cover the bottom of the insulated box.
6. Place up to FOUR (4) 81-slot cryovial cases (inside plastic bags) within the bio-shipment box.
7. Place plastic bags that each contains up to THIRTY (30) 3.0ml cryovials corresponding with the same patients within the bio-shipment box.
    a. Verify again that that the absorbent material is fully wrapped around the 3.0ml cryovials, and that no cryovials are in direct contact with dry ice. Dry ice will cause cryovials to crack.
8. Line the bottom, inside border, and all open space in the outer container with 3kg dry ice, broken into small pieces to facilitate compact packaging and ensure frozen temperatures.
9. Place the rest of the dry ice evenly on top of the plastic bags before closing the bio-shipment container.

10. Make sure all contents are present inside the bio-shipment box before sealing it.
    a. Seal the bio-shipment box as a regular package: **not-airtight**. Dry ice must be allowed to sublimate – sealing the box airtight will cause it to explode during shipping.

"Category A" Infectious Substance Label

1. NOTE: "Category A" Infectious Substance containers must be packaged separately from "Category B", but up to FOUR cryovial boxes containing either only "Category A" or "Category B" cryovials may be shipped together.
2. Affix the labels (infectious substance label, UN 2814, Cargo Aircraft) on the outside of the bio-shipment box to designate it as a Category A Infectious Substance.
3. Affix the Class 9 label outside of the bio-shipment box to designate it as containing dry ice.
4. Fill out the FedEx label completely, with the sender and recipient's full name and address, and affix it to the outside of the box.
5. Complete every section of the "Shipper's Declaration for Dangerous Goods."
6. Declarations MUST be typewritten or computer-generated. Handwritten declarations will not be accepted. Declarations MUST be printed in color to display the red-striped border. Always print at least 4 copies: provide 3 for the carrier and keep 1 for site records. Regulations require that sites must retain their copy of the Declaration for 375 days.
   A. Shipper: Enter your full name, address and telephone number
   B. Consignee: Enter full name and address of recipient. Include the text, "Person responsible for the shipment" followed by your name and phone number.
   C. Transport Details: Indicate shipment as 'restricted to cargo aircraft.' Airport of departure and destination will be filled out by the carrier, leave blank.
   D. Shipment Type: Cross out "radioactive" to indicate you are shipping a non-radioactive substance.
   E. UN or ID Number: On separate lines, enter '2814' for the "Category A" biospecimen and '1845' for the dry ice.
   F. Proper Shipping Name: Enter 'Infectious substance, affecting humans' and 'Dry Ice' respectively and exactly as they appear.
   G. Class or Division: Enter '62' for the biospecimen and '9' for dry ice
   H. Packing Group: Biospecimens are not assigned packing groups. Enter 'III' for dry ice.
   I. Quantity and Type of Packaging: Enter net quantity for each material. Use only metric units. At the bottom of this column, indicate the number and type of packaging used.
   J. Packing Instructions: Enter '602' for the biospecimen and '904' for dry ice
   K. Authorization: Leave this column blank.
   L. Additional Handling Instructions: An Emergency Contact number must be provided in this space. The Emergency Contact number provided must allow for direct and immediate access to a person knowledgeable of the shipment contents as well as appropriate procedures to follow in the event of an emergency involving the shipment. Phone numbers that only allow access to answering machines or answering services are not acceptable.
   M. Sign and date each copy of your Shipper's Declaration.
7. Fill out the UCSF DNA Bank Form, which includes all containers, and place it in a separately sealed leak-proof plastic bag inside the box.

8. Place enough dry ice to completely cover the bottom of the insulated box.
9. Place up to FOUR (4) 81-slot cryovial cases (inside plastic bags) within the bio-shipment box.
10. Place plastic bags that each contains up to THIRTY (30) 3.0ml cryovials corresponding with the same patients within the bio-shipment box.
    a. Verify again that that the absorbent material is fully wrapped around the 3.0ml cryovials, and that no cryovials are in direct contact with dry ice. Dry ice will cause cryovials to crack.
11. Line the bottom, inside border, and all open space in the outer container with 3kg dry ice, broken into small pieces to facilitate compact packaging and ensure frozen temperatures.
12. Place the rest of the dry ice evenly on top of the plastic bags before closing the bio-shipment container.
13. Make sure all contents are present inside the bio-shipment box before sealing it.
    a. Seal the bio-shipment box as a regular package: **not-airtight**. Dry ice must be allowed to sublimate – sealing the box airtight will cause it to explode during shipping.

VI. BIOSPECIMEN SHIPPING

A. Complete all necessary information requested on the pre-addressed airway bill.
1. Select “FedEx Priority Overnight” under “Express Package Service”
2. Select “NO” in Section 6: “Special Handling”

B. Contact FedEx at 1-800-463-3339 to arrange a pickup.

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 1

FORM 1: SITE SPECIMEN LOG

NATIONAL INSTITUTES OF HEALTH UCSF University of California San Francisco	**GO GRANT** **Transforming TBI Research and Clinical Care**	**BIOSPECIMENS & BIOMARKERS SITE SPECIMEN LOG** **RESEARCH SITE:**

Patient ID	Initial Blood Volume, Sample 1	Initial Blood Volume, Sample 2	Initial Blood Collection Date & Time	Blood Transf? (Y/N)	Plasma Aliquots: ID Numbers	Aqueous Blood Mixture / Whole Blood Cryovials: ID Numbers	Cryovial Box #	Packaging Date & Time	Shipment Date & Time	Ship-ment #	Infectious Substance, if known (list all)	Shipment Type (Cat. A / B)

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 2

FORM 2: UCSF DNA BANK – SAMPLE PROCESSING REQUEST FORM

UCSF DNA BANK - SAMPLE PROCESSING REQUEST FORM

Shipping Address:	Phone: (415) 514-9932 / (415) 514-9933	USPS Mailing Address:
Mission Bay/Lung Biology Center Rock Hall 19B, 5th Floor 1550 4th Street, Room RH 515 San Francisco, CA 94158	Fax: (415) 514-4365 http://medschool.ucsf.edu/dna	UCSF/Lung Biology Center Box 2911 San Francisco, CA 94143-2911

Date (*mm/dd/yyyy*):	05/01/2010		
Requestor's First Name:	John	**Requestor's Last Name:**	Yue
Principal Investigator:	Geoffrey T. Manley	**Department:**	Neurosurgery - UCSF
Account#:	4 4 4 9 5 6	**Fund#:**	2 1 5 0 2

Study Name/Number: Manley GO

DNA Bank Number	Sample ID	Date Drawn	Sample Processing	Tube Size	Tube Type
	SF-0001P1	04/27/2010	G	1.2ml	Purple EDTA
	SF-0001P2	04/27/2010	G	1.2ml	Purple EDTA
	SF-0001P3	04/27/2010	G	1.2ml	Purple EDTA
	SF-0001D1	04/27/2010	E	3.0ml	Purple EDTA
	SF-0001D2	04/27/2010	E	3.0ml	Purple EDTA
			Choose Letter	Tube Size	Purple EDTA
			Choose Letter	Tube Size	Purple EDTA
			Choose Letter	Tube Size	Purple EDTA

Comments: Blood collected in 2 separate 13 x 75 mm x 4.0 mL Purple -EDTA tubes; specimen centrifuged and plasma aliquoted; buffy coat combined from 2 tubes ; D = buffy coat; P = plasma

Sample Processing	Tube Type	Tube Size
E – DNA Extraction from Buffy Coat **G** – Plasma Storage	**EDTA – 13x75 mm x 4.0 mL** Purple original sample (x2)	3.0ml – Cells for DNA 1.2ml – Plasma Only

Date Received: _____ Initials: _____

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 3

FORM 3: SHIPPER'S DECLARATION OF DANGEROUS GOODS (EXAMPLE)

USE ONLY FOR CATEGORY A INFECTIOUS SUBSTANCES

SHIPPER'S DECLARATION FOR DANGEROUS GOODS

Shipper **John Smith** **123 Center St.** **San Francisco, CA 94143** **415-476-1300**	Air Waybill No. Page **1** of **1** Pages Shipper's Reference Number (optional)
Consignee **Dr. Paul Jones** **345 University Ave.** **Boston, MA 02010** **617-555-1000** Person Responsible for Shipment: John Smith, 415-476-1300	
Two completed and signed copies of this Declaration must be handed to the operator.	WARNING Failure to comply in all respects with the applicable Dangerous Goods Regulations may be in breach of the applicable law, subject to legal penalties.
TRANSPORT DETAILS This shipment is within the limitations prescribed for: *(delete non-applicable)* PASSENGER AND CARGO AIRCRAFT / CARGO AIRCRAFT ONLY **XXXX** Airport of Departure	
Airport of Destination	Shipment Type *(delete non-applicable)* NON-RADIOACTIVE / RADIOACTIVE **XXXXX**

NATURE AND QUANTITY OF DANGEROUS GOODS

Dangerous Goods Identification: UN or ID No.	Proper Shipping Name	Class or Division (Subsidiary Risk)	Packing Group	Quantity and Type of Packing	Packing Instructions	Authorization
UN2814	**Infectious substance, affecting humans (Hepatitis B virus)**	6.2		50 mL	602	
UN1845	**Dry ice**	9	III	4 KG **All packed in one fibreboard box.**	904	

Additional Handling Information

Emergency Telephone Number **Chem-Tel 800-999-1245**

I hereby declare that the contents of this consignment are fully and accurately described above by the proper shipping name, and are classified, packaged, marked and labelled/placarded, and are in all respects in proper condition for transport according to the applicable international and national governmental regulations. I declare that all of the applicable air transport requirements have been met.	Name/Title of Signatory **John Smith / Professor** Place and Date **San Francisco; September 29, 2005** Signature *(see warning above)*

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 4

TABLE A: INDICATIVE EXAMPLES OF CATEGORY A INFECTIOUS SUBSTANCES

UN # and Proper Shipping Name	Microorganism	
UN 2814 Infectious substance affecting humans	- *Bacillus anthracis* cultures - *Brucella abortus* cultures - *Brucella melitensis* cultures - *Brucella suis* cultures - *Burkholderia mallei* - *Pseudomonas mallei* - Glanders cultures - *Burkholderia pseudomallei* - *Pseudomonas pseudomallei* cultures - *Chlamydia psittaci* - avian strains cultures - *Clostridium botulinum* cultures - *Coccidioides immitis* cultures - *Coxiella burnetii* cultures - Crimean-Congo hemorrhagic fever virus - Dengue virus cultures - Eastern equine encephalitis virus cultures - *Escherichia coli*, verotoxigenic cultures - Ebola virus - Flexal virus - *Francisella tularensis* cultures - Guanarito virus - Hantaan virus - Hantavirus causing hemorrhagic fever with renal syndrome - Hendra virus - Hepatitis B virus cultures - Herpes B virus cultures - Human immunodeficiency virus cultures - Highly pathogenic avian influenza virus cultures	- Japanese Encephalitis virus cultures - Junin virus - Kyasanur Forest disease virus - Lassa virus - Machupo virus - Marburg virus - Monkeypox virus - *Mycobacterium tuberculosis* cultures - Nipah virus - Omsk hemorrhagic fever virus - Poliovirus cultures - Rabies virus cultures - *Rickettsia prowazekii* cultures - *Rickettsia rickettsia* cultures - Rift Valley fever virus - Russian spring-summer encephalitis virus cultures - Sabia virus - *Shigella dysenteriae* type 1 cultures - Tick-borne encephalitis virus cultures - Variola virus - Venezuelan equine encephalitis virus - West Nile virus cultures - Yellow fever virus cultures - *Yersinia pestis* cultures
UN 2900 Infectious substance affecting animals	- African swine fever virus cultures - Avian paramyxovirus Type 1 – Velogenic Newcastle disease virus cultures - Classical swine fever virus cultures - Foot and mouth disease virus cultures - Lumpy skin disease virus cultures - *Mycoplasma mycoides* - Contagious bovine pleuropneumonia cultures - Peste des petits ruminants virus cultures - Rinderpest virus cultures - Sheep pox virus cultures - Goatpox virus cultures - Swine vesicular disease virus cultures - Vesicular stomatitis virus cultures	

* This list is not exhaustive.

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 5

TABLE B: SUMMARY OF SHIPPING INFORMATION

Shipment Type	Proper Shipping Name	UN Number	Hazard Class	Packing Group (PG)	Packing Instruction (PI)	Max. Net qty./pkg. for Passenger Aircraft	Max. Net qty./pkg. for Cargo Aircraft
Category A infectious substance, affecting humans and possibly animals	Infectious substance, affecting humans	UN 2814	6.2	-	602	50 ml or 50 g	4 L or 4 kg
Category A infectious substance, affecting only animals (not humans)	Infectious substance, affecting animals	UN 2900	6.2	-	602	50 ml or 50 g	4 L or 4 kg
Category B infectious substance	Diagnostic specimens or Clinical specimens	UN 3373	6.2	-	650	4 L or 4 kg	4 L or 4 kg
Dry Ice	Dry Ice or Carbon Dioxide, solid	UN 1845	9	III	904	200 kg	200 kg
Non-infectious, transducing genetically modified organism or microorganism	Genetically modified micro-organisms	UN 3245	9	-	913	No limit	No limit

BIOSPECIMENS/BLOOD DRAW ATTACHMENT 6

DIAGRAM I: SHIPPING LABELS (EXAMPLE)

Figure 1.

Figure 2.

Figure 3.

Figure 4.

V. COMPONENT THREE: IMAGING (CT and MRI)

V.A. INCLUSION/EXCLUSION

INCLUSION

- Patients who are eligible to participate in the Project and give consent for access to initial CT brain scan
- Patients who pass the MRI screening questions (see "Exclusion")
- Outpatients who are capable of returning to the facility for a 3T Research MRI
- Inpatients: TBD

EXCLUSION

- Those who are not eligible to participate in the Project or who do not consent to a blood draw.
- Patients in any of the following categories CANNOT have an MRI:
    - Younger than 8 years old
    - Cardiac pacemaker / defibrillator
    - Pregnant or possibly pregnant
    - Aneurysm or aortic clip(s)
    - Carotid artery vascular clamp
    - Neurostimulator
    - Shunt (spinal or intraventricular)
    - Metal or wire mesh implants
    - Wire sutures of surgical staples
    - Harrington rods (spine)
    - Stents, filters, or coils (intravascular)
    - Any metal fragments or shrapnel
    - Internal pacing wires
    - Non-removable body piercing(s)
    - Electrodes (on body, head, or brain)
    - Any other electronically, magnetically, and mechanically activated implants and/or devices
    - Implanted devices for seizures (e.g. vagal nerve stimulator)
    - Worked extensively with metal – may have metal fragments in eye
- Patients in any of the following categories MIGHT NOT be eligible for an MRI; the decision is that of the study radiologist:
    - Insulin or infusion pump
    - Bone growth / fusion stimulator – non-ferromagnetic
    - Cochlear, otologic, or ear implant
    - Prosthesis or implant (eye, heart valve, etc.)
    - Artificial limb or joint – non-ferromagnetic
    - Vascular access port and / or catheter
    - Tattooed makeup (eyeliner, lips, etc.)
    - Breathing disorder
    - Claustrophobia
    - Hearing aid **(Remove before MRI)**
    - Dentures **(Remove before MRI)**
    - Nicotine patches **(Remove before MRI)**
    - Bone / joint pin, screw nail, wire, plate (Titanium is allowable)

NOTES:

- Study subjects who consent to an MRI within two weeks post-injury will be given the results of their structural MRI which may include important information regarding the subject's health and referral options. However, it must be explained to patients that this research MRI is not a substitute for a clinical diagnostic scan.

- Best case scenario would be to conduct MRI scans using 3T research-based machine (better quality and less expensive), but 1.5T will suffice (e.g. with inpatients).

- ACUTE SITES (UCSF/SFGH, UMCB, UMCP) will schedule patients for MRIs within 1 – 2 weeks post-injury with the goal being exactly SEVEN DAYS post-injury.

- REHAB SITE (MOUNT SINAI) will schedule patients for MRIs as soon as possible following acute hospital discharge.

UCSF University of California San Francisco	GO GRANT Transforming TBI Research and Clinical Care	Effective Date: 04/01/2010 Version No. 2

DRAFT Imaging Protocol: CT (all patients) and MRI (subset of patients)
Patient Screening, Scheduling, and Data Transmission

I. GENERAL INFORMATION

A. OBJECTIVE

1. This document describes the requirements for CT transmission for all patients, patient screening for MRI, MRI scheduling for a subset of patients, and data submission to a secure online repository.
2. Adherence to this protocol will ensure the accurate and relevant collection of radiologic data from qualifying patients in a safe and efficient manner.

B. SCOPE

1. This protocol applies to all radiologic material acquired as part of the GO Grant, and all persons involved in such acquisitions.

C. RESPONSIBILITIES

1. All personnel involved in patient recruitment will have completed the CITI, HIPAA, and other training as required by their local IRB.
2. Each site assumes responsibility for all research-related patient care, such as disclosing pertinent radiologic results to the patient and ensuring safety precautions are in place.
3. Each site is responsible for (1) transmitting the images of all patients' initial CTs that were completed as part of their clinical care, and (2) scheduling and transmitting the MRI images collected on a subset of those patients one to two weeks post-presentation.
4. Each site is responsible for following their IRB rules as they pertain to imaging transmission: whether that be identified or de-identified.
5. Each site is asked to confirm that their ED is adhering to the CT guidelines (attached).
6. UCSF's radiologist, Pratik Mukherjee, MD PhD, will implement a flexible and interactive imaging database capable of synthesizing different levels of detail across core injuries, and he will be the one to review all sites' collected radiologic data.

II. SUPPLIES

A. ATTACHMENTS

1. Article: Guidelines for CT Decision-Making in the ED
2. MRI Screening Form
3. CT and MRI Specifications

III. PATIENT SCREENING

A. PATIENT SCREENING FOR MRI

1. Patients will be screened for their suitability for an MRI during the consent process, but it is a good idea to have the screening done a second time (using the attached form) before the MRI appointment (see Section V).

IV. SCHEDULING PATIENTS

A. MRI SCHEDULING (Outpatients and Inpatients)

1. Determine if the patient will be able to return within 1 – 2 weeks for the 3T research-based MRI at China Basin or if s/he will likely still be hospitalized and is possibly already scheduled for the inpatient MRI.
2. Obtain the patient's availability for an MRI within one to two weeks of presentation, as well as any special needs or equipment that the patient would need at the time of the scan.
3. Discuss the patient's special needs and availability with the radiologist to assess their compatibility with the scan and the details of their appointment. If patient no longer qualifies, contact and inform the patient. Otherwise, ensure that the patient's special needs are addressed prior to scan.
4. Finalize the patient's MRI scan date and time with the patient, and on the MRI booking schedule as well as with the GO Grant radiology contact personnel.
5. Conduct at least two follow-up reminders via telephone, email, or mail; the second attempt to be made the day before the appointment to remind patient and to confirm transportation plans to and from the facility.

V. COORDINATING WITH MRI CONTACT PERSONNEL

A. DAY OF MRI SCANNING

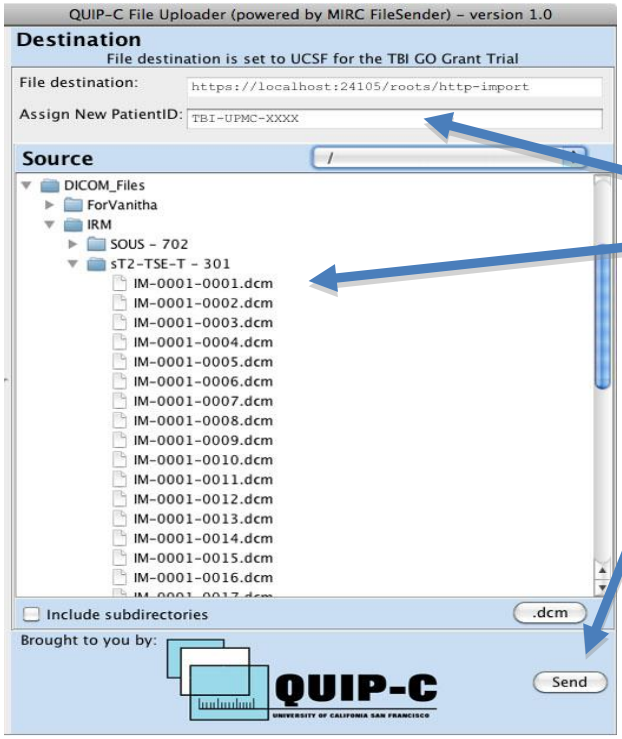
1. Meet arriving patients
2. Escort them to the imaging department
3. Ensure that all special needs and/or equipment are met before starting the scan
4. Ensure that qualified personnel certified in operation of the MRI scanner will be present for the duration of the scan
5. Ensure that the MRI scan results are shared with the patient
6. Escort them from the imaging department after their appointment
7. Verify contact information and future contact (if participating in 3- and/or 6-month follow-up)
8. De-identify the MRI file and upload it to the secure online imaging repository
9. Complete all pertinent information on the GO Grant database

VI. CT AND MRI TRANSMISSION TO UCSF IMAGING DATABASE

A. CT and MRI TRANSMISSION TO UCSF IMAGING DATABASE

1. An easy-to-use Java application has been developed that should run on any platform (Windows, Mac OS X, Linux) and can be used to anonymize and upload the imaging data that will be collected as a part of the GO Grant.
2. The application will open a simple window (see below) that will allow the user to select a directory or a set of files in a directory, type in the pre-defined GO Grant specific patient ID, and upload the imaging data to a custom DICOM node sitting on our research PACS at UCSF.
3. Prior to upload, the application will use the Clinical Trials Processor (CTP) software from the RSNA to automatically de-identify the images before sending the data. All transmission will be secured via VPN and SSL.
4. A Windows VPN client will also be provided with the distributed package that can be used to establish a point-to-point secure tunnel to the UCSF research PACS network. The GO Grant sites will share a unique username and password (TBD) for the VPN connection.

5. We have envisioned this application sitting on a computer that is able to export information from the clinical PACS system onto the local harddrive. From there a specified user will be able to use the uploader application to send the de-identified data to UCSF after connecting to VPN.



File Transmission Protocol

1. Assign New PatientID
2. Select *.dcm files/directories for upload
3. Click Send

VII. CT AND MRI DOCUMENTATION ONTO GO GRANT DATABASE

- To be determined …

IMAGING: ATTACHMENT 1

GUIDELINES FOR CT DECISION-MAKING IN THE EMERGENCY DEPARTMENT

The following article is from the Annals *of* Emergency Medicine Volume52, No. 6: December 2008, pages 714 – 748.

The article is titled “Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting”, and was written by the American College of Emergency Physicians (ACEP)/Centers for Disease Control and Prevention (CDC) Panel to revise the 2002 article “Clinical Policy: Neuroimaging and Decisionmaking in Adult Mild Traumatic Brain Injury in the Acute Setting”.

The article is 35 pages long, encompassing pages 7 – 42 of Section V: Component 4: Imaging

IMAGING: ATTACHMENT 2

MRI SCREENING FORM

Patients who answer 'yes' to any of the following questions CANNOT have an MRI:

☐ YES	☐ NO	Younger than 8 years old
☐ YES	☐ NO	Cardiac pacemaker / defibrillator
☐ YES	☐ NO	Pregnant or possibly pregnant
☐ YES	☐ NO	Aneurysm or aortic clip(s)
☐ YES	☐ NO	Carotid artery vascular clamp
☐ YES	☐ NO	Neurostimulator
☐ YES	☐ NO	Shunt (spinal or intraventricular)
☐ YES	☐ NO	Metal or wire mesh implants
☐ YES	☐ NO	Wire sutures of surgical staples
☐ YES	☐ NO	Harrington rods (spine)
☐ YES	☐ NO	Stents, filters, or coils (intravascular)
☐ YES	☐ NO	Any metal fragments or shrapnel
☐ YES	☐ NO	Internal pacing wires
☐ YES	☐ NO	Non-removable body piercing(s)
☐ YES	☐ NO	Electrodes (on body, head, or brain)
☐ YES	☐ NO	Any other electronically, magnetically, and mechanically activated implants and/or devices
☐ YES	☐ NO	Implanted devices for seizures (e.g. vagal nerve stimulator)
☐ YES	☐ NO	Worked extensively with metal – may have metal fragments in eye

Patients who answer 'yes' to any of these questions MIGHT NOT be able to have an MRI. There must be a discussion with the study radiologist to determine eligibility.

☐ YES	☐ NO	Insulin or infusion pump
☐ YES	☐ NO	Bone growth / fusion stimulator – non-ferromagnetic
☐ YES	☐ NO	Cochlear, otologic, or ear implant
☐ YES	☐ NO	Prosthesis or implant (eye, heart valve, etc.)
☐ YES	☐ NO	Artificial limb or joint – non-ferromagnetic
☐ YES	☐ NO	Vascular access port and / or catheter
☐ YES	☐ NO	Tattooed makeup (eyeliner, lips, etc.)
☐ YES	☐ NO	Breathing disorder
☐ YES	☐ NO	Claustrophobia
☐ YES	☐ NO	Hearing aid **(Remove before MRI)**
☐ YES	☐ NO	Dentures **(Remove before MRI)**
☐ YES	☐ NO	Nicotine patches **(Remove before MRI)**
☐ YES	☐ NO	Bone / joint pin, screw nail, wire, plate (Titanium is allowable)

IMAGING: ATTACHMENT 3

ADULT CT PROTOCOLS

	NCT	PCT	CTA	CECT
Image Acquisition Mode	Helical Pitch: 0.8-1:1	2 phases: - 1st phase: 1 image per second, duration = 30-45 seconds - 2nd phase: 1 image per 2-3 seconds, duration = 30-45 seconds total duration of the acquisition at least 70-90 seconds	Helical Pitch: 1-1.5:1	Helical Pitch: 0.8-1:1
Gantry Rotation	1 second per gantry rotation (can be decreased down to 0.5 second for agitated patients)	1 second per gantry rotation (up to every 3 seconds with “shuttle” or “toggle table” mode)	0.4-0.8 second per gantry rotation	1 second per gantry rotation (can be decreased down to 0.5 secnd for agitated patients)
Image Acquisition Parameters	120-140 kVp, 200-400 mA dose modulation recommended to reduce dose (noise index 4-6)	80 kVp, 100 mAs	120-140 kVp, 200-400 mA dose modulation recommended to reduce dose (noise index 4-6)	120-140 kVp, 200-400 mA dose modulation recommended to reduce dose (noise index 4-6)
Coverage and Slice Thickness	whole brain coverage 2.0-3.75mm slice thickness slice interval = slice thickness	maximal coverage possible based on CT scanner configuration (minimal coverage of 20 mm slab per contrast bolus injection preferable; two boluses is suggested to double coverage for all CT scanners with under 4 cm detector length unless precluded by contrast dose considerations) focus on supratentorial compartment/anterior circulation 5-10 mm-thick slices field of view ~24 cm	from the aortic arch to the vertex 0.5-1.5mm slice thickness slice interval = 80% slice thickness	whole brain coverage 2.0-3.75mm slice thickness slice interval = slice thickness
Slice Orientation	parallel to hard palate	parallel to hard palate; lowest slice through the proximal middle/anterior cerebral artery (above the orbits)	parallel to hard palate	parallel to hard palate
Contrast Material:	none applicable	350-370 mg/mL iodinated contrast material; high concentration, low/iso osmolar contrast preferred; follow local guidelines for contrast-induced nephropathy prevention		
Contrast Volume	not applicable	35-50 mL, followed by 20-40 mL saline flush	40-70 mL, followed by 20-40 mL saline flush	contrast from PCT/CTA
Injection Rate	not applicable	4-6 mL per second (power injector required) same injection rate for contrast and saline	same as for perfusion-CT	contrast from PCT/CTA
IV Access	not applicable	18-20 gauge IV line right antecubital vein preferred (for anatomical reasons, reduces pooling of contrast, lowers the risk of extravasation and minimizes streak artifact at thoracic inlet in CTA portion)		
Miscellaneous		PCT can be performed before or after CTA		

PEDIATRIC CT PROTOCOLS

	0-6 months	6-12 months	1-10 years	10-18 years
kVp	80	80	80	80
mAs	60	60	80	100
Number of images	40	30	35	40
Time reconstruction interval between successive images	0.5 sec	1 sec	1 sec	1 sec
Duration of data acquisition	20 sec	30 sec	35 sec	40 sec
Used amount of iodinated contrast material	1 cc/kg	1 cc/kg	1 cc/kg	1 cc/kg
Injection rate	1 cc/sec	1.2 cc/sec	1.5 cc/sec	2 cc/sec
Delay between beginning of intravenous administration of contrast material and data acquisition *	3 sec	4 sec	5 sec	5 sec

IMAGING: ATTACHMENT 3, continued

3T MRI TRAUMA PROTOCOL

Sequence	2D FLAIR	GRE/ SWI	DWI (GE,opt)	3D T2	3D T1	FLASH 2D (opt)
Orient	Obl. Axial	Obl. Axial	Obl. Axial	Sag	Sag	Obl. Axial
TR (ms)	9000	30	5000	2500	1950	800
TE (ms)	78	20	Minimum	359	2.26	20
TI (ms)	2500				900	
FA (degree)	150	15	90	variable	9	20
FOV (mm^2)	256x192	256x192	256x256	256x256	256x256	256x192
Matrix size	256x256	512x256	128x128	256x256	256x256	256x256
Nz/TH (mm)	32/4	64/2	32/4	192/1	176/1	32/4
Voxel size(mm)	1x1x4	0.5x1x2	2x2x4	1x1x1	1x1x1	1x1x4
#Acq./#DTI dirn	1	1	2	1	1	1
Fat Suppr	yes	no	yes	no	no	no
Slice oversa	0	25%	0	0	45.5%	
Phase Enc. Dir	R to L	R to L	A to P	A to P	A to P	R to L
Parallel Imaging	2/47	2/24	2/24	2/24	2/24	2/24
BW	250	100	1346	751	200	180
Echo spac. (ms)	9.8		0.83	3.16	6.8	
Flow Comp	no	yes		No	no	yes
Turbo factor	15		128	141		
b-val (sec/mm^2)			0,, 1000			
Time	**2:44**	**4:18**	**1:27**	**4:02**	**4:33**	**2:54**

IMAGING: ATTACHMENT 3, continued

1.5T MRI TRAUMA PROTOCOL

Sequence	**2D FLAIR**	**GRE/ SWI**	**DWI (GE,opt)**	**T2 TSE tran**	**T1-MPRAGE**	**FLASH 2D (opt)**
Orient	Obl. Axial	Obl. Axial	Obl. Axial	Obl. Axial	Sagittal	Obl Axial
TR (ms)	9540	50	5400	7000	2000	1110
TE(ms)	114	40	Minimum	106	3.22	26
TI (ms)	2500				1000	
Flip Angle (degree)	150	15	90	160	8	20
FOV (mm^2)	256x192	256x192	256x256	256x192	256x256	256x192
Matrix size	256x256	512x256	128x128	256x256	512x256	256x256
Nz/TH (mm)	32/4	64/2	32/4	32/4	120/2	32/4
Voxel size(mm)	1x1x4	0.5x1x2	2x2x4	1x1x4	0.5x1x2	1x1x4
#Acq./#DTI dirn	2	1	3	1	1	1
Fat Suppr	no	no	yes	no	no	no
Phase Enc. Dir	R to L	R to L	A to P	R to L	R to L	R to L
Parallel Imaging	2/30	2/24	2/24	None	None	
BW	201	80	1502	130	160	80
Echo spac (ms)	9.5		0.75	11.8	10	
Flow Comp	no	yes	no	no	no	yes
Turbo factor	29		128	17		
b-val (sec/mm^2)			0/1000			
Time	**2:53**	**5:47**	**2:27**	**2:55**	**8:32**	**3:35**

VI. COMPONENT FOUR: OUTCOMES (THREE- AND SIX-MONTHS)

VI.A. INCLUSION/EXCLUSION

INCLUSION:

- Three-month follow-up:
    - Patients eligible to participate in the Project who are younger than 18 years old and consent to a follow-up phone call three months post presentation (GOSE Pediatrics).
    - Patients eligible to participate in the Project who are aged 18 years and older who consent to a follow-up phone call three months post presentation.
    - TO BE DISCUSSED: Translations

- Six-month follow-up:
    - Patients eligible to participate in the Project who are younger than 18 years old who consent to a follow-up phone call six months post presentation (GOSE Pediatrics).
    - Patients eligible to participate in the Project who are aged 18 years and older who consent to complete a battery of neurocognitive tests six months post presentation.
    - TO BE DISCUSSED: Translations

EXCLUSION:

- Three-month follow-up:
    - Those who are not eligible to participate in the Project or who do not consent to a three-month follow-up.
    - TO BE DISCUSSED: Translations

- Six-month follow-up:
    - Those who are not eligible to participate in the Project or who do not consent to a six-month follow-up.
    - TO BE DISCUSSED: Translations

NOTES:

- If a subject cannot participate, but a surrogate is available, we will ask surrogates to answer functional outcome measures.

- Study subjects who consent to participate in the three- or six-month follow-up outcome measures could benefit from being followed in terms of intervention and referrals for any new symptoms.

- Dr. Wayne Gordon will conduct training for the RAs and neuropsych technicians who will be administering tests. Details TBD.

- We will need to defer to interventional drug studies (e.g. ProTECT) to make sure we do not contaminate their outcome measures.

UCSF University of California San Francisco	**GO GRANT** **Transforming TBI Research and Clinical Care**	Effective Date: 04/01/2010 Version No. 2
Outcome Measures: 3- and 6-month Follow-up **Timeline, Measures Used, Scheduling, Scoring, Data Entry, Data Storage**		

I. GENERAL INFORMATION

A. OBJECTIVE

1. This document describes the outcome measures identified by the inter-agency Traumatic Brain Injury-Common Data Elements (TBI-CDE) Outcomes workgroup that address the documentation of the natural course of recovery from TBI, prediction of later outcome, and measurement of treatment effects, allowing the comparison of outcomes across multiple studies.
2. Adherence to this protocol will ensure that patients selected for three- and six-month follow-up will be evaluated using a common set of measures.

B. SCOPE

1. This protocol applies to all outcomes testing conducted by project staff at the three- and six-month assessment time points.

C. RESPONSIBILITIES

1. All personnel involved in neurocognitive testing will have completed the CITI, HIPAA, and other training as required by their local IRB, as well as specialized training for each of the neurocognitive measures.
2. Each site assumes responsibility for all research-related patient care and ensuring that precautions are in place.
3. The primary purpose of the three-month telephone follow-up GOSE (for patients 18 and older) and GOSE Pediatrics (for patients younger than 18) will be for global outcome information and tracking of patients to potentially increase the percentage who will be available for the more extensive follow up at six months.
4. Only specially-trained personnel may administer the six-month follow-up neurocognitive battery of tests (for 18 and older) and the GOSE Pediatrics (for patients younger than 18). Some tests can be completed on the telephone and/or mailed to the patient, but the ideal situation would be to meet face-to-face.

II. SUPPLIES

A. MEASURES

1. Subjects 18 years and older:
    a. Glasgow Outcome Scale Extended (GOSE)
    b. California Verbal Learning Test – II (CVLT-II)
    c. Trail Making Test (TMT)/Heaton norms
    d. Wechsler Adult Intelligence Scale (WAIS-IV) Processing Speed Index
    e. Brief Symptom Inventory – 18 Item (BSI – 18)
    f. Rivermead Post Concussive Symptom Questionnaire (RPQ)
    g. Craig Handicap Assessment & Reporting Technique (CHART – SF)
    h. Satisfaction with Life Scale (SWLS)
    i. PTSD Checklist – Civilian (PCL-C)
    j. Functional Independence Measure (FIM) – ONLY Pittsburgh and Mount Sinai
2. Subjects younger than 18 years:
    a. Glasgow Outcome Scale Extended Pediatrics (GOSEP)

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III. SCHEDULING PATIENTS

A. All eligible patients will have already consented for the three- and/or six-month follow-up upon admission.
B. Obtain the patient's availability as well as any special needs.
C. Conduct two follow-up reminders via telephone, email, or mail; the second attempt to be made the day before the appointment to remind patient and to confirm transportation plans to and from the facility.

IV. DATA COLLECTION, SCORING, AND DATABASE ENTRY

A. Each measure will have different instructions for collection, scoring, and data entry.
B. TBD: Norms, translations, testing goals, versions.
C. TBD: Training for the administration of all of the tests.

V. OVERVIEW OF MEASURES

❖ **Glasgow Outcome Scale Extended (GOSE) for patients 18 and older**
TIMING: Three- and Six-month Follow-up
DOMAIN: Global Outcome
DESCRIPTION: 8 questions (each with subparts), Administered
The Glasgow Outcome Scale Extended (GOSE) is a revision of the original Glasgow Outcome Scale (GOS) that provides eight, rather than five, categories of outcome: (1) Dead, (2) Vegetative State, (3) Lower Severe Disability, (4) Upper Severe Disability, (5) Lower Moderate Disability, (6) Upper Moderate Disability, (7) Lower Good Recovery, and (8) Upper Good Recovery. GOSE ratings are easily recoded to GOS ratings. Ratings are based on patient consciousness, independence, ability to work, social and leisure activities, social relationships, and other residua from TBI. Structured interviews are provided to facilitate ratings. This scale is the most commonly used TBI global outcomes and there is an extensive literature demonstrating reliability and validity for each scale. Use of these scales permits comparison to much of the world literature on TBI outcome.

❖ **Glasgow Outcome Scale Extended Pediatrics (GOSEP) for patients younger than 18**
TIMING: Three- and Six-month Follow-up
DOMAIN: Global Outcome
DESCRIPTION: 8 questions (each with subparts), Administered
An adaptation of the original Glasgow Outcome Scale (GOS), the pediatric version provides five categories of outcome: (1) Good outcome, (2) Moderately disabled, (3) Severely disabled, (4) Vegetative, (5) Dead. Ratings are based on patient consciousness and other residua from TBI. Structured interviews are provided to facilitate ratings. This scale is the most commonly used TBI global outcomes and there is an extensive literature demonstrating reliability and validity for each scale. Use of these scales permits comparison to much of the world literature on TBI outcome.

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1. **California Verbal Learning Test – II (CVLT – II)**
   TIMING: Six-month Follow-up
   DOMAIN: Neuropsychological Impairment
   DESCRIPTION: TBD (Short vs Standard vs Alternate forms)
   New items provide more comprehensive information than ever before. Examinees are read a list of words, selected after careful study of their frequency of use across multiple demographic variables, and asked to recall them across a series of trials. In addition to recall and recognition scores, CVLT–II measures encoding strategies, learning rates, error types, and other process data. CVLT–II includes forced-choice items useful for detecting malingering, thereby helping to reduce false results. New options provide flexibility in test administration. You can use the Short Form when exam time is limited or when you need less detailed test information. The Short Form is also helpful when examinee fatigue is a concern, or severe memory or cognitive deficits make the Standard or Alternate Forms impractical. The Short Form features lists of nine words in three categories and takes only 15 minutes to administer (plus two delay periods totaling 15 minutes). The new Alternate Form prevents artificially inflated scores when re-testing is necessary. The Standard and Alternate Forms can be administered in 30 minutes, with an additional 30-minute delay.

2. **Trail Making Test (TMT) using Heaton norms**
   TIMING: Six-month Follow-up
   DOMAIN: Neuropsychological Impairment
   DESCRIPTION: 2 parts, administered, 5min deadline
   Trail Making Test (TMT) is a measure of attention, speed, and mental flexibility. The main advantages of the TMT are its sensitivity to the cognitive impairment associated with TBI, brevity, widespread use among neuropsychologists, and good reliability. Demographically-adjusted normative data are available for a wide age range. Practice effects are found over short retest intervals, but disappear after several administrations. After longer intervals, TMT scores show only modest change in healthy adults. Performance on TMT is affected by age with performance declining as age increases.

3. **Wechsler Adult Intelligence Scale (WAIS IV) Processing Speed Index**
   (Digit Symbol Coding and Symbol Search subtests)
   TIMING: Six-month Follow-up
   DOMAIN: Neuropsychological Impairment
   DESCRIPTION: 2 parts, administered, untimed
   This Index is based on Digit Symbol Coding and Symbol Search subtests of the WAIS IV. The concept being measured is the amount of time it takes to process a set amount of information, or the amount of information that can be processed within a certain unit of time. As part of the Wechsler Adult Intelligence Scale, it has extensive normative data, and excellent psychometric properties. It is clinically one of the most sensitive cognitive measures to neurologic conditions of the brain. It is culturally, racially, and ethnically sensitive. It is useable across literacy levels.

4. **Brief Symptom Inventory – 18 Item (BSI-18)**
   TIMING: Six-month Follow-up
   DOMAIN: Psychological Status
   DESCRIPTION: 18 items, self-reported
   The Brief Symptom Inventory 18 (BSI-18) is a short form of the Symptom Checklist-90-R. It is designed to provide a brief self-report measure of psychological distress and has three subscales (Depression, Anxiety, and Somatization), as well as a Global Severity Index. The self-report measure consists of 18 items rated on a 5-point rating scale, and can be completed either through paper-and-pencil or computerized administration formats. The BSI-18 was selected as a core measure because of its brevity, global assessment of common psychological issues in individuals with TBI, and sound psychometric characteristics. It can be used for initial assessment, as well as to monitor change in response to treatment.

5. **Rivermead Post Concussive Symptom Questionnaire (RPQ)**
   TIMING: Six-month Follow-up
   TITLE: DOMAIN: Post Concussive Symptoms
   DESCRIPTION: 16 items, self-reported
   The RPQ is a measure of post-concussion symptom presence and severity following TBI. It contains 16 items, which the participant rates in relation to pre-morbid functioning. The RPQ can be administered by written self-report or by in-person or telephone interview. The RPQ is most useful in assessing post-concussion symptoms in persons with mild to moderate TBI, but has also been used in patients with severe TBI. The RPQ total score does not appear to be associated with age, gender, cause of injury, or duration of posttraumatic amnesia in patients with TBI. The RPQ was selected as a core measure based on its sound psychometric characteristics and capacity to detect clinical changes in patients with mild TBI. The scale has been used to investigate the relationship between behavioral and neurophysiologic markers of injury and outcome prediction.

6. **ONLY Pittsburgh and Mount Sinai will be using this measure**
   Functional Independence Measure (FIM)
   TIMING: Six-month Follow-up
   DOMAIN: Cognitive and Motor Limitations
   DESCRIPTION: Cognition Subscale = 5 items, administered; Motor Subscale = 13 items, administered
   Selected as a legacy measure of both physical and cognitive activity limitations, this ordinal rating scale has the advantage of very widespread clinical use in TBI and other rehabilitation populations; multiple, validated response formats including observational ratings and self- or proxy report, either in person or by phone; and extensive use in studies of diagnostic accuracy, outcome prediction, and treatment effectiveness. Item response analysis of the FIM has confirmed a motor domain consisting of 13 items and a cognitive domain consisting of five items. These subscales may be used separately for different purposes. For example, Cognitive FIM scores predict amount of supervision (vs. physical assistance) received in the home setting, and predict falls even more robustly than Motor FIM. There is low correlation between Cognitive FIM and mental and physical health

measures, suggesting discriminant validity. Ceiling effects may limit the FIM's utility for longitudinal studies of TBI, although ceiling effects are less extreme for Cognitive vs. Motor FIM in moderate/severe TBI.

7. **Craig Handicap Assessment & Reporting Technique Short Form (CHART-SF)**
   TIMING: Six-month Follow-up
   DOMAIN: Social Role Participation
   DESCRIPTION: 6 subscales, 19 questions, administered, ~7min
   The CHART-SF was designed to provide a simple, objective measure of the degree to which impairments and disabilities result in handicaps in the years after initial rehabilitation. It contains six subscales: Physical Independence; Cognitive Independence; Mobility; Occupation; Social Integration; and Economic Self-Sufficiency. Rasch analysis indicates satisfactory separation of items along the handicap dimension and good item-fit within each subscale. It demonstrates good inter-rater, test-retest and subject-proxy reliability. Individuals reporting activity limitations have been shown to score significantly lower than those without activity limitations. It has also been shown to discriminate between individuals with TBI and stroke who report lower scores than those with other disabilities. CHART Cognitive Independence scores correlate higher with FIM cognitive subscale scores than FIM motor subscale scores.

8. **Satisfaction with Life Scale (SWLS)**
   TIMING: Six-month Follow-up
   DOMAIN: Perceived Health-Related Quality of Life
   DESCRIPTION: 5 items, self-reported
   The SWLS is a global measure of life satisfaction. The SWLS consists of five items that are completed by the individual whose life satisfaction is being measured. The SWLS has shown consistent differences between populations that would be expected to have different qualities of life (e.g., psychiatric patients or male prison inmates). The SWLS has also been found to change in the expected directions in response to major life events, and in patients receiving psychotherapy.

9. **PTSD Checklist – Civilian (PCL – C)**
   TIMING: Six-month Follow-up
   DOMAIN: PTSD
   DESCRIPTION: 17 items, self-reported
   The PCL is a standardized self-report rating scale for PTSD comprising 17 items that correspond to the key symptoms of PTSD. Two versions of the PCL exist: 1) PCL-M is specific to PTSD caused by military experiences and 2) PCL-C is applied generally to any traumatic event. The PCL can be easily modified to fit specific time frames or events. For example, instead of asking about "the past month," questions may ask about "the past week" or be modified to focus on specific events. The PCL is self-administered and respondents indicate how much they have been bothered by a symptom over the past month using a 5-point (1–5) scale, circling their responses. Responses range from "**1**" (Not at All) through to "**5"** (Extremely).

VII. APPENDICES

A. Three Sample Consent/Assent Forms

B. Draft Case Report Form Protocol

C. Outcome Measures

APPENDIX A: THREE SAMPLE INFORMED CONSENTS/ASSENT FORMS

SAMPLE 1: (SPECIFIC TO UCSF/SFGH)

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

FOR PERSONS AGED 13 AND OLDER

This is a medical research study being conducted by UCSF/SFGH. You are being asked to take part in this study because you have suffered a traumatic brain injury (TBI) within the last 24 hours and have had a CT scan completed here at San Francisco General Hospital as part of your clinical care.

Why is this study being done?
Dr. Manley and his research team are trying to learn more about head injuries. The main study procedures will take place at SFGH and the UCSF China Basin Imaging Center.

How many people will take part in this study?
We expect to enroll 300 patients at SFGH.

What will happen if I take part in this research study?
This will depend on your level of injury and your willingness to participate.

- **Component 1: ENROLLMENT/DATA COLLECTION:**

If you agree, we will obtain medical information collected by the emergency and hospital personnel who treated you since your injury. We will also be asking you some general questions about your history. In order to have the most complete information possible regarding your injury, we will also have access to your SFGH medical record, including your CT scan.

There are four more parts to the study; you can decide whether or not to do each one on an individual basis:

- **Component 2: BLOOD DRAW (SFGH)**

A small amount of blood, about 2 tablespoons, will be taken from a tube or catheter already in place as part of standard care. If you do not have one of these catheters in place as part of standard care, we will use a small needle to remove blood from a vein in your arm. We will obtain one blood sample only. This blood sample will be stored in the UCSF DNA Bank at Mission Bay. Genetic and protein testing will be performed to look for differences that may affect or predict recovery after traumatic brain injury. The results of genetic testing will not be made available to you. If you agree, some of the blood will be kept and may be used for future research, but your sample will be identified by an assigned identification number; your personal identifying information will not be shared.

- **Component 3: IMAGING (UCSF China Basin Campus)**

Within two weeks of your injury, we will use a brain-scanning machine called a magnetic resonance imager, or MRI. The MRI uses powerful magnets and radio waves to take pictures of your brain. You will not require sedation or medication for the MRI. For the imaging, you will be asked to change into a hospital gown and lie very still in an MRI tube for about one hour. The environment will be noisy and may feel claustrophobic, but it is not dangerous. You will be given earplugs to lessen the noise. You will be in frequent communication with the MRI technician and may press a button if you need assistance at any time. The basic structural MRI results will be made available to you.

- **Component 4: THREE MONTH FOLLOW-UP (telephone)**

Three months after your injury, we will contact you by phone to ask you questions about your recovery, which will take about 30 minutes. We will have an interpreter with us on the phone if that makes communication easier.

- **Component 5: NEUROCOGNITIVE TESTING AT SIX MONTHS (SFGH Brain and Spinal Injury Center)**

Six months after your injury, we will talk with you again to learn more about your recovery. If you are aged 18 years or older, we will also ask you to meet with us to complete some tasks and pencil and paper exercises to learn more about your memory, attention, and movement, which will take anywhere from 2 – 3 hours. You will have many chances to take breaks between the tasks.

How long will I be in the study?

The length of your time in the study depends on the degree to which you choose to participate. Study components start today and continue through the next six months, but you are free to participate in as many or as few components as you like and to withdraw at any time.

- Component 1 (Case Report Forms) will take approximately 30 minutes today,
- Component 2 (blood draw) will take 10 – 15 minutes today,
- Component 3 (MRI at China Basin in one or two weeks) will take about one hour for those aged 8 and older and who pass a screening test,
- Component 4 (three-month follow-up phone call) may take up to 30 minutes, and
- Component 5 (six-month follow-up phone call or meeting here at SFGH) may take up to 30 minutes for those younger than 18, and should take approximately 2 – 3 hours for those aged 18 and older.

If you choose to complete the entire study with us, you will participate for approximately five hours over the course of six months.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell one of the study doctors or another member of the study team if you are thinking about stopping or decide to stop. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest or if the study is stopped.

What side effects or risks can I expect from being in the study?

Participation in research may cause a loss of privacy, but information about you will be kept as confidential as possible. To protect your confidentiality, data and blood specimens will be coded (i.e., personally identifiable information will be removed) before being sent to any outside organizations. The recipients of this information will be asked to treat it confidentially, and your identity will not be disclosed in any publications. Your participation will not affect or take the place of the standard diagnostic procedures or treatment you may receive for your injury. For more information about risks and side effects, ask one of the study doctors.

- **Component 1: Case Report Form (SFGH)**

The risks may involve some degree of loss of privacy. This will be minimized as much as possible. To protect your confidentiality, data will be coded (i.e., personally identifiable information will be removed) and your identity will not be disclosed

- **Component 2: BLOOD DRAW (SFGH)**

The blood sample will be taken from a catheter or tube that is in place as part of standard care in the intensive care unit or with a small needle. The amount of blood taken is small and the procedure is considered to be of minimal risk. You may experience some temporary bruising if we need to draw blood using a needle. There is a risk of loss of confidentiality. To protect your confidentiality, data will be coded (i.e., personally identifiable information will be removed) before being sent to the UCSF DNA Bank at Mission Bay and any outside organizations. Your identity will not be disclosed. The results of genetic testing will not be made available to you. If your specimen is used for future research, we may give your specimens and certain medical information about you (for example, diagnosis, blood pressure, age if less than 85) to other researchers (including those outside of UCSF) but we will not give them your name, address, phone number, or any other information that would identify you.

Reports about any research will not be given to you or your doctor and no results will go into your medical record. The research will not change the care you receive. Your specimen and any information about you will be kept until it is used up or destroyed. It may be used to develop new drugs, tests, treatments or products. In some instances these may have potential commercial value. Your personal health information cannot be used for additional research without additional approval from either you or a review committee. Your specimens will be kept indefinitely. If you decide later that you do not want your specimens and information to be used for future research, you can tell us, and we will destroy any remaining identifiable specimens and information if they are no longer needed for your care. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

- **Component 3: MRI (UCSF China Basin)**

Not everyone can participate in this component, which is why we have a separate form for screening. If you are able to participate, your participation may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why we will provide earplugs. Some people sometimes experience mild dizziness during the MRI. You will not require sedation or medication for the MRI. You can stop the session at any time by pressing a button. This research MRI is part of the study and is not a substitute for a clinical diagnostic scan, but you will be told the results of your MRI and that might include important information regarding your health and referral options that would otherwise be missed. This information might include distressing news but everything will be explained to you, including instruction to follow-up with your doctor.

- **Component 4: THREE MONTH FOLLOW-UP VIA TELEPHONE**

Some of the interviews and questionnaires will ask you about personal information. You are not required to answer any questions that make you feel uncomfortable. In addition, all personal information will be kept confidential and will not be stored with your name**.**

- **Component 5: NEUROCOGNITIVE TESTING IN PERSON (SFGH Brain and Spinal Injury Center, Building 1)**

In this study, participants younger than 18 years old will receive a repeat of Component 4. Participants aged 18 and older will be asked about drug or alcohol use and other possibly illegal activities. The researchers will keep information about you as confidential as possible, but complete confidentiality cannot be guaranteed. During the interviews we will ask you questions about your mood and suicide. If you state that you have or have had suicidal thoughts, it will be documented in the research record. If you are actively suicidal, the RA will notify the psychiatrist on call at the hospital and follow their instructions.

Are there benefits to taking part in the study?

Study subjects who consent to an MRI within two weeks post-injury will be given the results of their structural MRI which may include important information regarding the subject's health. The study radiologist will explain the findings to you and you may be advised to follow up with your primary care physician. Similarly, study subjects who consent to participate in the three- and/or six-month follow-up outcome measures could benefit from being followed in terms of intervention and referrals for any new symptoms. Finally, this study will help doctors to standardize data collection for TBI patients and to learn more about what tests (genetics, blood proteins, and/or MRIs) may affect or predict recovery. It is hoped that this information will help in the treatment of future patients with traumatic brain injuries.

What other choices do I have if I do not take part in this study?

You have the choice not to participate in this study. If you choose not to participate, you will still receive the standard care for traumatic brain injury.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law, but if information from this study is published or presented at scientific meetings, your name and other personal

information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include: The National Institutes of Health (NIH) and the UCSF Committee on Human Research.

What are the costs of taking part in this study?
You will not be charged for any of the study activities.

Will I be paid for taking part in this study?
Yes. Component 3, the MRI scan(which is strictly for participants aged 8 years and older), will have a compensation of $75 and Component 5, the six-month follow-up meeting (which is strictly for participants aged 18 years and older), will have compensation for $125. Upon completion of each of these components, you will choose your method of payment: either in the form of a Gift Card (available immediately upon completion of the Component) or a check from the University of California (which will be mailed to you to within 6 to 8 weeks). You will need to provide your social security number in order to be paid by check. There will be no compensation for completing Components 1 (Case Report Forms), 2 (Blood Draw), or 3 (Three month follow-up phone call).

What happens if I am injured because I took part in this study?
It is important that you tell a member of the research team or one your study doctors, either Dr. Geoffrey T. Manley (415-206-6238) or Dr. Pratik Mukherjee (415-476-5538), if you feel that you have been injured because of taking part in this study. You can tell them in person or call them.

Treatment and Compensation for Injury:
If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to a study doctor about any questions, concerns, or complaints you have about this study. You can also call John Yue at 415-206-4457. If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

CONSENT
You have been given copies of this consent form to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled. If you wish to participate in any or all of this study's components, please sign your initials in the appropriate column(s) below, and then sign your full signature below that.

Component	YES (please initial)
Component 1/Basic Enrollment /Case Report Form today: Interview and access to SFGH Medical Chart (30 minutes)	_ _ (your initials)
Component 2, part 1: Blood draw today (10 – 15 minutes)	_ _ (your initials)
Component 2, part 2: Blood specimens may be kept for use in future research	_ _ (your initials)
Component 3: MRI at China Basin within one to two weeks (1 hour) **MUST BE AT LEAST 8 YEARS OLD AND PASS SCREENING TEST**	_ _ (your initials)
Component 4: telephone follow-up in 3 months (30 minutes)	_ _ (your initials)
Component 5: telephone follow-up in 3 months (30 minutes) **FOR PATIENTS YOUNGER THAN 18 YEARS OLD**	_ _ (your initials)
Component 5: follow-up meeting in 6 months: (2 – 3 hours) **MUST BE AT LEAST 18 YEARS OLD**	_ _ (your initials)

Date	Participant's Signature for Consent	Print Name
Date	Signature of Person Obtaining Consent	Print Name
Date	Translator Signature	Print Name

For patients aged 13 – 17

As the parent or legal guardian for _____, your signature below will give your permission for her/him to be included in this study (Case Report Form/interview/medical chart review) and to the following components that are marked:

○	Blood Draw
○	Blood Draw sample saved for future research
○	MRI
○	Three month follow-up phone call
○	Six month follow-up phone call

Date	Parent or Legal Guardian Signature for Consent	Print Name

For patients incapable of consenting for themselves:

The person being considered for this study is incapable of consenting for her/himself because of their medical condition. As legal surrogate, your signature below will give your permission for _____ to be included in this study. (Case Report Form/interview/medical chart review) and to the following components that are marked:

○	Blood Draw
○	Blood Draw sample saved for future research
○	MRI
○	Three month follow-up
○	Six month follow-up phone call (for patients younger than 18)
○	Six month follow-up meeting (for patients 18 years and older)

Date _____ Legal Surrogate Signature _____ Print Name _____

For patients who were initially incapable of consenting for themselves, but who are later able to do so:

Due to your injuries, we weren't able to talk with you about this study when you first came to the hospital.

Option 1: Instead, we talked with [name of parent, legal guardian, or surrogate] who agreed to let you start in the study.

Option 2: Instead, because neither you nor anyone else could consent for you, we used an approved waiver form so we could access your medical record and draw some blood.

Now that you are able to talk with us, you can decide for yourself whether or not you want to be enrolled in part or all of the study by writing your initials next to the components that you agree to

Component	YES (please initial)
Component 1/Basic Enrollment /Case Report Form today: Interview and access to SFGH Medical Chart (30 minutes)	_ _ (your initials)
Component 2, part 1: Blood draw today (10 – 15 minutes)	_ _ (your initials)
Component 2, part 2: Blood specimens may be kept for use in future research	_ _ (your initials)
Component 3: MRI at China Basin within one to two weeks (1 hour)	_ _ (your initials)
Component 4: telephone follow-up in 3 months (30 minutes)	_ _ (your initials)
Component 5: telephone follow-up in 6 months (30 minutes) for those younger than 18	_ _ (your initials)
Component 5: follow-up meeting in 6 months: (2 – 3 hours) for those aged 18 years and older	_ _ (your initials)

Date _____ Participant's Signature for Consent _____ Print Name _____

Date	Signature of Person Obtaining Consent	Print Name
Date	Translator Signature	Print Name

OR

I decline to continue participation in the study.

___ I DO consent for researchers to use information already collected for study purposes.

___ I DO NOT consent for researchers to use information already collected for study purposes.

APPENDIX A: THREE SAMPLE INFORMED CONSENTS/ASSENT FORMS, continued.

SAMPLE 2: (SPECIFIC TO UCSF/SFGH)

ASSENT TO PARTICIPATE IN A RESEARCH STUDY

FOR YOUTH 7-12 YEARS OLD

Why are we meeting with you?
We want to tell you about something we are doing called a research study. A research study is when doctors collect a lot of information to learn more about something. Dr. Geoffrey Manley and some other doctors here at San Francisco General Hospital are doing a study to learn more about children with head injuries. After we tell you about it, we will ask if you'd like to be in this study or not.

Why are we doing this study?
We want to find out how to better help people with head injuries. So we are getting information from lots of boys and girls like you. In the whole study, we will be talking with 300 people here at San Francisco General Hospital who have had head injuries. That will include people of all ages.

What will happen to you if you want to be in this study?
First, your parents will be asked if they give their permission for you to be in this study. They will also be asked if they agree to participate themselves, by doing some things like answering questions about you. If your parents don't agree, you cannot be in the study.

If your parents do agree, you still get to choose whether or not you want to be in the study.

If you and your parents do agree, here's what will happen next:

- Component 1: We will ask you and your parents some questions and also look at your medical record to get more information about your injury.

There are four more parts to this study, and you get to choose whether or not you want to do any or all of them. You can choose not to do any of them and no one will be angry with you. Here's a description of what those four other parts would involve:

- Component 2: If you agree to it, a small amount of your blood would be drawn. That means it will be taken by a needle in your arm. This will happen just one time, just today, and would take about 15 minutes. If you agree, part of the blood sample will be kept in a specimen bank for use in future research.

- Component 3: If you at least 8 years old, and if you agree to it, we would schedule you for an MRI nearby at the UCSF China Basin Campus, which is a way for us to see what your injury looks like on the inside. The machine is safe, but noisy, and we'd be asking you to lie still for an hour. You will not need sedation or medication for the MRI. This would happen one time within the next two weeks, and it would take about an hour.

- Component 4: If you agree to it, we would call you in three months to see how you are doing.

- Component 5: If you agree to it, we would call you in six months to see how you are doing.

Will this study hurt?

The stick from the needle to draw your blood might hurt, but the hurt would go away after awhile.

Will you get better if you are in this study?

No, this study won't make you feel better or get well. But the doctors might find out something that will help them take care of other people who get head injuries.

Will you be paid for taking part in this study?

Yes. If you are at least 8 years old and can participate in Component 3, the MRI scan, you will be given a gift card worth $75. There will be no compensation for completing Components 1 (Case Report Forms), 2 (Blood Draw), 3 (Three month follow-up phone call), or 5 (Six month follow-up phone call).

Do you have any questions?

You can ask questions any time. You can ask now. You can ask later. You can talk to me or you can talk to someone else.

Do you have to be in this study?

No, you don't. No one will be mad at you if you don't want to do this. If you don't want to be in this study, just tell us. Or if you do want to be in the study, tell us that. Or if you want to be in the study, but you don't want to do the additional parts, tell us that. And, remember, you can say yes now and change your mind later. It's up to you.

- **If you don't want to be in this study, just tell us.**
- **If you don't want to do the blood draw, just tell us.**
- **If you don't want to do the MRI, just tell us.**
- **If you don't want us to call in three months, just tell us.**
- **If you don't want us to call you in six months, just tell us.**

On the other hand,

- **If you want to be in this study, just tell us.**
- **If you want to be in the study and have a blood draw, tell us.**
- **If you want to be in the study and have a blood draw, and you want us to keep some of the blood for future research, just tell us.**
- **If you want to be in the study and have a blood draw, but you don't want us to keep some of the blood for future research, just tell us.**
- **If you want to be in the study and are eligible and interested in doing the MRI, tell us.**
- **If you want to be in the study and have us call you in three months, tell us.**
- **If you want to be in the study and have us call you in six months, tell us.**

Whatever you decide to do, you will have a copy of this form to keep.

****

SIGNATURE OF PERSON CONDUCTING ASSENT DISCUSSION

I have explained the study to _____(*print name of child here*) in language he/she can understand, and the child has agreed to be enrolled in the study (Case Report Form/interview/medical chart review) and to the following components that are marked:

○	Blood Draw
○	Blood Draw sample saved for future research
○	MRI

○	Three month follow-up phone call
○	Six month follow-up phone call

Signature of Person Conducting Assent Discussion

Date

Name of Person Conducting Assent Discussion (print)

ADDENDUM FOR MINORS AGED 7 - 12 WHO WERE INITALLY CONSENTED BY A PARENT OR LEGAL GUARDIAN BUT WERE INCAPABLE OF VERBAL ASSENT AT THE TIME.

Due to your injuries, we weren't able to talk with you about this study when you first came to the hospital. Instead, we talked with [*name of parent or legal guardian*] who agreed to let you start in the study.

Now that you are able to talk with us, please tell us whether or not you want to be in part or all of the study as follows:

- If you don't want to be in this study, just tell us.
- If you don't want to do the blood draw, just tell us.
- If you don't want to do the MRI, just tell us.
- If you don't want us to call in three months, just tell us.
- If you don't want us to call in six months, just tell us.

On the other hand,

- If you want to be in this study, just tell us.
- If you want to be in the study and have a blood draw, tell us.
- If you want to be in the study and have a blood draw, you want us to keep some of the blood for future research, just tell us.
- If you want to be in the study and have a blood draw, but you don't want us to keep some of the blood for future research, just tell us.
- If you want to be in the study, are eligible, and want to do the MRI, tell us.
- If you want to be in the study and have us call you in three months, tell us.
- If you want to be in the study and have us call you in six months, tell us.

SIGNATURE OF PERSON CONDUCTING ASSENT DISCUSSION

I have explained the study to _____(*print name of child here*) in language he/she can understand, and the child has agreed to be in the study and to the following components that are marked:

○	Blood Draw
○	Blood Draw sample saved for future research
○	MRI
○	Three month follow-up phone call
○	Six month follow-up phone call

Signature of Person Conducting Assent Discussion | Date

Name of Person Conducting Assent Discussion (print)

OR

I decline to continue participation in the study.

___ I DO consent for researchers to use information already collected for study purposes.

___ I DO NOT consent for researchers to use information already collected for study purposes.

APPENDIX A: THREE SAMPLE INFORMED CONSENTS/ASSENT FORMS, continued.

SAMPLE 3: (SPECIFIC TO UCSF/SFGH)

INFORMED PARENTAL CONSENT
FOR YOUTH 7-12 YEARS OLD TO PARTICIPATE IN A RESEARCH STUDY

You have received a copy of this form because your child has suffered a traumatic brain injury (TBI) within the last 24 hours and has had a CT scan completed here at San Francisco General Hospital as part of clinical care.

You are being asked to consent for your child to take part in this research study. This is a medical research study being conducted here at UCSF/SFGH doctors Geoffrey T. Manley, MD, PhD, and Pratik Mukherjee, MD, PhD.

Participation in the study is voluntary, which means you can choose whether or not you want your child to participate. Before you can make your decision, you will need to know what the study is about, the risks and possible benefits of being in this study, and what you or your child will have to do in this study. The research team is going to talk to you about the research study and this consent form. This form gives you important information about the study. Please take time to review this information carefully and ask any questions that you have.

Why is this study being done?
Dr. Manley and his research team are trying to learn more about head injuries. The main study procedures will take place at SFGH and the UCSF China Basin Imaging Center.

How many people will take part in this study?
We expect to enroll 300 patients at SFGH.

What will happen if your child takes part in this research study?
You and your child will choose whether or not to participate in any or all parts of the study.

- **Component 1: ENROLLMENT/DATA COLLECTION:**

If you and your child agree, we will obtain your child's medical information collected by the emergency and hospital personnel. We will also be asking you some general questions about your child's history. In order to have the most complete information possible regarding your child's injury, we will also have access to her/his SFGH medical record, including her/his CT scan.

There are four more parts to the study; you and your child can decide whether or not to do each one on an individual basis:

- **Component 2: BLOOD DRAW (SFGH)**

If you and your child agree, a small amount of blood, about 2 tablespoons, will be taken from a tube or catheter already in place as part of standard care. If your child does not have one of these catheters in place as part of standard care, we will use a small needle to remove blood from a vein in her/his arm. We will obtain one blood sample only. This blood sample will be stored in the UCSF DNA Bank at Mission Bay. Genetic and protein testing will be performed to look for differences that may affect or predict recovery after traumatic brain injury. The results of genetic testing will not be made available. If you and your child agree, part of the blood sample will be kept in the specimen bank for use in future research.

- **Component 3: IMAGING (UCSF China Basin Campus)**

If your child is at least 8 years old, and if you and your child agree, we will schedule her/him for an appointment for an MRI within the next two weeks. The MRI uses powerful magnets and radio waves to take pictures of the brain. You will not need sedation or medication for the MRI. For the imaging, s/he will be asked to change into a hospital gown.

S/he will be asked to lie very still in a tube for about one hour. The environment will be noisy and may feel claustrophobic, but it is not dangerous. S/he will be given earplugs to lessen the noise. S/he will be in frequent communication with the MRI technician and may press a button if s/he needs assistance at any time. The basic structural MRI results will be made available to you.

- **Component 4: THREE MONTH FOLLOW-UP (telephone)**

If you and your child agree, we will contact you by phone in three months to ask you and your child questions about her/his recovery, which will take about 30 minutes. We will have an interpreter with us on the phone if that makes communication easier.

- **Component 5: SIX MONTH FOLLOW-UP (telephone)**

If you and your child agree, we will contact you by phone in six months to ask you and your child questions about her/his recovery, which will take about 30 minutes. We will have an interpreter with us on the phone if that makes communication easier.

How long will your child be in the study?

The length of time in the study depends on the degree to which you and your child choose to participate. Study components start today and continue through the next six months, but your child is free to participate in all or some of the components and to withdraw at any time.

- Component 1 (Case Report Forms) will take approximately 30 minutes today,
- Component 2 (blood draw) will take 10 – 15 minutes today,
- Component 3 (MRI at China Basin in one or two weeks) will take about one hour,
- Component 4 (three-month follow-up phone call) may take up to 30 minutes, and
- Component 5 (six-month follow-up phone call) may take up to 30 minutes.

If you and your child choose to complete the entire study with us, participation will be approximately three hours over the course of six months.

Can your child stop being in the study?

Yes. Your child can decide to stop at any time. Tell one of the study doctors or another member of the study team if you or your child are thinking about stopping or decide to stop. The study doctor may stop your child from taking part in this study at any time if he/she believes it is in your child's best interest or if the study is stopped.

What side effects or risks can your child expect from being in the study?

Participation in research may cause a loss of privacy, but information will be kept as confidential as possible. To protect confidentiality, data will be coded (i.e., personally identifiable information will be removed) before being sent to any outside organizations. The recipients of this information will be asked to treat it confidentially, and your child's identity will not be disclosed in any publications. Your child's participation will not affect or take the place of the standard diagnostic procedures or treatment s/he may receive for her/his injury. For more information about risks and side effects, ask one of the study doctors.

- **Component 1: Case Report Form (SFGH)**

The risks may involve some degree of loss of privacy. This will be minimized as much as possible. To protect your child's confidentiality, data will be coded (i.e., personally identifiable information will be removed) and your child's identity will not be disclosed

- **Component 2: BLOOD DRAW (SFGH)**

The blood sample will be taken from a catheter or tube that is in place as part of standard care in the intensive care unit or with a small needle. The amount of blood taken is small and the procedure is considered to be of minimal risk. Your child may experience some temporary bruising if we need to draw blood using a needle. There is a risk of loss of confidentiality. To protect your child's confidentiality, data will be coded (i.e., personally identifiable information will be removed) before being sent to the UCSF DNA Bank at Mission Bay and any outside organizations. Your child's identity will not be disclosed. The results of genetic testing will not be made available to you. If you agree to allow your child's specimen to be used for future research, we may give your child's specimens and certain medical information about her/him (for example, diagnosis, blood pressure, age) to other researchers (including those outside of UCSF) but we will not give them your child's name, address, phone number, or any other information that would identify her/him. Reports about any research will not be given to you, your child, or your doctor and no results will go into your child's medical record. The research will not change the care your child receives. Your child's specimen and any information about her/him will be kept until it is used up or destroyed. It may be used to develop new drugs, tests, treatments or products. In some instances these may have potential commercial value. Your child's personal health information cannot be used for additional research without additional approval from either you or a review committee. Your child's specimens will be kept indefinitely. If you decide later that you do not want your child's specimens and information to be used for future research, you can tell us, and we will destroy any remaining identifiable specimens and information if they are no longer needed for your child's care. However, if any research has already been done using portions of your child's specimens, the data will be kept and analyzed as part of those research studies.

- **Component 3: MRI (UCSF China Basin)**

Not everyone can participate in this component, which is why we have a separate form for screening. If your child is able to participate, participation may mean some added discomfort. In particular, your child may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why we will provide earplugs. Some people sometimes experience mild dizziness during the MRI. Your child can stop the session at any time by pressing a button. Your child will not require sedation or medication for the MRI. This research MRI is part of the study and is not a substitute for a clinical diagnostic scan, but you will be told the results of your child's MRI and that might include important information regarding her/his health and referral options that would otherwise be missed.

- **Component 4: THREE-MONTH FOLLOW-UP VIA TELEPHONE**

Some of the questions will ask about personal information. You or your child can refuse to answer any questions that make either of you feel uncomfortable. In addition, all personal information will be kept confidential and will not be stored with your child's name**.**

- **Component 5: SIX-MONTH FOLLOW-UP VIA TELEPHONE**

Some of the questions will ask about personal information. You or your child can refuse to answer any questions that make either of you feel uncomfortable. In addition, all personal information will be kept confidential and will not be stored with your child's name**.**

Are there benefits to taking part in the study?

Study subjects who consent to an MRI within two weeks post-injury will be given the results of their structural MRI which may include important information regarding health and referral options. The study radiologist will explain the findings to you and you may be advised to follow up with your child's primary care physician. Similarly, study subjects who consent to participate in the three- or six-month follow-up outcome measures could benefit from being followed in terms of intervention and referrals for any new symptoms. Finally, this study will help doctors to standardize data collection for TBI patients and to learn more about what tests (genetics, blood proteins, and/or MRIs) may affect or predict recovery. It is hoped that this information will help in the treatment of future patients with traumatic brain injuries.

What other choices do you have if your child does not take part in this study?
You have the choice whether or not to allow your child to participate in this study. If you decide that you do not want your child to participate, s/he will still receive the standard care for traumatic brain injury.

Will medical information be kept private?
We will do our best to make sure that the personal information in the medical record is kept private. However, we cannot guarantee total privacy. Personal information may be given out if required by law, but if information from this study is published or presented at scientific meetings, names and other personal information will not be used. Organizations that may look at and/or copy your child's medical records for research, quality assurance, and data analysis include: The National Institutes of Health (NIH) and the UCSF Committee on Human Research.

What are the costs of taking part in this study?
You will not be charged for any of the study activities.

Will your child be paid for taking part in this study?
Your child will receive a gift card worth $75 for completing Component 3, the MRI scan. There will be no compensation for completing Components 1 (Case Report Forms), 2 (Blood Draw), 3 (Three month follow-up phone call), or 5 (Six month follow-up phone call).

What happens if your child is injured because s/he took part in this study?
It is important that you tell a member of the research team or one the study doctors, either Dr. Geoffrey T. Manley (415-206-6238) or Dr. Pratik Mukherjee (415-476-5538), if you feel that your child has been injured because of taking part in this study. You can tell them in person or call them.

Treatment and Compensation for Injury:
If your child is injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814.

What are my child's rights if s/he takes part in this study?
Taking part in this study is a choice. You and your child will choose whether or not to take part in the study. If you decide that your child may take part in this study, s/he will be asked for her/his verbal assent. If you do not want your child to take part in the study, then your child will not be in the study.

No matter what decision you make, there will be no penalty to you or your child and neither of you will not lose any of your regular benefits. Leaving the study will not affect your child's medical care, and you and/or your child can decide to leave the study at any time. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to a study doctor about any questions, concerns, or complaints you have about this study. You can also call John Yue at 415-206-4457. If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

CONSENT

You have been given copies of this consent form to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about your child. PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to allow your child to participate or to withdraw at any point in this study without penalty or loss of benefits to which s/he is otherwise entitled. If you want your child to participate in

any or all of this study's components, please sign your initials in the appropriate column(s) below, and then sign your full signature below that.

Component	YES (please initial)
Component 1/Basic Enrollment /Case Report Form today: Interview and access to SFGH Medical Chart (30 minutes)	_ _ (your initials)
Component 2, part 1: Blood draw today (10 – 15 minutes)	_ _ (your initials)
Component 2, part 2: Blood specimens may be banked for use in future research.	_ _ (your initials)
Component 3: MRI at China Basin within one to two weeks (1 hour)	_ _ (your initials)
Component 4: telephone follow-up in 3 months (30 minutes)	_ _ (your initials)
Component 5: telephone follow-up in 6 months (30 minutes)	_ _ (your initials)

Date	Parent or Legal Guardian's Signature for Consent	Print Name
Date	Signature of Person Obtaining Consent	Print Name
Date	Translator Signature	Print

APPENDIX B: DRAFT CASE REPORT FORM PROTOCOL

APPENDIX C: OUTCOME MEASURES AND INSTRUCTIONS (WHERE AVAILABLE)