Development of an Ontology for Rehabilitation: Traumatic Brain Injury

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Dedication

For Ruby, the greatest three-legged dog who ever lived. You're a good girl, Ruby.

Abstract

Traumatic Brain Injury (TBI) rehabilitation interventions are very heterogeneous due to injury characteristics and pathology, patient demographics, healthcare settings, caregiver variability, and individualized, multi-discipline treatment plans. Consequently, comparing and generalizing the effectiveness of interventions is limited largely due to non-interoperable domain data. Addressing domain data interoperability through standardization can help unpack the "black-box" of rehabilitation treatment research. This paper describes the development of a foundational non-surgical, non-pharmaceutical ontology for TBI rehabilitation to facilitate domain interoperability. A conceptualization of the clinical domain was developed through a triangulation of data sources in order to create context and to serve as the underlying source for an ontology. A set of classes with primitive ontological relations based on the conceptualization was assembled in the Protégé Ontology Editor. The ontology is designed to facilitate further granularity of classes, properties, and instances as a collaborative hub for domain engagement. It is proposed that the ontology will aid in identification of effective rehabilitation components through the facilitation of comparative effectiveness research (CER).

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Chapter 1 Introduction

The September 2004 National Institutes of Health (NIH) *Roadmap for Medical Research* shifted the biomedical research paradigm in the United States by redefining the future context of research into three unique themes: New pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise (1). Summarily, this called for a redesign of the discovery and research process, creating frameworks for collaboration, sharing, and interoperability of data to improve the speed, quality, and efficiency of healthcare (2). While improving healthcare delivery was the core motivation for this proposal, inherent was the role of information technology as key to its success.

A significant consequence of this has been a recalibration of the relationship between biomedical research and clinical practice to allow continual knowledge flow so that one can inform the other. To achieve this flow, researchers and clinicians must use data and information systems that are interoperable. Localized models of information exchange are no longer acceptable as biomedical research is expected to aspire to a sharing and communication-based platform as medicine matures in the technology age (3). However, the challenges of interoperability of information systems and clinical terminologies as facilitators pose significant, foundational barriers to achieving research networks that resemble the NIH roadmap (4).

Confounding the technical problems of shareable healthcare knowledge are the challenges presented by respective healthcare domains and by the variability among patients, caregivers, settings, and administrative factors. Complicated systems of payment, care coordination, patient diversity, diagnosis and treatment variability, discordance over treatment efficacy and an abundance of anecdotal health information available through the Internet has created an often incoherent healthcare information ecology. The broad key question that emerges is how the increasing complexity of healthcare and healthcare information can be leveraged to not only clarify and complement one another but to facilitate the translational roadmap designed by the NIH.

Post-acute physical medicine rehabilitation for traumatic brain injury (TBI) exemplifies the challenges of healthcare information interoperability. TBI is a complex medical condition whose outcome varies by patient demographics, injury etiology and pathology, and by highly heterogeneous courses of post-acute interventions. The total effect of this complexity is a fragmented, non-interoperable healthcare information system in terms of comparative effectiveness research (CER). Consequently, developing treatment theory, identifying effective treatment components, sharing treatment data, and thus specifically informing patient care is difficult due to an underdeveloped domain standards that can facilitate both human and computer understanding, analysis, and sharing. The domain of TBI rehabilitation and research has many challenges to overcome to achieve a standardized, shareable information network that successfully "interoperates" and allows research and treatment to inform one another.

In order to be able to satisfy the translational goals of the NIH roadmap in the case of traumatic brain injury and similarly complex neurological condition physical medicine rehabilitation research, a domain schema for interoperability is needed. Thus, an ontology for post-acute TBI, physical medicine rehabilitation is proposed as a step toward enhanced clinical data interoperability, comparison of treatments, and evidence-based care. This discusses the challenges of physical medicine rehabilitation (non-drug, non-surgical) research in the context of TBI and describes a domain conceptualization and consequent ontology aimed at a standardized codification to support TBI physical medicine rehabilitation data sharing and research.

Rehabilitation services in TBI and other complex neurological conditions are often driven by factors other than efficacy of treatment. The ability and willingness of payers to provide resources for services often determines the selection of services and at what intensity. Clinicians from multiple respective disciplines attempting to deliver a unified set of services for a single patient can result in a contamination of treatments that mitigates or undoes the effect of another treatment. Additionally, payment coding systems confound the problem as disciplines may use different codifications or may define the same codes differently resulting in a lack of clarified descriptions of actual services delivered. Together, these factors obfuscate the delivery and codification of services in regard to the patient, impairment, treatment, outcome and use of treatment data for research (5).

The effect of these factors on patient care is two-fold: One, clinical research is limited by the consequent difficulty in making relevant comparisons of treatment efficacy and to then make broader statements of effectiveness across patient populations. The personalized nature of a disease like TBI necessitates granularity to inform treatment customization. Conclusive evidence of effectiveness requires a clear, nuanced understanding of the inputs and outputs of treatments. Second, underdeveloped standards and clinical information systems limit the power of treatment and research data. Domains as highly variable and context-dependent as TBI rehabilitation require structure and semantics of clinical terminologies that support reasoning functionality as means to develop personalized treatment programs.

Ontologies are information tools used for data aggregation and retrieval and serve as means for domain communication. They are assembled using domain-dependent terms, definitions, and relationships between terms to classify information related to the important concepts of the domain. They provide a common language which clinicians and researchers can leverage for the alignment of knowledge across settings. This alignment allows for increasingly refined data sets that can be analyzed to generate new hypotheses for treatment, to further test existing ones, and to ultimately contribute to knowledge bases. The implication for patient care is that clinicians are able to design dynamic theory-based treatment programs that address the unique needs of a complex pathology like TBI.

The use of an ontology to address issues of clinical complexity in TBI rehabilitation research is summarized by Chute's "Cycle of Patient Data Generating Medical Knowledge and Improved Care" framework (6). This portrays the idealized flow of data generated from patient encounters into information systems where further healthcare knowledge can be gleaned and fed back into subsequent patient encounters. It suggests the power of interoperability in terms of an iteratively improved treatment feedback loop. The placement of "Data Standards" and "Semantics" in the center of the model demonstrates the importance of an ontology. The framework portrays a generalized model for the problem statement, aims, and objectives of this project (Figure 1).

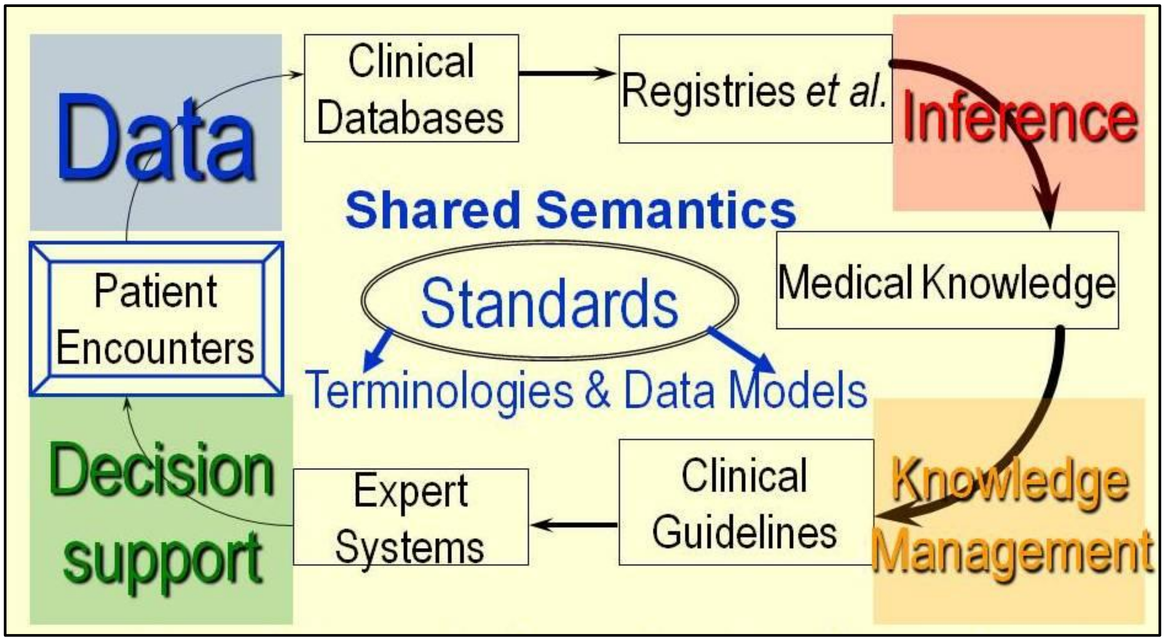

Figure 1. Interoperability of Clinical Data.
Used with permission of CG Chute, MD DrPH Mayo Clinic, Department of Health Sciences Research (6).

1.2 Problem Statement

Evidence-based medicine requires production of and access to best available evidence to inform treatment. The complexity of measuring the effect of rehabilitation in TBI makes determining the best treatments across settings and patient groups difficult and therefore impedes the evidence-based medicine process. Improving domain knowledge interoperability through standardization addresses this gap through syntax and semantics, allowing clinicians, researchers, and clinical information systems to leverage aligned data models through standardized exchange formats. Treatments will always reflect the particulars of locality to some degree, but a foundational common language that can normalize idiosyncrasies of data for sharing, can be used to "unpack" the individual components of a treatment program. Parsing granular components can identify new treatment theories and provide refinement for extant theories. Discussing post-acute,

multiple-discipline rehabilitation programs in general, Whyte and Hart state that "[A]ttempts to define treatments in a more systematic fashion, with greater uniformity of concepts and language, would further enhance communication across rehabilitation disciplines and between practitioners and consumers of rehabilitation"(7), p.641.
This study presents the development of a domain conceptualization and ontology for post-acute, multi-disciplinary traumatic brain injury physical medicine rehabilitation. By facilitating domain interoperability through standardization and semantics, TBI rehabilitation can better demonstrate the clinical data cycle of Chute's model. The problem statement is formally stated as:

> An ontology for Traumatic Brain Injury (TBI) rehabilitation (non-pharmacological, non-surgical) is needed to facilitate domain interoperability, treatment theory refinement, and comparative effectiveness research.

Considering Chute's statement that "to name something implies knowledge of its form," then the unparsed and unnamed "black box" of traumatic brain injury rehabilitation lacks a tool that can codify and explore its nature (8). Methods to systematically disaggregate the "black box" of rehabilitation interventions to help determine which factors lie along the causal pathway to patient-centered outcomes are needed (9). The result will be a shared understanding of the components and activities in the rehabilitation process that can better facilitate human and computational communication, improve the comparative effectiveness review process, and feed back into improved quality of care (7). Although psychopharmacology and surgical procedures commonly interact in TBI rehabilitation programs, they are not included in the scope. Design consideration will be given to interaction with emerging classifications in these domains(10).

1.3 Aims & Objectives

Aims:

1. Develop a domain conceptualization of post-acute Traumatic Brain Injury (TBI) rehabilitation.
2. Codify foundational classes and properties for a TBI physical medicine rehabilitation ontology.
3. Align domain conceptualization and ontology entities with comparative effectiveness review (CER) process .

Objectives:

1. Identify key foundational rehabilitation and TBI rehabilitation domain sources.
2. Develop source concept extraction method.
3. Validate concept extractions.
4. Develop intermediate knowledge representation (IR) of domain conceptualization.
5. Align intermediate representation with CER components.
6. Assemble TBI rehabilitation ontology class hierarchy, definitions and properties.

1.4 Significance

A report from a 2007 symposium on general post-acute physical medicine rehabilitation stated that “[m]easurement of rehabilitation interventions was regarded as a major topic and was acknowledged to be the ‘weakest leg’ of the stool, whether the focus is on specific treatment content or measures of organizational structure, process or communication” (11), p. 454. From a domain that is a major component of most TBI rehabilitation programs, Bilder explicitly details the need for concept representation and ontology development within neuropsychology (12). Finally, Hart noted in 2009 that in the domain of TBI physical medicine rehabilitation, "we lack a common language for specifying the critical *contents* of rehabilitation treatments as well as the *processes* by which we think of their effects" (13), p.825. Collectively, these statements portray the urgency from the field to continue development of standardized terminology and data models for TBI and other complex neurological condition rehabilitation.

Implicit within these assertions is that conducting interventions based on lore or other historical momentum could put patients at risk of harm (14). The tenets of evidence-based medicine require the field to improve its research base and facilitate the knowledge flow from research into practice. Whyte and Hart summarize this problem in stating that "[r]igorous definition of rehabilitation treatments, supported by theory, will facilitate needed efficacy research, will allow replication of that research, and will ultimately foster dissemination of effective treatments into clinical practice" (15), p.639.

The NIH Roadmap was the beginning of a number of legislative steps that directly and indirectly frame the need for biomedical ontology projects. The 2009 American Recovery and Reinvestment Act (ARRA) allocated $1 billion to improving quality in healthcare, including $300 million to the Agency for Health Research and Quality (AHRQ) for comparative effectiveness reviews (16). More specifically, the *2010-2014 National Institute on Disability and Rehabilitation Research (NIDRR) Long-Term Research Plan* stated that disability research should work to "[a]dvance understanding of barriers to and facilitators of knowledge translation," "[i]nvestigate mechanisms for successful knowledge translation," and "[p]romote the dissemination of knowledge generated through research and development by communicating in understandable language and formats that are accessible to all stakeholders, including policy makers" (17), p. 2566-67.

1.5 Rationale

A traumatic brain injury is a complex, bio-psychosocial medical condition that requires a complex intervention (7). It is largely viewed by providers and payers as a single event needing limited treatment, but in reality it is a chronic disease process that puts patients at greater long-term risk for neurological disorders, neurodegenerative diseases, neuro-endocrine disorders, psychiatric disease, and a variety of physical impairments (18). Its complexity in treatment design and research is further highlighted by the number of factors shown to have significant impact on outcomes, including the injury etiology and pathology, patient demographics, patient environment, treatment setting, caregiver variability, theoretical foundation of treatment plan, timing of services, and highly individualized treatment design (15). This phenomenon is referred to as the "black box" of complex intervention research as services are commonly delivered as a packaged program and outcomes are measured using broad tools which do not adequately identify the active ingredient of the intervention program.

Building a biomedical ontology is a time-consuming, difficult process as evidenced by the scope and collaborative effort of such prominent ontology projects such as the Gene Ontology (19). Achieving consensus of terminology and definitions from domain experts involves negotiation and ongoing iterations. Therefore, this project is presented as a foundational step toward a refined TBI physical medicine rehabilitation ontology that interacts with other neurological ontologies. It will serve as a methods model and a first iteration artifact with which the domain can interact and refine. As such, qualitative methods approach using sources grounded in research and practice was used here as a means to conceptualize the important concepts for domain communication. This diversity of sources, coupled with methods designed to satisfy validity criteria, ensures that the steps and results present a rigorous approach and meaningful contribution.

1.6 Description of Chapters

Chapter 2 discusses the principles of biomedical data interoperability and biomedical ontologies as means to facilitate. Chapter 3 is a review of the literature to present the background and complexity of TBI rehabilitation and the implications for comparing the effectiveness of interventions. Chapter 4 describes the methodology used to develop the TBI rehabilitation domain conceptualization, validation, and ontology. Chapter 5 presents the results of these methods and in Chapter 6 the connection of the results to the problem statement is discussed, along with implications and next steps. Finally, Chapter 7 summarizes the conclusions and contribution.

Chapter 2 Literature Review: Ontologies and Domain Conceptualization

2.1 Introduction

The foundation of Biomedical Informatics is the use of data, information, knowledge, and wisdom as integral pieces of the healthcare research and delivery process. Data are the atomic bits of cognition, generated through the delivery of care. Data aggregates, attains structure, and becomes information. Knowledge is obtained by using information in the context of a problem. Connecting knowledge to other knowledge forms wisdom, which ultimately represents a depth of understanding of a particular domain or matter which allows for informed decision-making (20). Implicit is the dynamic flow between these states of cognition. Informatics is the interdisciplinary field that "studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, motivated by efforts to improve human health" (21). The mechanics of informatics involve methods, computation, data schemas and computational languages, coding systems, controlled terminologies, and ontologies for the storage, retrieval and use of biomedical data, information, and knowledge (22). The path from data to wisdom to patient care using informatics tools can be referred to as "interoperability" which applies to multiple levels from bits of data to the content of large computerized knowledge bases in disparate settings. Informatics provides a framework for determining the interoperability needs of a clinical domain and a set of tools to address the needs.

2.1.1 Interoperability

Interoperability is defined by the Institute of Electrical and Electronics Engineers (IEEE) as the "[a]bility of a system or a product to work with other systems or products without special effort on the part of the customer" or the "ability of two or more systems or components to exchange information and to use the information that has been exchanged" (23). Interoperability can be considered in the context of daily life, as in the design of light bulbs from different manufacturers that all conform to fit a universal socket type or the ability of a compact disc playing in any brand of player. Interoperability is made possible by the implementation of standards (23).

2.1.1.1 Interoperability in Healthcare

In healthcare, interoperability is "the ability of health information systems to work together within and across organizational boundaries in order to advance the effective delivery of healthcare for individuals and communities" (24), Appendix B, P.190: original source Wikipedia. There are three levels of health information technology interoperability (25):

1. "Foundational" interoperability which allows data exchange from one information technology system to be received by another and does not require the ability for the receiving information technology system to interpret the data.
2. "Structural" interoperability which defines the structure or format of data exchange (i.e., the message format standards) where there is uniform movement of healthcare data from one system to another such that the clinical or operational purpose and meaning of the data is preserved and unaltered. Structural interoperability defines the syntax of the data exchange.

3. “Semantic” interoperability provides interoperability at the highest level, which is the ability of two or more systems or elements to exchange information and to use the information that has been exchanged. Semantic interoperability takes advantage of both the structuring of the data exchange and the codification of the data including vocabulary so that the receiving information technology systems can interpret the data.

The difficulty of healthcare interoperability is demonstrated by the diversity of activities requiring a degree of interoperability in a single healthcare system (26):

1. Requests for investigations such as laboratory tests and radiology
2. Prescriptions for medication and other therapy
3. Orders for nursing care, equipment, meals, and patient transport
4. Investigation reports from laboratories, imaging, and other diagnostic departments
5. Administrative data such as patient registration and identification; admissions, discharges, and transfers (ADT); and appointments
6. Letters and memos from one clinician to another, including referral, clinic, and discharge letters
7. Transfer and merging of electronic medical records
8. Information used for management, audit, and monitoring
9. Commissioning, billing, and accountancy

Each activity has multiple users and unique requirements. The confluence of clinical, administrative, financial, and regulatory data demonstrates the challenges for health care systems.

2.1.1.2 Progression of Terminologies & Systems

While healthcare data can be expressed in many forms (i.e., a heart rate reading, radiology image, item in a clinical note), the atomic element for system interoperability is a shareable clinical terminology, which may or may not have an associated coding system, that serves as a surrogate for data as it subsequently translates to information and knowledge (8). Indeed, controlled clinical terminologies are foundational aspects of dynamic processing, clinical research, billing, legal issues, data sharing, and data reporting (27). The importance of clinical terminologies is expressed by the notion that "without a controlled, predefined vocabulary, data interpretation is inherently complicated, and the automatic summarization of data may be impossible" (27), p. 59.

Addressing problems of interoperability in healthcare information technology first requires a consideration of the very nature of what is to be shared between systems. With knowledge transfer as the putative goal, parsing knowledge to its shareable elements is a requirement. The question then becomes, what constitutes knowledge? On a philosophical level, the field of epistemology has explored this question for several centuries (28). Relating more specifically to modern biomedical domains, knowledge can be viewed as a formal or informal presentation of data or as a set of heuristics derived through experience. The parsing process walks knowledge back to information which is viewed as "organized data." Data thus becomes the building block of interoperability meaning that this is the key level of analysis for issues of information and knowledge sharing (29)(22).

Several broad standardized terminologies and numerous domain-specific terminologies are used in biomedicine. Perhaps the best known and most widely used is the International Classification of Disease (current version, ICD-10). Initially developed as a mortality reporting system, this is a hierarchical terminology with families of terms for diagnoses, health status, disabilities, procedures, and reasons for healthcare contact (30). SNOMED-CT, another major clinical terminology, is a multi-axial, post-coordinated terminology that uses an *is_a* hierarchy to represent more complex medical concepts. Diagnostic Related Group (DRG) codes for classifying hospitalizations and Current Procedural Terminology (CPT) for diagnostic and therapeutic procedures are both examples of widely used controlled terminology systems for billing and reimbursement. The Logical Observation Identifiers Names and Codes (LOINC) system of codes provides a standard method of identifying laboratory and clinical results (http://loinc.org/). The American Nursing Association (ANA) recognizes 12 reference and interface terminologies including the Omaha System, a patient-centered point-of-care terminology designed for use across the continuum of care, research, and education (31).

Many clinical terminologies map to the Unified Medical Language System (UMLS) which serves as a coordinated environment for more than 1 million terms from >100 sources (32). Developed at the National Library of Medicine beginning in 1986, the UMLS collects terms into its "Metathesaurus," assigns each term a "Lexical Unique Identifier" (LUI) and groups them into concepts that are assigned a "Concept Unique Identifier" (CUI) and are linked through a set of defined semantic relationships. The contents of the UMLS can be summarized as having unified terminologies, definitions, taxonomies and semantics. There are three UMLS Knowledge Sources:

1. The Metathesaurus - more than one million biomedical concepts from >100 source vocabularies.

2. The Semantic Network - 133 categories and fifty-four relationships between categories for labeling the biomedical domain.
3. The SPECIALIST Lexicon & Lexical Tools - provide lexical information and programs for language processing; includes UMLS Terminology Services (UTS).

The UMLS Terminology Services' (UTS) MetaMap tool is a program that uses Natural Language Processing (NLP) to provide access to UMLS concepts from biomedical text. It uses lexical and syntactical analysis of text to achieve linkage to a UMLS CUI or CUIs. Text can be input and processed in customizable manners and output is human-readable, consisting of three parts (33):

1. The phrase itself.
2. The candidates, a list of intermediate results consisting of Metathesaurus strings matching some or all of the input text. In addition, the preferred name of each candidate is displayed in parentheses if it differs from the candidate, and the semantic type of the candidate is also shown.
3. The mappings, combinations of candidates matching as much of the phrase as possible.

MetaMap uses a linear combination of linguistic measures of centrality, variation, coverage, and cohesiveness to yield a composite normalized score of 0 (no match) to 1000 (perfect match) with UMLS concepts (34). A match score >800 is generally considered to be strong (33). MetaMap parses input text with part-of-speech tagging, uses lexical and syntactic analysis functions to generate all possible variants of the text, identifies and maps candidate terms, and finally disambiguates the terms/phrases as part of an output set. Figure 2 shows an example of MetaMap XML output.

```
Phrase: "timing"
>>>>> Phrase
timing
<<<<< Phrase
>>>>> Candidates
Meta Candidates (Total=2; Excluded=0; Pruned=0; Remaining=2)
  1000   Timing [Temporal Concept]
  1000   Timing (Timing, LOINC Axis 3) [Conceptual Entity]
<<<<< Candidates
>>>>> Mappings
Meta Mapping (1000):
  1000   Timing [Temporal Concept]
Meta Mapping (1000):
  1000   Timing (Timing, LOINC Axis 3) [Conceptual Entity]
<<<<< Mappings

Phrase: ";"
>>>>> Phrase
<<<<< Phrase
Processing 00000000.tx.3: mobility;

Phrase: "mobility"
>>>>> Phrase
mobility
<<<<< Phrase
>>>>> Candidates
Meta Candidates (Total=4; Excluded=2; Pruned=0; Remaining=2)
  1000   Mobility (Mobility as a finding) [Finding]
  1000   Mobility (Qualitative mobility) [Qualitative Concept]
   928 E Mobile [Functional Concept]
   928 E Mobile (Clinic / Center - Mobile) [Health Care Related
Organization,Manufactured Object]
<<<<< Candidates
>>>>> Mappings
Meta Mapping (1000):
  1000   Mobility (Mobility as a finding) [Finding]
Meta Mapping (1000):
```

Figure 2. UMLS MetaMap Output Example.
"Timing" and "Mobility" were input into MetaMap Web Access tool and analyzed based on part-of-speech tagging, and lexical and syntactic matching. Candidate terms with respective Semantic Types are shown as "Meta Candidates" along with score, with 1000 being a perfect match (34).

The importance of the UMLS is that it addresses the rapid development of specialized terminologies emerging from healthcare as computation becomes more common and powerful. Standardization can align the information at certain levels but the diversity of healthcare still requires granularity from domains. Rector states that "all terminologies should be mapped to UMLS CUIs and LUIs, either by their originators or in collaboration with the U.S. National Library of Medicine" (35), p.54.

2.1.1.3 Principles of Healthcare Interoperability Development

A well-designed controlled terminology or system is necessary for healthcare interoperability and thus requires clear definition and understanding of purpose. Chute admits that there is some confusion in the literature about the use of the word "terminology" itself. He suggests that many people (himself included) assume using the word subsumes all problems of the interoperability of clinical coding systems. However, he concludes that "[p]ractically, we mean the naming problem, enabling clinical users to invoke a set of controlled terms that correspond to formal concepts organized by a classification schema" (8), p.299. Rector defines a clinical terminology as "the meaning, expression, and use of concepts in statements in the medical record or other clinical information system" and extends the ramifications for their use as "reasoning which can be performed on the basis of the classification, relations and comparison of isolated concepts from a medical record or information system" (36), p. 4. Cimino further delineates that a controlled biomedical terminology should be able to (37), p. 305-06:

1. Capture what is known about the patient.
2. Support storage, retrieval, and transfer of information with as little information loss as possible.
3. Support aggregation and reuse of data.
4. Support inferencing and conceptual reasoning.

Terminologies range from simple term lists to highly expressive, logic-based information schema and therefore offer levels of functionality depending on the clinical context. For example, a glossary of terms with definitions provides information that can be useful for a particular, relatively simple information use context. If the same word list comprises a vocabulary within a structured syntactic language such as XML, it not only carries more metadata as a set, but it also increases the use of the words between different systems. Adding further semantics to this structure in the form of logic structures significantly increases the expressive power and interoperability of the content (the now-enhanced initial word list) and therefore improves the ability to reason over the content (38).

Development of clinical terminologies is a difficult process. Achieving consensus definitions of terms and determining a structure that is neither too coarse nor too granular are challenges that can ultimately render a terminology useless if not correctly addressed (39). Equally troublesome is the need for terminologies to align with other terminologies and systems. Interoperability requires that a clinical terminology simultaneously be: 1) understandable by humans, 2) usable and intuitive and fit into healthcare routines, and 3) be predictable for software engineers (36).

Cimino simplifies this characterization by noting, “[t]he multipurpose nature of vocabularies refers to their ability to be used to record data for one purpose (such as direct patient care) and then be used for reasoning about the data” (39), p.9. Rector summarizes the challenges of clinical terminology development as (36):

1. Scale and complexity.
2. Scaled rigorous representations.
3. Clinical pragmatics.

Achieving a certain quality threshold in only a subset of these levels severely compromises the utility of a terminology.

Many of the computational problems that arise when using current terminology systems are structural. For example, SNOMED has an acyclic structure meaning that the logic of the terms goes from A → B, but not B → A, limiting the expressiveness and creating rigid relationships that form “diamond hierarchies” of multiple inheritance resulting in logic loops (40). Further structural problems occur when terms appear in multiple locations of the structure, often a result of a problem in representing multiple semantic types of the same term (41). An example of the problems this can create has its foundations in the “conceptualist” (as opposed to the “realist”) approach to controlled terminologies, such as that of SNOMED-CT. Reliance on concepts can result in terms and codes that are confusing and redundant, such as:

128477000 Abscess (disorder)

44132006 Abscess (morphologic abnormality)

In this case “Abscess” appears twice in the coding system, once as a clinical finding and once as a morphological abnormality, causing confusion when determining what it is actually attempting to reflect in reality and contributing to invalid computational processes (42). Equally problematic is the use of “not otherwise specified” as a classification descriptor in a terminology. This is a sort of short-cut used to avoid the rigor of terminological consensus which presents serious complications to the overall functionality of a controlled terminology applied in a computerized reasoning system (39).

The confluence of healthcare, information systems, and human subjectivity presents multiple levels of difficulty for the development and use of clinical terminologies. According to Rector, 1999 (p.5-6), these reasons can be summarized as:

1. The scale and the multiplicity activities tasks and users it is expected to serve is vast.
2. Conflicts between the needs of users and the requirements for rigorously developed software must be reconciled.
3. The complexity of clinical pragmatics – support for practical use for data entry, browsing, and retrieval – and the need for testing the pragmatics of terminologies implemented in software.
4. Separating language and concept representation is difficult and has often been inadequate.
5. Pragmatic clinical conventions often do not conform to general logical or linguistic paradigms.
6. Both defining formalisms for clinical concept representation and populating them with clinical knowledge or ‘ontologies’ are hard – and that their difficulty has often been underestimated.
7. Determining and achieving the appropriate level of clinical consensus is hard and requires that the terminology be open ended and allow local tailoring.
8. The structure idiosyncrasies of existing conventional coding and classification systems must be addressed.
9. The terminology must be coordinated and coherent with medical record and messaging models and standards change must be managed, and it must be managed without corrupting information already recorded in medical records.
10. Change must be managed, and it must be managed without corrupting information already recorded in medical records.

2.1.1.4 Healthcare Data Standards

A standard is "a set of characteristics or qualities that describes features of a product, process, or service" (43). Examples of general standards areas are sets of industry-specific definitions, sets of construction codes for materials and building, or safety criteria to which a garment must adhere (43). They are developed by collaboration of industry sectors, trade associations, consumer groups, scientific groups, or government agencies (regulatory standards) and are developed for reasons including safety, security, quality, functionality, flexibility (44). In biomedicine, the need for standards arises when the diversity of clinical representation systems becomes a barrier to delivering effective care within a domain, thus leading to either an ad hoc, de facto, government mandate, or group consensus approach to creation (30).

International standards development efforts serve to coordinate creation and management of terminologies that aligns disparate efforts and mitigates for localized variability. Clinical data standards are "consensual specifications for the representation of data from different sources or settings" (45), p.687. Essentially, standards development assures that controlled terminologies adhere to design specifications that maximize utility and that can be applied in broad medical settings. Groups such as the International Health Terminology Standards Development Organisation (IHTSDO), the ISO-TC215 technical committee, and the American National Standards Institute (ANSI) provide guidance for standards and standards development protocols. The Clinical Data Interchange Standards Consortium (CDISC) is a prominent example in the areas of clinical research standardization (http://www.cdisc.org/).

The Office of the National Coordinator's (ONC) "Standards and Interoperability (S & I) Framework" provides an integrated model for stakeholder groups to collaborate on standards development and serves as a resource for implementation. In addition to coordinating work developed around the CMS "Meaningful Use" (MU) initiative of the Health Information Technology Act (HITECH), the S & I works with IHTSDO and ANSI and has contributed to industry standards in the areas of (46):

1. Specifications
2. Implementation guides
3. Information models
4. Vocabulary and value sets
5. Test tools and data
6. Reference implementations

Clinical domains and particular clinical information systems may require varying degrees of adoption within and between these areas. Logic implies that increased use of standards within each of these areas ultimately allows for easier systems integration. "One of the greatest challenges in identifying data standards for the clinical research domain is to reconcile the requirements of varied investigators and data users with the need for common standards" (45), p. 689. Other challenges of standardization lay in the diverse needs of stakeholders, difficulty in obtaining consensus, technology limitations, consistency of implementation, and in evaluation (45). In many ways, standards challenges are similar to those of controlled terminology development.

2.1.1.5 Semantic Web

The importance of biomedical data interoperability is increasingly extending beyond the information systems of one or several health systems. Establishing a model of interoperability among the entire structure of the World Wide Web is a goal of the World Wide Web Consortium (W3C) and is often referred to collectively as the "Semantic Web." The Semantic Web principle is to link data within currently linked Web documents. The W3C is itself a standards development organization that seeks to help developers achieve Semantic Web criteria (http://www.w3.org/). A W3C Recommendation is a "specification or set of guidelines that, after extensive consensus-building, has received the endorsement of W3C Members and the Director. W3C recommends the wide deployment of its Recommendations. W3C Recommendations are similar to the standards published by other organizations" (47).

The W3C areas of standardization for the Semantic Web are (47):

1. Linked Data – RDF-annotated data meant to connect atomic information pieces across the Web.
2. Vocabularies – terms to define concepts and relationships being represented.
3. Query – information retrieval across Web resources.
4. Inference – reasoning capabilities to discover new relationships between resources.
5. Vertical applications – aligning Semantic Web approaches within domains.

The W3C toolkit for achieving these goals includes standardized languages such as Resource Description Framework (RDF), the Web Ontology Language (OWL), SPARQL Protocol and RDF Query Language (SPARQL), and Simple Knowledge

Organization System (SKOS). RDF is a data interchange standard that uses a subject-predicate-object structure and an accompanying Universal Resource Indicator (URI) to make a statement about a Web resource. These are referred to as "triples." RDF uses a graph-based structure which is more efficient in terms of computation and relationship building than hierarchal data structures such as XML. The expression of ontologies is encoded using OWL and the W3C exchange and storage syntax for integrating OWL ontologies into the Web is RDF/XML (47). OWL is based on the principles of RDF structure but includes more vocabulary for describing properties and classes than RDF, including class property restrictions. Thus, OWL can express the qualities of ontology properties described such as "symmetry" or "transivity" which allows systems to make sense of first-order logic. This allows inferencing to create new triples (and thus new knowledge), as demonstrated by the following example of "transivity" using parts of an automobile and their relationships (48), slide 30:

"Piston *isPartof* Engine;"

"Engine *isPartof* Automobile;"

therefore,

"Piston *isPartof* Automobile"

A Uniform Resource Identifier (URI) is assigned to each triple expression. A URI looks like a Web Uniform Resource Locator (URL) but it does not necessarily point to a webpage. Rather, it is a surrogate for a thing in the Semantic Web and is comprised of three elements:

1. Resource – thing being described.
2. Property – relationship between things. The RDF properties are: *type*,

subClassof, subPropertyof, range, domain, label (human readable name for a resource), *comment* (human readable description).

3. Class – bucket used to group things.

The URI can be expressed as a triple that look like a series of URLs or can be expressed in XML using the logic structure of the "Piston-Engine-Automobile" example above. SPARQL is an RDF query language used to retrieve and manipulate data stored in RDF format. SKOS is "a common data model for sharing and linking knowledge organization systems via the Web. Using SKOS, concepts can be identified using URIs, labeled with lexical strings in one or more natural languages, assigned notations (lexical codes), documented with various types of note, linked to other concepts and organized into informal hierarchies and association networks, aggregated into concept schemes, grouped into labeled and/or ordered collections, and mapped to concepts in other schemes" (47).

2.2 Ontology

An idealized controlled terminology would be a one-to-one relationship with reality, meaning one term in a controlled clinical vocabulary representing one entity (thing, process, idea, etc.) in the real world (49). However, healthcare is too complex for one terminology to be wholly representative and interoperable for proper information exchange (30). Therefore, biomedicine has increasingly turned to the use of ontologies as a means to represent the realities of healthcare research and delivery. An ontology uses terminology but through the additional use of classes, attributes, relationships, instances, and reasoning, is able to provide a rich representation of biomedical domains, which in turn, can be computed and shared. Just as a schema provides the framework for a database, an ontology provides the framework for discourse within a scientific domain in the form of a machine-processible, human-understandable description of that domain (50).

Ontology translates from Greek as essentially the study of existence (51). In a very general sense, an ontology is "the study of the traits which all existing things have insofar as they exist" (52), p. 14. Ontologies are ways in which the world (or universe, depending on perspective) can be described as a "systematic, formal, axiomatic development of the logic of all forms and modes of being"(53), p.640. Ontologies are rooted in the real or natural world, an approach that provides demarcation from human knowledge and subjectivity (52,54). They are created by classifying reality and adding semantics and syntax to create relationships between classifications.

Though ontologies incorporate a terminology as part of their structure, their rich representation and specification resembles, and in fact can be codified as, computer software programs. They provide "a semantic repository of systematically ordered relevant concepts in medicine" that serve as a "framework for several systems using terms from several natural languages" (55), p.96. This framework is "a specification of a conceptualization, a body of knowledge, describing facts assumed to always be true by a community of users"(53), p.199. In healthcare domains, ontologies are ways that complex biomedical entities, processes, and systems can be brought into a single language or interface for processing and communicating. The ontology itself inherently represents the shared knowledge of a biomedical domain (56). Some examples of large-scale biomedical ontologies are the GALEN project in Europe (57) and the Gene Ontology project (19).

Ontologies provide a "concept-oriented" or "entity-oriented" (entity is used to describe the ontological surrogate for a concept) representation as opposed to the object-oriented nature of much of computer programming. This allows for more flexibility and efficiency in program design as objects and references to objects work together to create "instantiations" that allow for control-flow relationships separate from data structures (50,58). Design of an ontology relies on a taxonomic class structure and uses class properties with restrictions to create instances which, taken together, constitute a knowledge base (56). Entity-orientation requires the terms used in design be explicit and universal, meaning they should adhere to Cimino's seminal Desiderata criteria of non-redundancy, non-vagueness, and non-ambiguity, among others (39,59). Adherence to an upper or domain-independent ontology classifies concepts into "continuants" or tangible entities, and "occurrents" or processes, but does not concern itself with specific values yielded in instantiation (42).

There are two broad categories of ontologies, 1) ontologies of reality and 2) ontologies of information (60). An ontology of reality is a model of a partitioned domain in the world. It is a language and schema for the representation and communication of knowledge within its domain. For example, the Gene Ontology models genes, gene products, and gene sequence (19). Ontologies of information classify information artifacts in a manner conducive to storage and retrieval. For example, an ontology can be used to harmonize different knowledge bases (61). In terms of formality of specification, ontologies can be classified as either highly informal, semi-informal, semi-formal or rigorously formal (62). All ontologies can be used as computational models for use in information systems.

2.2.3 Philosophical Approaches

Philosophically, there are several approaches to the design of an ontology: "Realism," "Perspectivalism," "Fallibilism," and "Adequatism" (51). Realism is concerned with representations of that which exists and that scientific knowledge can thus verify and leverage to produce further knowledge. Perspectivalism considers the multiple layers of complexity extant in the universe and partitions these into distinct axes of knowledge as demonstrated by the variegated worlds of microscopic sciences to the macroscopic studies of the universe. In other words, a "thing" in nature may have multiple levels of expressing its existence. "Fallibilism" qualifies realism due to the innate subjectivity of human perception, therefore compromising the use of terms such as "universal" and thus framing scientific rigor as a never-ending process to refine descriptions of knowledge (an extension of the "observer effect" from the field of physics). "Adequatism" incorporates many of the previous approaches into a broader recognition that all levels of complexity interact in ways that are often not understandable but that we must strive to consider in the quest for further theories of reality.

Realism or "Universality" of ontological representation is the approach advocated by biomedical ontology scholars such as Barry Smith and entails "some basic commitments to 1) the reality of the world and 2) your own reality as part of the world. Let us call these the basic principles of realism" (63), p.57. They stress that this is the only approach that should be taken in the design of ontologies as it assures the connection between real-world entities and the applications of ontology. Realism assures a modular set of terms which reflect the Aristotelian approach of "*is_a*" subsumption in the vein of the biological classification of organisms (64). An ontology is truly an ontology "only if the intended referents of its representational units are real universals and real relationships amongst such universals on the side of reality"(65).

Regardless of philosophical underpinning of representation, an ontology must be developed from a "Positivist" perspective which asserts that no ontology class should have a complementary class of the negative. In other words, the class makes an assertion about that which exists, not about that which does not. Positivism is consistent with Cimino's Desiderata criterion that non-existence or ill-defined class membership ("not elsewhere classified") be avoided in controlled terminologies. In addition, classes should portray "intelligibility" (should be understandable) and "univocity" (classes should be distinct, therefore should have discernible differences) (39,52).

2.2.4 Application in Biomedicine

Reusable domain ontologies "serve as the universal building blocks for construction of intelligent computer systems" (50), p.230. They provide heuristics for problem solving and are modular components for applications. Re-use characteristics allow for components of one ontology to directly inform the design of another. The ultimate result of linked ontology pieces contributes to the "Open World Assumption" that states one can "say anything about anything," a foundational principle of the Semantic Web. This is opposed to the "closed world" of traditional databases which are limited to the contents of a particular repository. As modular design pieces, ontologies can be therefore be applied across diverse systems for facilitating data, information, and knowledge use while simultaneously adhering to W3C standards (66,67).

Ontologies are used to make domain assumptions explicit, separate domain from operational knowledge, analyze and reuse domain knowledge, and share understanding of a domain (68). Applications for ontologies are broad as they show value within a domain (69), across health systems (70) and in facilitation of bench research to patient care (71). According to the National Center for Biomedical Ontology (NCBO), an ontology enables data aggregation, improves searching, and detects new associations where previously undetected (72). Biomedical ontologies' functional roles are described as knowledge management, data integration, and decision support (73). Table 1 shows use areas for ontologies and specific descriptions of biomedicine ontology application areas are (55):

1. Knowledge sharing – a representation of the knowledge of a domain.
2. Interoperability – capability of systems to exchange data.
3. Reusability of software components – meaning and relations are effectively standards between existing systems and developing CDS and reasoning tools.
4. Global models for knowledge – universal terminologies and properties for knowledge bases.
5. Description of huge amounts of information – increase in health information is mitigated through information indexing of ontologies.

Table 1. Ontology Use Areas.
Examples of biomedical ontologies that demonstrate utility as defined by Smith and Shah, 2008 (74). These application areas fit into more general categories of ontology utility as described by Uschold and Gruninger, 1996 (62).

General Ontology Uses (62)	**Specific Application Uses** (74)	**Biomedical Ontology Examples**
Communication	Reference for naming things	Foundational Model of Anatomy (FMA)(75)
	Representation of encyclopedic knowledge	Gene Ontology (GO)(19)
Interoperability	Representation of semantics of data for information integration	UMLS (33)
	Specification of data exchange formats	HL7(26)
Systems Engineering	Specification of information models	Biomedical Resource Ontology (BRO) (71)
	Computer reasoning with data	PhenoDigm (76)

Application of biomedical ontologies include clinical research design (77) the development of knowledge bases (54) and tools with which to query them (78), and in Clinical Decision Support (CDS) (73). A CDS knowledge base can be considered an extension or an instantiation of an ontology (50). Specific examples of significant biomedical ontology development projects include the Gene Ontology (19), the Foundational Model of Anatomy (79), and the Neuroscience Information Framework Standard (NIFSTD) (80). The latter includes an "ontology, a comprehensive collection of common neuroscience domain terminologies woven into an ontologically consistent, unified representation of the biomedical domains typically used to describe neuroscience data (e.g., anatomy, cell types, techniques)" (80), p.2. The National Center for Biomedical Ontologies serves as a coordinating body of ontology best practices and guidelines (72).

2.3 Ontology Development

There are no standardized methods for developing an ontology (81). Each ontology is as unique as the domain it is representing, as evidenced by the various methods from literature and employed in other projects. Two common features are a collaborative approach and an iterative development trajectory (80,82,83). There are some general unifying principles that can guide the process. Broadly speaking, four steps to building a domain ontology include (84):

1. Capture knowledge of a given domain (TBI Rehab) and develop requirement specification.
2. Conceptualize knowledge in a set of Intermediate Representations (IR).
3. Implement conceptual model in a formal language or description logic.
4. Evaluate the ontology with respect to frame of reference during each phase and between phases of their life-cycle.

Actions within these respective steps are summarized as (85):

1. Explicitly determine and demarcate the subject-matter or domain of the ontology.
2. Gather information: Determine what the universals and relations amongst universals dealt with in this subject-matter are.
3. Concretize this information in the form of a representational artifact, such as a written document, grid, etc.
4. Regiment the information contained in this representational artifact in order to ensure:
    - Logical, philosophical and scientific coherence
    - Coherence and compatibility with other relevant ontologies

- Human intelligibility.

5. Formalize the regimented representational artifact in a computer tractable language.

6. Implement the representational artifact in some specific computing context

The first four steps describe an "Intermediate Representation" (IR) model of ontology development consisting of capturing domain knowledge in a series of tables or other knowledge management tools. Use of an IR as domain conceptualization links the important components of the domain to the subsequent ontological choices. An IR can be used for data capture, analysis, communication, and knowledge base.
Constraints of an ontology include the limits based on philosophical axioms: "realism," "fallibilism," "perspectivalism," and "adequatilism" (86). In other words, how they are assembled can affect their functionality. This includes understanding the domain to be represented, the goals of the ontology, and the artifacts informing creation (87). Therefore, relying on good design principles is key and developing evaluation frameworks propel refinements.

2.3.1 Structure and Components of an Ontology

Ontologies use first-order logic in processing, which is declarative, compositional, and context-independent and comprised of an object, a relation, and a function (35). First-order logic is exemplified by the Aristotelian assertion that "All men are mortal. Socrates is a man. Therefore, Socrates is mortal." The structure is expressed as "term(A)→genus(B)→differentia(C)" or An "A" *is_a* "B" *that_is* "C." This is the basis of computation but also gives the ontology a human-understandable statement expressed as "A human("A") is an animal("B") that is rational(C)." First-order logic allows inferencing between classes to create new "triples" and thus new knowledge, as described in the automobile example from the Semantic Web section, 2.1.1.5. A further example of this ontological expression with the "class" designator using human anatomy:

"classOrgan *isPartof* classBody"

"classBody *isPartof* classHuman"

therefore:

"classOrgan *isPartof* classHuman"

This structure allows ontologies to identify and express rich relationships in an acyclic fashion, as opposed to the cyclic structure of many healthcare terminological structures such as SNOMED. Acyclic expressions create a graph structure that makes reasoning easier than the tree structure of cyclic systems in terms of computer processing power (88).

2.3.1.1 Classes

"Classes describe concepts in the domain" (56), p.3. Classes are types of objects that exist in the real world. They have relations in an ontology and are defined and delineated through a definition and a unique identifier (OBO). Ontology classes differ from traditional database object-oriented classes. One important distinction is that an ontology entity can belong to multiple classes. In an example of a fictional ontology of "Family," this would mean that a represented entity could simultaneously be a member of the "Thing" class, the "Person" class, the "Mother" class, and the "Daughter" class. "A class can be defined as a collection of particulars falling under a term in such a way that the term applies to every member of the collection, and every particular to which the term applies is a member of the collection" (51), p. 18.

Memberships in classes can be expanded or constrained through the term hierarchy and/or through defined properties (relations). Entities can be members of as few or as many classes as the ontology creator desires ("disjoint" membership). This allows a user to explicitly select the classes that members of a selected class cannot also belong to. However, most of the time classes do not need to be explicitly coded as disjoint, as would be the case for class-types "Mother" and "Father" which, based on the criteria of membership for their respective class, would be redundant if marked as disjoint. Multiple-inheritance allows for nuanced relationships to be identified through reasoning and instantiations. This is another key difference in terms of the robust nature of an ontology versus an object-oriented model which limits classes to single-inheritance and thus limits the power to infer multiple aspects of relationships (49).

2.3.1.2 Hierarchy of Terms

Building the first-order Aristotelian logic structure portrayed in the automobile and anatomical examples above begins by creating a simple taxonomy of terms, or class names. Another way to describe the structure is the classic taxonomy with roots, branches, and leaves in the "Linnaeus System of Classification" which describes the organizational hierarchy of living organisms. This structure is maintained through formalization of the ontology language (such as OWL) which ensures consistent understanding within the particular domain of application.

The *is_a* taxonomy expresses a "subclass" relationship of classes meaning if a user asserts that "Class B *is_a* Class A," then all instances of Class B are also instances of Class A and all instances of Class B inherit the characteristics of Class A ("inherence"). For example, one can say that "Football (subclass) *is_a* Sport (class)." Therefore, the class “Football” has the general characteristics of a “Sport” but also contains characteristics that distinguish it from other “Sport” subclasses, such as “Baseball” or “Hockey.” An expression of a sub-class thus bears all the qualities of the parent or “super” class in addition to its own characteristics of differentiation.

The names of classes are not as important as is the structure and the criteria for membership. Adhering to the “universal” representation philosophy, the class contains things which bear the characteristics of that class, regardless of the name (74). In other types of controlled terminologies a name change can present serious data degradation (37). Class names in an ontology can safely evolve without degradation assuming types consistently bear the class qualities (89).

2.3.1.3 Relations or Properties

Relations (properties) are the formalized links between classes that further facilitate reasoning power. Schwarz and Smith, 2008 describe four principles for selecting ontological relations that reflect the philosophical approaches discussed previously (90):

1. The relations must be genuine ontological relations. This means that they obtain between entities in reality, independently of our experience or methods of learning about them.
2. The relations domain-neutral relations which could appear, in principle at least, in any biomedical ontology.
3. The relations must obtain universally. A statement of the form A relation B must obtain for all instances of A, and not just (for example) for some statistically representative selection.

4. The relation must be definable in a simple, yet rigorous, way.

In general terms, there are two types of ontological relationships: taxonomies (*is_a*, *part_of*) and associative relationships (nominative, locative, association of properties). These partition classes that express a particular characteristic or quality (*part_of*=partonomy). Ontology properties use first-order logic to express concepts such as "symmetry" or "transivity" between the classes. The Open Biomedical Ontology (OBO) guidelines suggest default use of three relations that should be in most ontologies to provide basic reasoning functions: *is_a*; *disjoint_from*; *inverse_of*.

Primitive ontology relations are generally recommended for initial ontology development in order to improve harmonization between ontologies and to reduce the processing power that increases with the addition of more diverse property types (51). Schwartz and Smith, 2008 describe four criteria for selecting relations (90):

1. The relations in question must be genuine ontological relations.
2. The relations are those domain-neutral relations which could appear, in principle, in any biomedical ontology.
3. The relations must obtain universally. A statement of the form A relation B must obtain for all instances of A, and not just (for example) for some statistically representative selection.
4. The relation must be definable in a simple, yet rigorous, way.

Applying a particular relationship (i.e., *hasPart*) to multiple classes is one level of specification, but adding properties to the relation itself refines the nature of these relationships and creates unique distinctions and assertions (51). For example, properties, like classes, can be organized into hierarchical taxonomies of type (*hasName* divided into *hasFirstName*) and can be applied at the class level or at the instance level (87). The class level relations specify general relations that exist between classes and instance relations between two instances of the classes existing in the real world. Characteristics of properties that should be considered when defining relations (51):

Symmetry – *A* bears relationship *R* toward *B*, *B* also bears relationship *R* to *A*.

Reflexivity – *A* bears relationship *R* toward *B* also bears the same relationship to itself (*A*).

Transitivity – *A* bears relationship *R* to *B*, *B* bears same relationship to *C*, *A* thus bears same relationship to *C*.

2.3.1.4 Instances

An instance in an ontology is the expression or realization in reality of a class. They bear the qualities of the class(es) they belong to but represent an actual example of that class in the ontological domain. For example, "'Romeo' is a man because he instantiates the universal (class) 'man'"(64).

2.3.2 Design Principles

Uschold and Gruninger summarize ontology development into six steps: a motivating scenario, use of informal competency questions, development of a formal terminology, use of formal competency questions, designing formal axioms, and finally, using the ontology to develop completeness theorems(62). For a well-designed ontology, Gruber, 1993 proposes five general design qualities(91):

1. Clarity – objective, formalized, natural language definitions; effectively communicate the distinctions of a domain to a human.
2. Coherence – logically consistent axioms; internal consistency.

3. Extendibility – conceptual foundation for anticipated tasks that can be extended and specialized; redefining shouldn't be needed but it can evolve.
4. Minimal encoding bias – avoiding system or coding scheme specifics to maintain use in diverse applications; interoperable in language.
5. Minimal ontological commitment – base choices on the weakest theory to allow the users to specialize and instantiate to assemble their own conclusions.

The Open Biological and Biomedical Ontologies Foundry and the NCBO have developed "best practices" in ontology design (81). Examples of their guidelines include the harmonization of ontologies through the Basic Formal Ontology (BFO), use of the OBO Relations Ontology (RO) or other standard relationship types, the use of ontology design patterns (ODP), and the leveraging of other reference ontologies (92). Brief discussion of select principles follows.

2.3.2.1 Upper Ontology

Use of an upper-ontology provides the highest level structural template for interoperability between domains of representation (93). The Basic Formal Ontology (BFO) was developed to serve as a unifying upper ontology for biomedical domain ontologies. Large biomedical ontologies such as the NIFSTD project adhere to the BFO standard meaning other ontologies can interoperate through the BFO (80). The BFO is broadly accepted as the biomedical ontology standard to ensure the interoperability of ontologies (94).

2.3.2.2 Leveraged Ontologies

Reuse of extant ontologies is important for two reasons: 1) to build on other ontologies, saving time and resources and 2) to ensure integration and harmonization between terminologies. The first point can be summed by the adage, "why reinvent the wheel?" Designing ontologies is difficult, time-consuming work so taking advantage of extant work simply makes sense for expeditious reasons. Second, interoperability is key to maximizing the utility of a domain ontology (72). A primary goal of the OBO Foundry is "to create a set of orthogonal ontologies, where ontology developers reuse terms from other ontologies rather than define their own" (95), p. 2.

Given the challenges of ontology design, reusing existing ontologies is as much a recommendation of efficiency as utility. Further, leveraging and linking multiple ontologies contributes to overall biomedical harmonization and interoperability. The multiple axes of a shared, interoperable index of ontologies have the potential to manifest exponential growth in multi-domain networks of biomedical synergy. The importance of this point is demonstrated by the activities of the NCBO which aims to facilitate the interoperability of a large suite of ontologies resulting in a "mega-thesaurus" of computable biomedical domain languages (72).

The NCBO's BioPortal and the OBO Foundry are two of the largest biomedical ontology repositories. Both have tools that allow ontology designers to explore existing ontologies to identify potential re-use opportunities. "The two recognized ways to reuse terms are for one ontology to refer explicitly to a term id from another ontology…and for one ontology to use the cross-referenced property in the OBO format to indicate that a term is defined in another ontology" (95), p.5.

2.3.3.3 Ontology Design Patterns (ODP)

In software design, certain modeling issues occasionally reappear across different programs. To address this, engineers have recognized the use of generic design patterns as templates that can be replicated independent of project or system (96). Similarly, ontologies design patterns (ODP) have emerged that serve as validated structural templates that can be incorporated into a new ontology design. Use of ODPs strengthens the overall ontological design and consequently saves time (97). An example of an ODP is a “normalization” pattern for simplifying poly-hierarchies through the use of restrictions on relations (98).

2.3.2.4 Competency Questions

Ontology development literature recommends the use of “competency questions” to serve as a type of validity during the ontology build process, ensuring that the completed ontological artifact maintains its utility in answering the motivational research question (62). They serve as iterative quality benchmarks and subsequently serve as means by which the ontology aims can be measured. Two types of competency questions can be applied. “Formal” competency questions, examples of which are the OBO design principles, serve as means of addressing the degree to which good ontology design choices have been made (87). “Informal” competency questions are used to ensure that the ontology contains the information needed to answer particular research questions (56). Informal competency questions guide domain conceptualization and extraction of its putative terminology and align the ontology with its ultimate purpose (62).

2.4 Domain Conceptualization and Intermediate Representation

A knowledge representation (KR) is a tool that provides communication for a domain, the rules of which (semantics and syntax) can be formalized (99). A KR can be understood through a description of the five fundamental roles it serves (100):

1. A KR serves as a surrogate for a thing.

2. It is a set of ontological commitments describing how a part of the world can be considered.

3. A fundamental theory of intelligent reasoning in terms of three components:
   - fundamental conception of intelligent reasoning
   - set of inferences that the representation sanctions
   - set of inferences it recommends.

4. Medium for computation.

5. Medium for human expression.

A KR is an important tool for describing reality and using reasoning to infer further knowledge about that domain of reality. Conceptual graphs, RDF schema, or an ontology are examples of different KR formats (101).

2.4.1 Intermediate Representation as Conceptualization of Knowledge Representation

An ontology is a knowledge representation (87). Gruber, as noted, describes an ontology as "a specification of a conceptualization" (54). Therefore, an ontology is an artifact that represents the knowledge and the specification of a domain. To serve the roles outlined above by Davis et al., a KR requires a clear understanding of the domain if it is to serve as a surrogate and present a foundation for reasoning and communication in the domain. In this sense, conceptualizing a domain refers to the process of identifying the context and components that characterize that domain. "Minimally, a conceptualization involves concepts and probably also their specifications" (63), p.71. In this sense, not only is an ontology a KR, but so are the knowledge artifacts assembled to inform the development of the ontology in the form of Intermediate Representations. The function of a domain conceptualization as ontological intermediate representation (IR) (100):

1. Characterizes a TBI rehabilitation encounter and serves as a "surrogate" or Intermediate Representation for an ontology.
2. Provides domain-validated entities to ensure meaningful reasoning through inferences of the class expressions.
3. Informs ontological commitments.
4. Supports a medium for computation and human expression domain communication model.

In order to assemble a KR, Grenon, 2008 describes six steps:

1. Look at the world.
2. Gather facts about the world.
3. Represent the world.
4. Conjecture the presence of sophisticated structures and existence of other entities.
5. Validate conjectures through inference and experiment.
6. Infer further structures and entities.

A "pragmatist conceptualization" consists of identifying that which is of utility to the domain (102). As previously discussed, Gomez-Perez and Fernandez, 1996 recommend an Intermediate Representation (IR) as means toward a KR. Therefore the IR is an iterative step toward a domain conceptualization of reality that reflects the concepts considered important for domain communication.

2.5 Ontology Evaluation

Approaches to evaluation are as diverse and non-standardized as ontology design itself (103). The context of the ontology use and the various levels of complexity present differing aspects of interest for measuring and consequently, differing approaches and measurement criteria (104). In very broad terms, the goal of evaluation is to identify mistakes and omissions of the content and to provide an assessment of the build and management process (105).

2.5.1 Categories of Evaluation

Four specific approaches to evaluation have been identified by Brank et al. (106): comparison to a "gold standard," use of the ontology in an application and evaluating the results, comparison with domain source data, and human-based assessment of the ontology based on comparison of several domain sources. Six levels of evaluation that map to one or more of these approaches include: Lexical/conceptual, hierarchy/taxonomy, semantic relations, context/application, syntactic, and architecture/structure. These can be assessed by one of four methods; either comparison of the ontology to the syntax of the ontology language, in an application, through data sources, or by humans. The various levels of evaluation are indicative of the complexity in ontology design. Structure and content equally contribute to the utility of an ontology and therefore evaluation considers multiple levels of each characteristic. These levels and methods are portrayed in Table 2.

Table 2. Approaches to Ontology Evaluation.
Levels of an ontology that can be evaluated and the respective approaches to measure those criteria. All levels can be evaluated by human assessment. Adapted from (106), p.167.

	Approach to Evaluation		
Level	**Golden standard**	**Application-based**	**Data-driven**
Lexical, vocabulary, concept, data	X	X	x
Hierarchy, taxonomy	X	X	x
Other semantic relations	X	X	x
Context, application		X	
Syntactic	X		
Structure, architecture, design			

2.6 Ontology Development Environments

Numerous ontology development environments are available, including NeOn (http://neon-toolkit.org/wiki/Main_Page), Sigma, (http://sigmakee.sourceforge.net/), and the Protégé Ontology Editor and Knowledge Acquisition System (http://protege.stanford.edu/). Types of ontology tools include comprehensive environments, vocabulary prompting tools, XML/OWL/RDF modeling tools, mapping, and visualization tools (107). Types of features include tools for developing terminologies, visualization tools, mapping applications and interfaces for authoring in particular languages such as OWL or RDF.

The NCBO hosts a suite of tools, process recommendations and hosts a repository, Bioportal, where ontologies can be explored for compatibility and reuse. The NCBO BioPortal library, which currently houses over 270 biomedical ontologies, ensures integration, harmonization, and leveraging opportunities (108). The NCBO toolkit is free and accessible through the Web.

2.6.1 Protégé

A 2003 review of ontology tools used 15 criteria to evaluate biomedical ontology development tools and concluded that Stanford University's open-source Protégé-2000 (now Protégé) was strong in "user interface, the extendibility using plug-ins, the functionality that the plug-ins provide (such as merging) as well as the different formats that can be imported and exported" (109), p.1570. Protégé is used as an ontology design interface and for collaboration, inferencing, and reasoning. Protégé can be used as a downloadable, free and open-sourced version or as a Web-based version (Web Protégé) which creates a hub for larger-scale, multi-developer projects. It has mapping, visualization, reasoning, and ontology recommender tools, and can easily be "plugged into" applets using Application Programming Interface (API) tools that allow for deployment in applications. It is compatible with Open Knowledge Base Connectivity (OKBC), an application programming interface specification for accessing knowledge bases stored in knowledge representation systems which assures interoperability. Protégé is aligned with the NCBO toolkit allowing for easy import/export, merging, leveraging, and sharing including the BioPortal library of over 270 biomedical ontologies, ensures integration, harmonization, and leveraging opportunities (108).

Protégé is being used in such projects as the development of ICD-11 (83), the Foundational Model of Anatomy (FMA) project (75), and by many of the integrated resources in the Neuroscience Information Framework (NIF) (80), among others. These projects demonstrate not only the wide acceptance of the ontology functionality within Protégé but also the role Protégé is serving as a collaborative environment for large terminology and ontology projects requiring a great deal of user input and coordination.

The scope and authoritative nature of these projects suggests Protégé is viewed as an increasingly important ontology environment.

The 3.x series of Protégé supports ontology design in a frame-based environment. The 4.x series is built as next generation to adhere on an OWL 2.0 framework, providing closer relationship to the W3C Semantic Web principles (110). The 4.x series uses the open source, Java-based OWL API which is a standards-based interface specification for OWL ontologies, thus ensuring interoperability with other systems (111). Version 4.3 of Protégé was released in April, 2013.

Protégé enables a user to intuitively structure ontologies using a knowledge model which is compatible with the OKBC protocol, consisting of (110):

1. a set of classes
2. a set of slots (properties)
3. a set of instances of those classes

Protégé provides tools for the management and validation of ontologies. Validation is provided by using plug-in reasoners that allow inferences to be made of the ontology in order to demonstrate whether the structure of the design can successfully create instances, referred to as "consistency checking" (does a new entity assertion yield instances consistent with the logic of other instances?) (110,112). Another reasoning task that Protégé tools allow is "sub-sumption testing" which tests whether or not one class is a subclass of another class (112). Further examples of Protégé reasoning include "satisfiability" (does an entity satisfy first-order logic of the hierarchy and properties?), and "retrieval" (are all instances of a class found?). Protégé provides plug-in reasoners to perform these tasks which can demonstrate structural consistency and test the descriptive logic through information retrieval, validating the content of the ontology (97). The most common reasoners used in Protégé are Pellet, Fact++, HermiT and increasingly, Elk (113).

Finally, the various storage formats of Protégé ontologies (OWL, RDF, XML, HTML) allow flexibility in sharing and application. The ability to store in these particular formatting languages makes Protégé-developed ontologies conform to the Semantic Web standards of the W3C (111). These formats also provide human-readable options.

Chapter 3 Traumatic Brain Injury and Physical Medicine Rehabilitation

3.1 Introduction

Issues of interoperability in clinical systems are complicated further by complex neurological conditions. The difficulties in developing standardized terminological and data systems are compounded when the reality they represent presents multiple levels of variability in patients, condition, treatment options, patient trajectory, and outcomes. This complexity obfuscated the identification of best courses of treatment and their external validity.

Multi-disciplinary, post-acute rehabilitation exemplifies these challenges, both in clinical complexity and in consequent problems of interoperability. Outcomes in neurological disease treatment depend on many factors that make each case unique and limit prognostic power. Traumatic brain injury (TBI) research difficulty is compounded by the complexity of the brain and its ability to repair. In the context of the Chute interoperability model, the need for TBI rehabilitation data standardization is clearly needed to improve the ability of practice to inform research.

3.1.1 General Post-Acute Physical Medicine Rehabilitation

Physical medicine rehabilitation is "a medical specialty concerned with…evaluation and management of persons of all ages with physical and/or cognitive impairment and disability" (114). Also referred to as "Physiatry," rehabilitation is also concerned with the "prevention, diagnosis, and treatment of disorders…that may produce temporary or permanent impairment." It "provides integrated care in the treatment of conditions related to the brain, muscles, and bones, spanning from traumatic brain injury to lower back pain" (115). Interdisciplinary teams typically deliver these services as a coordinated suite of services and include specialists from neuropsychology, physical therapy, occupational therapy, nursing, physical medicine, recreational therapy, rehabilitation counseling, social work, and speech/language pathology (116). Characteristics of the rehabilitation treatment approach exemplify the complexity in post-acute physical medicine and rehabilitation. Rehabilitation crosses "integrative and cross interdisciplinary boundaries" employs "medical, social, psychological, vocational, and a-vocational information to create and formulate a comprehensive evaluation, to understand the whole patient…across broad settings" (117). Participants often extend beyond clinicians and patients to include family members (118). Settings for rehabilitation vary due to the patient's need and access to services (119) and services are delivered in long-term care centers, sub-acute rehabilitation facilities, rehabilitation specialty centers, outpatient (community) settings or in the patient's home (120). Telemedicine is being increasingly explored largely as means to mitigate cost and service access (121,122).

Although post-acute rehabilitation nominally occurs at a time-point post-insult or disabling clinical event when a patient is able to participate and shows potential for improvement, the rehabilitative process begins in acute care (123). Strictly speaking, rehabilitative services as a delineated, defined set occur once primary care clinicians and physiatrists make a coordinated determination for a patient's discharge to the next level of care (124). Patient pathways to rehabilitation are dependent on demographic, injury, health history, and access factors (125).

Specific to neurological diseases such as stroke or traumatic brain injury, the recovery process involves 1) neural recovery and 2) functional recovery. Neural recovery describes the repair of physical/physiological damage due to the injury/insult/disease. Functional recovery is the practice of addressing deficits of functionality of varying levels from Activities of Daily Living (ADL) domains to global domains of life integration (7). Both neural and functional processes are factors in neurological diseases and both equally guide the rehabilitation process (Ikramuddin F, personal communication, 2013).

To address these neurological disease recovery processes, two approaches to rehabilitation treatments can be taken (126):

1. Compensatory - adaptive behaviors to enable recovery of a lost function through a new way to perform a task.
2. Restorative – repair, restructure, or rebuild damaged neural networks to regain a previous skill.

A clinician makes an assessment of a patient's needs based on impairment level and designs progressive rehabilitation strategies based on one or both of these approaches (127). The goals of treatment are "a) to increase the person's capacity to process and interpret information and b) to improve the person's ability to function in all aspects of family and community life" (128), p.106. Steps in designing a rehabilitative treatment plan (129):

1. Identify the target problem(s).
2. Identify the theoretical treatment approach for parsed problem.
3. Design activities to deliver theoretical approach for each problem.

The trend of recovery further guides treatment plans and execution (Ikramuddin F, personal communication, 2013). This manifests an ever-evolving cycle of assessment, treatment design, and outcome (130). Implications are treatment plans that vary widely based on the particular variables of a patient, the injury, the clinician, characteristics of the setting and can depend on nuance such as a patient's mood or engagement on a particular day (130). Also confounding is the level of spontaneous recovery (5).

3.1.1.1 International Classification of Function, Disability, and Health (ICF)

Rehabilitation treats impairment but goals are multi-faceted aspects of participation, or distal effects of function. In other words, the activities performed in a particular rehabilitation encounter may be discussed and measured at differing levels of analysis. While the goal of a specific activity within a physical therapy treatment encounter may be targeted at a patient's gait, the clinician designing the treatment strategy and conducting the session may be as interested in the patient's improvement in mobility as in how the level of ability affects his/her ability to maintain employment (5).

The 2001 International Classification of Function, Disability, and Health (ICF) presented a model of disability classification that reflected this multi-level aspect of rehabilitation programs. The ICF shifted focus away from specific disablements toward a holistic continuum on which all patients experience varying degrees of "ablement" (131). The model classifies body functions and structure in one domain, with activity and participation in two other respective domains. Since an individual's functioning and disability occurs in a context, the ICF also includes environmental factors. "Moreover, ICF is grounded in the principle of universality, namely that functioning and disability are applicable to all people, irrespective of health condition, and in particular that disability…is a feature of the human condition" and "a universal phenomena" (132), p.3. Figure 3 portrays the model with three levels of consideration for outcome research.

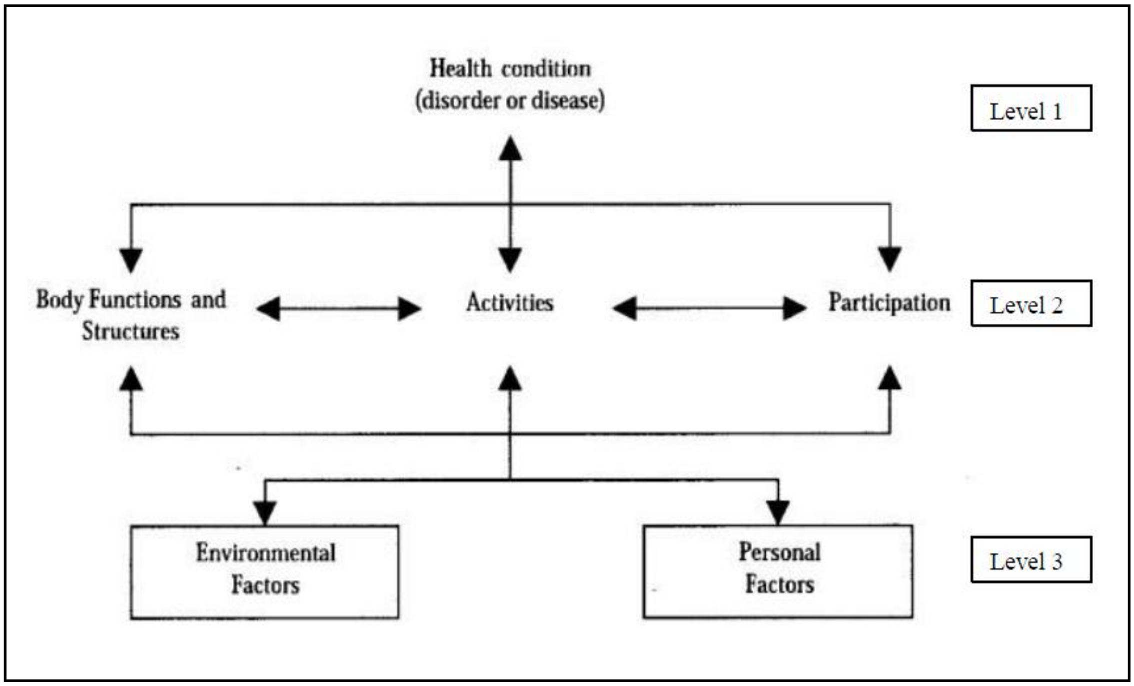

Figure 3. International Classification of Function Model of Disability.
This widely used model for individual functional status was developed by the World Health Organization (WHO) (133).

"The concepts of human performance and quality of life that form the basis for the World Health Organization's International Classification of Function (ICF) contributes to the conceptual foundation of PM & R" (117). Rehabilitation generally addresses one of the levels of the ICF model: Level 2, "Body Structure, Body Function, Activity, Participation" but also must consider factors at the other two levels (134). Steiner et al., 2002 demonstrated this use of the model as a tool for problem-solving in rehabilitation (135). For traumatic brain injury patients, Scarponi et al., 2009 state that using the ICF framework is key in designing and classifying effective rehabilitation interventions (136). It has also been validated as a means for classifying TBI patients in terms of functionality (137).

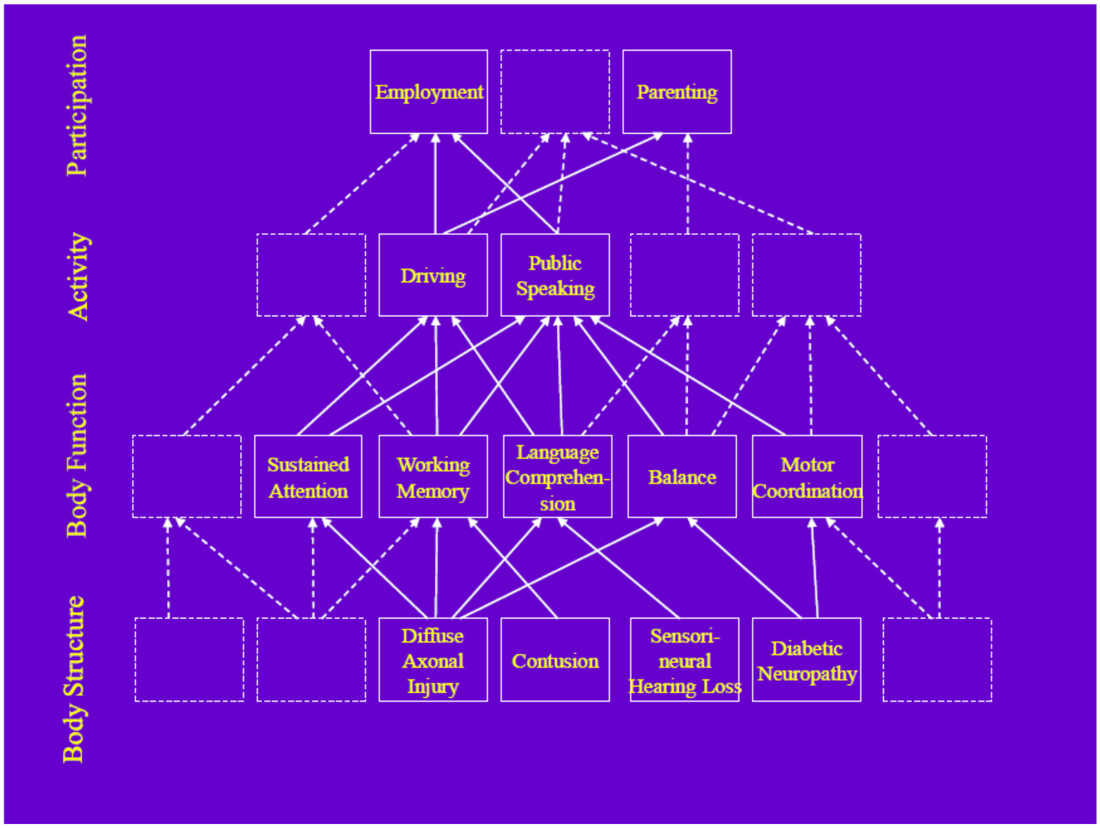

Figure 4. Models of Rehabilitation Research.
Used with permission of John Whyte, MD, PhD,Moss Rehabilitation Research Institute. Levels of the ICF Model (Body Structure, Body Function, Activity, and Participation) are used to organize and link the interaction of rehabilitation activities. Complexity of condition, the goals of particular interventions, and the indirect relationship to global outcomes are shown (138), p. 43.

John Whyte portrays the levels of complexity of rehabilitation ranging from a specific area of disability through the goals of treatments within an integrated ICF model (Figure 4). The figure shows how problems at the various levels of "ablement" can interact while individual rehabilitation treatments are designed to target discrete components of a specific problem within a box (i.e., "Working Memory"). Each box in the figure represents an independently complex ecosystem of patient, injury, treatment and outcome. This demonstrates the complexity in coordination of a suite of services that address a specific problem but that also need to work together synergistically to ultimately reflect net gains ascending to the global outcome “Participation” level (139). This highlights the need to understand participation and environment, two crucial factors of the ICF model which are not well researched in the TBI domain (140).

3.1.1.3 General Physical Medicine Rehabilitation Research Literature

In a commentary article concerning how effectiveness of post-acute rehabilitation is determined, two fundamental questions were posed (141):

1. Does rehabilitation help?
2. Does the rehabilitation enterprise make a difference in a patient’s clinical trajectory?

Kane describes measuring effectiveness through an equation: f(baseline, patient clinical characteristics, demographics, treatment) (141). However, the question that *a priori* frames much of the post-acute rehabilitation literature is also posed by Kane when he posits that in assessing rehabilitation programs, “[u]ltimately, the first question may become, ‘What is rehabilitation?’” (p.1500). He notes that rehabilitative services typically start in the acute setting while conversely, services that occur in the post-acute setting are not always “rehabilitative.” Timing thus becomes an issue for clinical research in determining effectiveness based on the volume of a particular service or services. Further, spontaneous recovery is not fully measureable, confounding the assessment of intervention (142).

Whyte and Hart call the definition of rehabilitation treatments the most underdeveloped area of rehabilitation. Their concern extends Kane’s concern beyond clinical research and into how this lack of definition can affect the subsequent delivery of care. They summarize the problem as a broken feedback loop that echoes the Chute model. They describe a functioning feedback loop as (7):

1. Clinicians and researchers articulate hypotheses and mechanisms of treatment effects.
2. Treatments are defined in objective and operational terms.
3. Practice contributes to refinement of definitions.

Without clearly defined treatments, the ability to perform clinical research with the necessary rigor and therefore answer Kane's second questions is limited. Kane's concern is that the domain has not established a direct connection between the changes in a patient's condition to the inputs of rehabilitation programs. He states that barriers of methodology in research such as study design, measuring interventions, establishing outcomes, timing of outcome measurement, consumer perspectives, and case-mix of the patient have not allowed the creation of a solid theory base to prove the effectiveness of rehabilitation (141). Bellg et al. emphasize that "[q]uestionable internal and external validity may make it impossible to draw accurate conclusions about treatment efficacy or to replicate a study" (143), p. 444.

Hart notes that treatments must be codified in a manner that makes them repeatable. She describes this issue of "manualization" as one of a continuum of specificity from very specific "scripting" of a rehabilitation session to very flexible philosophical frameworks or tool kits from which a session may be designed (129). The personalization and lack of standardized rehabilitation treatments results in high degrees of variability in description and delivery. She further states that artifacts "fall along the continuum of specificity" (13), p. 828. Together with the coarseness of existing controlled terminologies and coding systems, items on the flexible end of the spectrum likely are not suitable for comparison. Thus, the level of manualization of treatments is viewed as an objective for improving research methodology and delivery of care (143,144).

The level of specificity with which one describes the rehabilitative actions in a particular session or within a longitudinal program presents several issues. Since treatments are often adjusted based on immediate patient feedback and performance, the activities in a session can be fluid and dynamic and therefore difficult for clinicians to capture (143). While emerging technologies such as video recordings of sessions may allow for more scrutiny of the particulars of a session, a certain amount of detail regarding the clinician activities and patient performance is assumed to go uncaptured (145). Further, non-templated, free-text clinical notes assure a lack of standardized language is used to communicate these activities. The implications of this are relevant for describing the contents of a rehabilitation program, comparing these contents, and for the design of treatment guidelines and manuals which describes step-by-step actions at a grounded level (129).

The multiple levels of rehabilitation, as illustrated by Whyte and the ICF, contribute further to problems of effectiveness comparison. Activities and goals in a rehabilitation program range from micro to macro. The issue is in determining which aspects of a multi-factorial program are comparable. Is the effect of services best measured at the program-level or at the level of individual components? Hart (129) frames the areas for comparison as being either:

1. Content

2. Processes

Whyte and Hart (7) describe the measurement levels in slightly more detail as:

1. Global level.
2. Intensity of treatment within a specific discipline.
3. Treatment for specific functional problem.
4. Therapy content and process.

Therefore, performing research requires multiple levels of consideration with each respective level containing varying degrees of confounding methodological concerns described by Kane and others and as modeled by the ICF. Selecting appropriate outcome measures is challenging due to both content of treatment and the levels of rehabilitation targeted by the treatments.

Treatment theory is the evidence that supports the enactment of a particular rehabilitation strategy or activity (7). Use of theory in rehabilitation “specifies the mechanism by which a proposed treatment changes its immediate target” (142), p.S103. A clinician may theorize that based on a patient assessment, he may benefit from activities that have demonstrated significant positive results for similar patient profiles and assemble services based around this theory. “Theories can exist on a spectrum from “macro” theories, which seek to explain a wide range of phenomena in the world (e.g., the laws of thermodynamics), to more “micro” theories, which seek to provide a mechanistic explanation for very specific phenomena” (146), p.203. This is the same for rehabilitation.

“Treatment theories can narrow the scope of possible active ingredients by clearly specifying how the treatment is believed to act” (130), p.99. However, the problem in development and refinement of treatment theories cascades from the methodological issues described above. The inability to parse in inputs of a treatment program and compare them blurs the causal path between theory and outcome (141). Additionally, rehabilitation currently lacks validated theories upon which to base treatment and generate further hypotheses (142).

Several other areas of rehabilitation contribute to complexity and research difficulty. The variability of treatment delivery in terms of the clinician's level of training and skill (141) and behavior (143) are thought to be demonstrable factors in determining effectiveness of treatments. Understanding how the multi-disciplinary care team is organized, what the roles are, and how they function are of interest (141). The context of treatment delivery plays a role as does the aforementioned case-mix of an individual patient (7,141). The lack of a common metric across treatment settings defies comparison of treatments and the timing of measurement is relevant to understand patient trajectories and spontaneous recovery (141).

The complexity of identifying this causative pathway and answering Kane's questions increases when nebulous concepts such as "patient engagement" (7), "object of action" (142), "enablement theory" (5), "therapeutic alliance" (147), "treatment receipt" and "treatment enactment" (143) are considered. The nature of these concepts does not lend itself to codification and parsing for research. They are not quantifiable, lack standard universal definition, and are difficult to codify. Some, such as "enablement theory" which is used to describe the causal relationships (the arrows) between the levels of the ICF model are simply placeholder descriptions for future research. As Whyte and

Barrett (142) point out, the ICF does not necessarily identify the catalysts that spur these relationships.

3.1.1.4 Complexity in Healthcare

According to the United Kingdom Medical Research Council, a complex intervention is comprised of more than one components acting both independently and interdependently that are characterized by behaviors such as frequency or timing and the manner in which the behaviors are structured and delivered. It has a varying number of different elements which contribute to the overall function of the program without specifying the 'active ingredient' of the total set of treatment elements (148). They are further described as comprised of multiple levels for delivery and as having a high degree of variability and often a great deal of customization (149). Complex interventions are designed to demonstrate effectiveness that reflects “more than the sum of the parts” (150), p.413.

Neurological diseases such as traumatic brain injury, stroke, and spinal cord injury (SCI) are considered complex in their assessment, treatment, and outcome measurement (9). Complexity in treating these conditions manifests as highly localized, customized, and non-manualized programs whose end result for comparative effectiveness research is a heterogeneous body of evidence that limits meaningful measurements of effectiveness and comparison across programs (151). Rehabilitation programs employing varying intensities of multiple disciplines within a personalized treatment plan which is delivered by different caregivers in different settings, defies the uniformity needed to perform relevant comparison across studies (152). Additionally, the multiple levels of consideration required to fully assess a rehabilitation program includes such ethereal factors as patient engagement and participation, therapeutic alliance, and variation in therapist behavior (7). Further, post-acute rehabilitation as a general field lacks standardized outcome measures and struggles with issues of timing as some rehabilitation services can occur in the acute setting and the fact that not all services occurring in post-acute care are necessarily rehabilitative (141). In terms of defining, measuring, and sharing intervention data and knowledge, complex interventions thus present numerous barriers.

Whyte and Hart (7) describe the traditional approach to the understanding of complex interventions as a "black box." The black box comes from the field of mathematical theory which describes the "input-output relation is given by a postulate schema according to which the response is, in general, a nonlinear functional of the input" (153), p. 346. They illustrate rehabilitation as a black box within which the chemistry of change occurring between inputs (treatments) and outputs (outcomes) as an opaque mystery, incapable of being unpacked and understood. They posit this as an outdated model in clinical rehabilitation research and instead frame the issue as something that simply required different levels of consideration which should be parsable and understood as individual components while still working toward an understanding of the synergistic effects of the total suite of services within this "box."

Hart (129) describes three levels of analysis for complex interventions:

1. Theory – pre-defined, stating the mechanism of the action.
2. Specific actions of therapist and/or patient as verifiable by an objective observer.
3. Translation of operations into usable artifacts such as coding systems or manuals.

She parses one and two into the following three steps:

1. Treatment coded as “common” to many studies such as therapeutic alliance or something or “specific” which is closer to the experimental treatment unique to the particular instance at hand.
2. Particular code from step one (i.e., therapeutic alliance).
3. Specific therapist actions.

By approaching service program design in this manner, links between theory, treatment, and outcome can be better identified by an investigator and research hypotheses can be developed to contribute granularity to the linkage between these components.

3.1.1.5 Related Neurological Pathologies - Spinal Cord Injury & Stroke Rehabilitation

Several neurological pathologies are considered to demonstrate complexity in treatment and research in terms of patient, intervention, and outcome variability. Most notably, traumatic brain injury, (TBI), spinal cord injuries (SCI) and stroke research are often used in parallel terms (154). In terms of rehabilitation, they are all Special Interest Groups (SIGs) within the America Academy of Physical Medicine and Rehabilitation (117) and all three conditions (TBI, SCI, and stroke) are part of the National Institute for Neurological Disorders and Stroke (NINDS) disease conditions (155). However, the degree of complexity is relatively controlled in SCI and stroke compared to TBI as patients either tend to be more homogenous (stroke) or more uniform and predictable in the disease process (spinal cord injury) (145). As a consequence of this relative homogeneity, more classification and manualization of treatments has to date been completed in these fields (9,156). Though TBI, SCI, and stroke are all distinct, unique conditions, rehabilitation classification efforts in each domain offer significant leveraging value.

The "SCIRehab" project demonstrates the diversity of services in post-acute rehabilitation. A "practice-based evidence" (PBE) methodology was employed to identify and classify the components of spinal cord injury rehabilitation treatments. More than 1,500 patients from six treatment centers in the United States were included. A set of documentation tools and processes were developed to capture the activities at point-of-care and these were implemented by each respective discipline involved in the rehabilitation programs. The results show a mix of disciplines at varying intensities, with a notable increase in the diversity of services in non-inpatient settings (157).

A similar effort performed for a stroke rehabilitation setting identified parsable components of rehabilitation and provided a model taxonomy. The authors included criteria for an intervention classification system based on their experience which included concepts consistent with clinical terminology design such as granularity and parsimony (9). Both sets were developed using "practice-based evidence" which has been demonstrated as a recommended means of identifying and codifying complex treatments (158).

3.2 Traumatic Brain Injury

According to 2010 Centers for Disease Control research, 1.7 million people in the United States sustain traumatic brain injuries (TBI) per year (159). The main causes of civilian TBI are motor vehicle accidents, acts of violence, and to a much lesser extent, sports injuries. Alcohol is a factor in roughly half of TBI accidents (160). Additionally, the United States military is reporting a dramatic increase in TBIs due to a significant growth in military theaters since 2000 and TBI is now referred to as "the signature wound" of the Iraq war (161). Medical diagnoses of military TBI rose from 10,963 in 2000 to 31,353 in 2010, an increase of 286% (162). The military reports 220,430 TBI incidents from 2000 to August 2011 (163). The total yearly cost of civilian TBI in the US in 2000 was more than $60 billion, and has risen as healthcare costs continually increase (164).

3.2.1 TBI Background

Traumatic brain injury is a form of acquired brain injury and is classified according to type (open vs. closed) and severity of injury. A closed injury occurs when the skull and brain have not been penetrated as in the case of a vehicle crash and an open injury is typically exemplified by a gunshot wound. Damage can be localized or throughout the brain (diffuse axonal injury) and is measured by length of lost-consciousness (LOC) and coma, level of memory loss, and through post-injury structural scans of the brain (Cranial Tomography or Magnetic Resonance Imaging) (18).

Traumatic brain injury is generally defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (165), p.1637. More specifically the TBI Model Systems research centers describe TBI as "damage to the brain tissue caused by an external mechanical force as evidenced by medically documented loss of consciousness or post-traumatic amnesia (PTA) due to brain trauma or by objective neurological findings that can be reasonably attributed to TBI on physical examination or mental status examination" (166). About 25% of civilian TBI diagnoses per year are classified as moderate-to-severe (159).

3.2.2 TBI Pathology & Recovery

A person generally experiences a variety of short and long-term symptoms that depend on the severity of the initial insult and on subsequent secondary injuries which are caused by either a lack of oxygen and/or blood to the brain or an increase in intracranial pressure (brain tissue swelling). The structure and function of the brain are altered by the injury resulting in physical, cognitive, and/or behavioral problems (160). Immediate complications can arise due to the injury itself and often due to poly-trauma which accompanies many TBI diagnoses, especially in combat settings (167). These complications often include one or more of the following: hematomas, seizures, hydrocephalus or post-traumatic ventricular enlargement, cerebrospinal fluid leaks, infections, vascular injuries, cranial nerve injuries, pain, bed sores, vomiting, or multiple organ system failure (160,168).

The standard for measuring the severity of brain injury is the Glasgow Coma Scale (GCS), a 15-point test that measures eye opening, best verbal response, and best motor response. The high end of each of the respective GCS scores suggests full awareness and functioning while the low end suggests no awareness or functionality or a vegetative state (169). Baseline post-injury severity is classified as score ranges from 3-8 severe, 9-12 moderate, 13-15 mild (160). However, this measure is currently receiving increased scrutiny as a standardized measure due to the growing use of sedatives and neuromuscular blocking agents in the immediate, pre-hospital setting. These are hypothesized as causing artificially low GCS scores upon hospital admission which potentially weakens the long-term predictive value of the GCS score when used to design patient treatment plans and measure outcomes (170,171). Table 3 shows the predominant TBI severity and rating methods.

Table 3. Traumatic Brain Injury Severity Levels.
Adapted from Corrigan et al. (172), p.74.

Criteria	Mild	Moderate	Severe
Structural Imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness	< 30 minutes	30 minutes to 24 hours	>24 hours
Alteration of Consciousness/ Mental State	<24 hours	>24 hours	>24 hours
Post-Traumatic Amnesia	0–1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best available score in 24 hours)	13–15	9–12	3–8

Moderate or severe traumatic brain injury may cause a person to suffer from a combination of symptoms including severe and persistent headaches, bouts of vomiting or nausea, convulsions or seizures, overall sleepiness, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation. These effects often cause disabilities depending on the severity and brain-location of the initial injury, patient age, and general health at the time of injury (160). The more common disabilities fall into the areas of cognition, sensory processing, communication, and behavioral/mental health and often present as a complex system of co-morbidities in a single individual (160). This case-mix of disabilities presents the most significant challenge in treatment program design and in outcome measurement (129). The typical TBI case includes combinations of depression, anxiety, disinhibition, aggressiveness, lack of initiation and expression, other cognitive deficits and physical disabilities (128). Finally, a severity assessment of moderate or severe is considered significantly different from a mild diagnosis in terms of pathology, treatment, and outcomes (173).

Outcomes for traumatic brain injury are generally regarded as a patient's ability to reengage with every day activities as compared to their pre-injury life situation. The particular effects of an injury may linger but the patient's ability to productively function in society is the ideal measure of recovery. Although intermediate measures of functionality can provide some assessment of patient rehabilitation, program design and measure should incorporate validated scales of community integration and/or vocational status to determine patient outcomes (174–176).

3.2.3 TBI Rehabilitation Interventions

In acute care, patients are stabilized to alleviate poly-trauma and are subsequently considered for rehabilitation referrals. Upon discharge, moderate-to-severely diagnosed patients typically follow one of six pathways: Rehabilitation, then to home/community; rehabilitation, then to home/community with outpatient services; rehabilitation, then to long-term care; long-term care with no initial rehabilitation; discharge to home, or discharge to home with outpatient services (125). Referral to rehabilitation may be determined by a physician using a variety of assessment tools (e.g., Glasgow Coma Scale, Rancho Los Amigos scale) to determine readiness for rehabilitation (124). A rehabilitation plan is typically multi-modal and incorporates varying disciplines in varying intensities and is subject to constant adjustment based on patient progress and participation, and due to the diverse needs of a typical TBI patient. Further, the type of insurance, level of therapeutic alliance, access to services, and level of social/family support system may determine post-acute treatment strategy (177).

Rehabilitation programs are typically in-patient or outpatient and researchers have grouped them into four broad categories: Programs that address and measure functional gains; programs that address early interventions; programs of varying intensity; and programs that are integrated or holistic (178). Functional programs focus on performance of everyday activities and generally use outcomes such as the Functional Independence Measurement (FIM), Barthel Index (BI), or Activities of Daily Living (ADL) measures (179,180). Programs concerned with the timing and intensity of interventions seek to address the issue of spontaneous recovery (a confounding variable for measuring effectiveness) and the amount of treatment necessary to improve outcomes (181,182). Increasingly, research is exploring the seminal holistic approaches of Ben-Yishay and Prigatano as the complex nature of TBI and variability in pathology by patient is thought to require more complex, multi-modal approaches to rehabilitation (183,184).

Patients receive rehabilitation services that reflect the holistic model that includes individually tailored treatment programs in the areas of physical therapy, occupational therapy, speech/language therapy, physiatry (physical medicine), psychology/psychiatry, and social support (160). These multi-disciplinary programs are becoming standard post-acute care as recent systematic literature reviews report increased use, though they report that evidence demonstrating effectiveness is at best, lacking (185,186). However, consensus is emerging that the ability to truly perform comparative effectiveness research is compromised by the black box effect which makes it difficult to identify the active ingredient on the causal pathway (7).

The goals of a TBI rehabilitation program are “to increase the person’s capacity to process and interpret information and to improve the person’s ability to function in all aspects of family and community life” (128), p.106. Services in a holistic program can include cognitive rehabilitation in the form of attention process training memory training and/or strategies to address planning and organizing deficits (187). Treatments for behavioral and emotional disorders may include psychotherapy and "manipulation" of the patient's environmental antecedents and consequences in order to decrease maladaptive behaviors and to increase more positive, adaptive behaviors (188). Neuromotor disorders are common, as are the concomitant problems associated with poly-trauma, resulting in the need for customized physical and occupational therapies (189). Many interventions crossing discipline boundaries aimed at addressing Activities of Daily Living (ADLs)/Instrumental ADLs can incorporate aspects of occupational therapy, physical therapy, vocational, social work, etc. (Ikramuddin F, personal communication, 2013). Finally, patients often receive specialty consultations from clinical domains such as Optometry or Nursing (190,191).

3.2.4 TBI Outcomes

The Veteran's Administration has mandated outcome reporting using the Mayo-Portland Adaptability Inventory (MPAI-4) (192) and Functional Independence Measure (FIM) (193). The MPAI-4 is used to assess outcomes in post-acute brain injury rehabilitation settings and is comprised of 35 items on three subscales (Ability, Adjustment, and Participation). The FIM is an 18-item task-based assessment used to measure the level of function in areas of ADLs. Global outcome scales include the GOS, Community Integration, Return to Work/School (175).

The use of global outcome measures in TBI rehabilitation is increasing as the condition is understood to affect multiple domains of ADLs, function, community integration, work/school status and other aspects of personal and familial relationships. A lack of cohesiveness in outcomes is reported in the research literature because domains are parsed or different outcomes are being used. The utility of functional/short-term measures is in question due to it being a life-long condition. The question that is of increased importance is whether there is a link between clinically significant short-term outcomes and long-term, global outcomes. Further, measuring how these outcomes are sustained remains a challenge.

3.2.5 Measuring and Comparing Interventions

Variability in patient demographics and personal factors, injury characteristics, and the inherent complexity of rehabilitation programs result in less-than-ideal measurement and comparison of rehabilitation outcomes (7). Contrasted with the traditional randomized controlled trial (RCT) from the pharmaceutical domain, with its rigorous adherence to developing control groups and statistical measures of effect, performing a comparative study of complex rehabilitation interventions confounds nearly all characteristics of an RCT. Withholding a potentially beneficial treatment from a TBI rehabilitation control group simply to create an RCT-type experimental design is viewed as unethical (14). Designing clear uni-modal interventions and comparing the outcome differences between two groups presents a more ethical and feasible model, but variability in practice makes adhering to proscribed protocols difficult, if not impossible (144). Further, the challenge for assessing the effectiveness TBI rehabilitation includes both quantitative and qualitative components which are not easily summed into a single statistic and often work in a synergistic manner (118). Finally, the timing of services confounds the definition of rehabilitation as “rehabilitative” interventions are standard practice for acute TBI care, regardless of whether they are part of a nominal rehabilitation program (120).

3.2.6 TBI Rehabilitation Research Literature

The literature describes multi-disciplinary rehabilitation as a treatment program consisting of interventions from at least two disciplines (145). Typically, these disciplines include physical, behavioral, neuropsychology (cognitive), occupational, social work, vocational, and increasingly services which may be described as "Alternative Therapies." Descriptions of interventions depend on the scope of the treatment. Programs are typically described in very general terms and targeted functional treatments are described in more detail (194).

Prigatano, 1984 and Ben-Yishay, 1973 are generally considered to be foundational TBI multi-disciplinary rehabilitation research models (183,184). The programs in these studies have informed the standard programs of care used in contemporary care and research. Though widely discussed and critiqued, these studies serve as historical reference points in TBI rehabilitation design and research.

The literature illustrates the difficulty in identifying comparable intervention components and making meaningful conclusions based on study populations, methods, and outcomes (185,195). Using control groups is considered unethical due to the possibility of withholding potentially beneficial treatment for a treatment arm (14). Assembling comparable groups is difficult due to patient and injury heterogeneity and the lack of standardized assessments and outcome measures (i.e., intermediate vs. long-term outcomes) inhibits cross-site comparison.

External validity of studies are limited due to the variation of condition and small sample sizes. Most frequently, the reviews discuss the difficulty in making relevant comparisons between studies and therefore caution against making broad, confident assertions about the external validity of any particular program of services. The literature generally concludes that MD rehabilitation programs show anecdotal evidence and provide justification to continue to not only provide services but to continue to explore improved means for research.

A high degree of variance among intervention programs and the terms used to describe occurs. Recent systematic reviews of TBI interventions summarize that variability in treatment components, intensity, and settings characterize the literature (174,185,186). A low degree of variance between programs is expected in terms of the particular theories and disciplines used in practice. The high variance items express the very need for this project while the low variance items support the use of a treatment theory design approach. The challenge lies in the ability to map terms used in disparate programs to create a unified conceptual hierarchy.

3.3 Systems Approaches

The complexity and variability described in the previous sections affect clinical data use and often confound the research process. This compromises the incorporation of new medical knowledge into future treatment interventions. Discussion of comparative effectiveness reviews follows with examples of current efforts to addressing this in TBI research. Finally, a discussion of TBI rehabilitation at a Veterans Administration hospital is presented to illustrate the grounded reality.

3.3.1 Donabedian as Quality Framework

Though originally a healthcare quality assessment framework, Donabedian's seminal "Evaluating Medical Care" framework is flexible and has been applied to diverse research areas such as patient safety (196), health systems assessment (197) and patient satisfaction (198). The framework establishes parameters on the healthcare process within which research and discussion can occur to determine the effectiveness of care delivery in local settings and across settings.

3.3.2 Evidence-Based Medicine and Comparative Effectiveness Research

An important component of the NIH's roadmap and indeed in all aspects of healthcare delivery is the concept of evidence-based medicine (EBM). EBM describes a healthcare knowledge process that facilitates the percolation of best-available evidence to key stakeholders in the discovery, research, and delivery realms and includes the integration of individual clinical expertise and high-quality research (199). This translates to a model that combines a clinician's experience with a toolbox of best-available research evidence to make informed, patient-centered decisions (199).

3.3.2.1 Evidence-Based Medicine Applications

"Evidence based medicine is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions" and is comprised of four general steps: 1) formulate a clear clinical question from a patient's problem; 2) search the literature for relevant clinical articles; 3) evaluate (critically appraise) the evidence for its validity and usefulness; 4) implement useful findings in clinical practice (200), p. 1122. Well-designed clinical information systems and knowledge bases which inform treatment guidelines and Clinical Decision Support (CDS) aid in these steps.

3.3.2.2 Comparative Effectiveness Research (CER)

Systematic literature reviews or comparative effectiveness research (CER) are the primary means of performing these research evaluations. According to the Agency for

Health Research and Quality (AHRQ), CER is “designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options” (201). It directly contributes to a knowledge base of effective health interventions that serves to inform busy clinicians, providers, patients, and policy makers who may not have the time or resources to analyze and compare emerging research. The systematic steps aimed at critically evaluating a body of research (including publications, grey literature, and non-published data) in a comparative review are typically (202):

1. Formulate a focused (clinical) question.
2. Develop a method of locating relevant evidence, including explicit criteria addressing content and methodological quality.
3. Develop methods for abstracting, summarizing, and synthesizing the evidence.
4. Locate the relevant studies and assess their methodological validity and quality.
5. Abstract and synthesize the relevant information. This may be done qualitatively, or quantitatively, in which case the systematic review is a meta-analysis.
6. Draw conclusions for practice, policy, or future research, which are based narrowly on the evidence, taking into account its quantity, quality, and consistency.

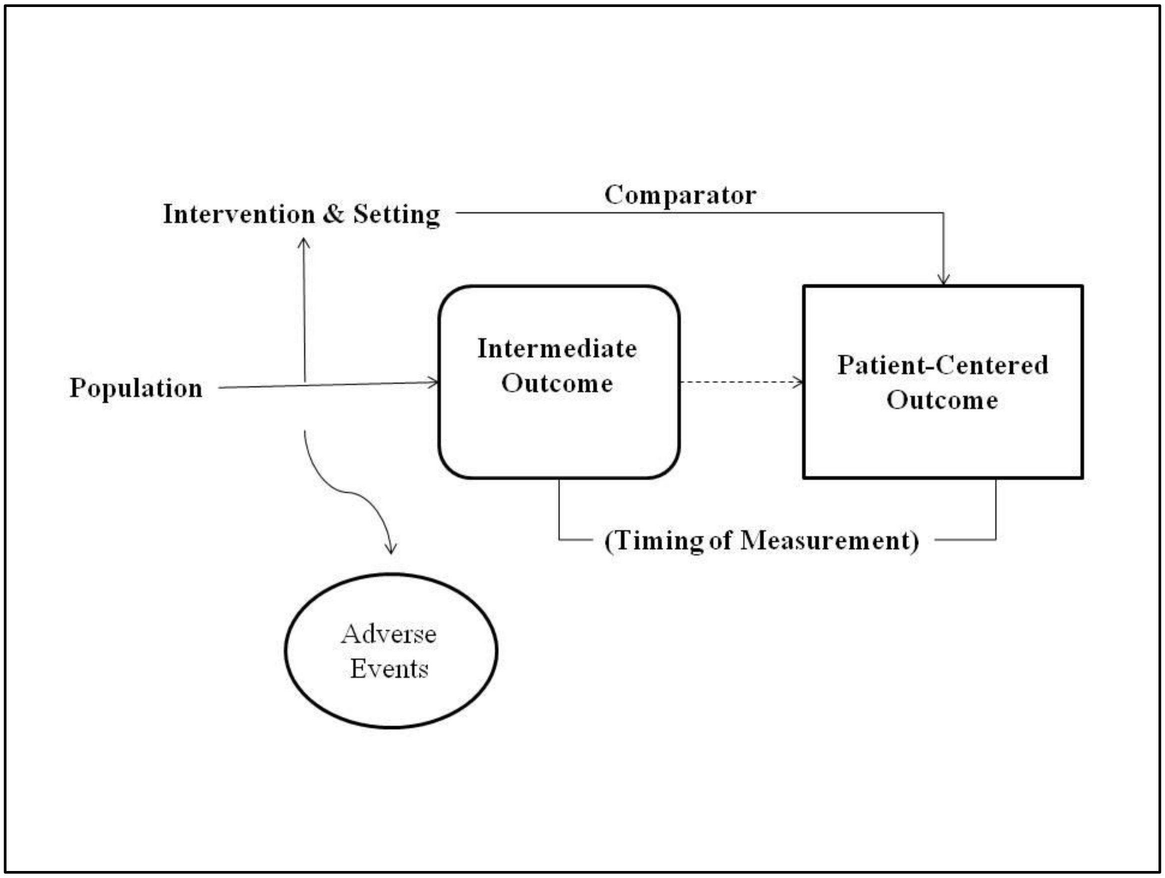

Figure 5. Agency for Health Research and Quality (AHRQ) Review Framework. Portrays the "PICOTS" (Population, Intervention, Comparator, Treatment, Setting) used to model systematic reviews (203).

AHRQ approaches these steps through an analytical framework pictured in Figure 4 using six categories for study extraction: Population, Intervention, Comparator, Outcome, Timing, and Setting (PICOTS), as portrayed in Figure 5 (204). This model and Cochrane CER have been applied most commonly to RCT-study designs that typify pharmaceutical research, relevancy to broader domains of clinical research such as rehabilitation is considerable. Practice-based evidence (PBE) and alternative study design are definitely to be considered but these basic elements of comparison are still necessary to compare interventions and outcomes.

CER is performed by government agencies such as AHRQ in the United States, the Cochrane Collaboration in the U.K., or by other privately funded foundations and organizations (205). Results of CER are generally communicated in the form of a report which describes the background of the problem, the types of evidence for consideration, the criteria by which studies were included in the review, overall quality ratings and global evidence grades (206,207). In the United States, the Preventive Services Task Force assigns grades to evidence and degrees of certainty of beneficial effect based on AHRQ review activities (208). Clinical domains may also collect conclusions from these and other literature reviews into “best practice” documents hosted by professional organizations such as the Brain Trauma Foundation treatment guidelines or the National Center for the Dissemination of Disability Research Knowledge Translation Center (166,209).

Reports are disseminated through conferences, publications, advertising campaigns, and provide background for further research and care guidelines, medical training programs and are incorporated into knowledge bases for clinical decision support (CDS) applications (210). These grades, reports, guidelines, and literature repositories become the knowledge bases that inform treatment and are the basis for future research. CER is considered the highest standard of research evidence as demonstrated by the ascending strength portrayed in Figure 6.

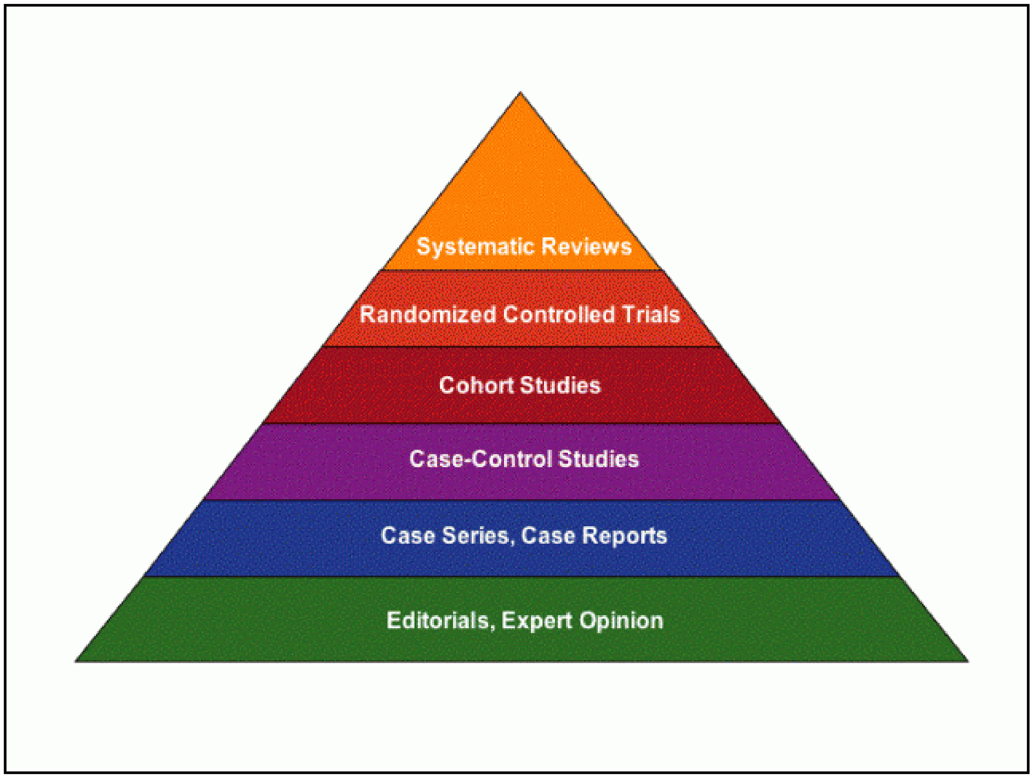

Figure 6. Hierarchy of Evidence.
Hierarchy of evidence for clinical research. Strength of evidence grades are higher with ascending levels of the pyramid. Creative Commons License, Attribution-Non Commercial-Share Alike 2.5 Generic (CC BY-NC-SA 2.5) (211).

When conducting CERs, AHRQ recommends assigning a "Strength of Evidence" (SOE) grade, typically codified as "High," "Medium," "Low" or "Insufficient" to reflect the confidence that reviewers express about the true overall effect of the studies reviewed. "[SOE] evidence systems incorporates not only study design but also many other facets of the evidence, including study conduct, presence or absence of bias, quantity of evidence, directness (or indirectness) of evidence, consistency of evidence, and precision of estimates" (212), p. 514. Risk of bias concerns the internal validity of the study design, consistency is degree of directional agreement of effect across included studies, directness is the link from the treatment to the health outcome, and precision is essentially the confidence interval around the summary effect of included studies (212).

For complex intervention research, many barriers exist to individual study design that compound when making comparisons across studies. Considering the four SOE criteria, the challenges are apparent. Some approaches are proposed to address these issues are exploration of alternative study designs, development of refined statistical models, and consideration of other types of evidence (149,213).

3.4 TBI Domain Metadata

Sources representing grounded TBI rehabilitation data were identified including standardization efforts in TBI and a set of clinical treatment notes. These source types are described as means of assessing the link between the literature and the current state of TBI data.

3.4.1 Neuroinformatics

Neurological research has been a leader in developing informatics tools and processes. Significant data standardization and ontological work has been done by the NIH-funded Neuroscience Information Framework Standardized (NIFSTD) project, which has developed a broad ontology aimed at describing and accessing neuroscience resources (80). The NeuroLex (formerly BIRNLex) and Cognitive Atlas projects are other examples of neuroscience ontologies (214,215). Both projects are models for biomedical ontology development in general and are increasingly demonstrating utility of application in research.

3.4.2 TBI Data Standards – Common Data Elements (CDE)

The National Institute for Neurological Disorders and Stroke (NINDS) Office of Clinical Research, part of the NIH, has addressed neurological disease research data standardization through the “Common Data Elements” (CDE) project. The CDE project began in 2006 as means to standardize the use of clinical research data to better align results across studies and more effectively aggregate information. (216). Development and curation has been led by NINDS with direct clinician engagement through work groups to inform domain content. NINDS works as a coordinating body for each disease area’s work, which is conducted by respective teams of clinical and data experts which currently represent 13 neurological disease conditions.

As part of the NINDS CDE methodology, development and curation of domain-specific CDEs is led by a NINDS Program Manager in close collaboration with clinical domain experts. The development process is typically conducted through a series of meetings and iterative reviews of candidate elements. The process of version development varies due to factors particular to each domain (e.g., participant engagement, external forces such as incentives or policy) but is ideally designed to last 12-18 months (155).

Use of the elements varies by domain due to many factors. Some condition elements such as Parkinson’s Disease are more established and enjoy broad engagement from the field (217). Other examples of NINDS-funded studies using CDEs are in Epilepsy (218) and Spinal Muscular Atrophy (SMA) (219). The overall CDE methodology includes development of domain-specific Case Report Forms (CRFs) as templates for use by clinical researchers in NINDS/NIH or other funded projects. CRF use thus assures engagement and alignment with the CDE data standards.

The CDE project provides a first step to align data. This project reflects an understanding by the field of the need for increased standardization to mitigate complexity, ambiguity, and difficulty in performing CER. Within TBI research, CDEs are the authoritative data standard. The NIH/Department of Defense collaborative Federal Interagency Traumatic Injury Research (FITBIR) database is built using the TBI CDEs (220). NINDS-funded research requires CDEs for clinical data reporting (155) and the CDE working group has partnered with the International Neuroinformatics Coordinating Facility (INCF) to align CDE development with other clinical data standard development processes and to aid the CDE in becoming a global standard. Uses of the TBI CDEs include by the 17-center National Institute on Disability and Rehabilitation Research (NIDRR)-funded TBI Model Systems of Care (221) and clinical research (222,223). The scope of the effort and engagement from clinicians, researchers, government agencies, and research foundations such as OneMind4Research (224) solidifies the CDE set as an authoritative source for understanding the needs and uses of data in TBI treatment.

The TBI CDEs are among the more developed and relatively mature CDE sets. "Version 1.0" was released in 2006 and the current version, 2.0 was released in June, 2012. Eight broad categories of data ("Domains") within a CDE disease serve as parent groups that subsume all other CDEs (twenty-two "Sub-Domains" in TBI). The development of domain-specific CDEs is organized by a set of "Core" elements which are common to most research conducted within any of the specified neurological diseases. Included with each respective element is a 17-column data dictionary which supplies the user of that particular CDE with instructions for use including such information as “Permissible Value,” “Referent Data Source,” and “Definition” of the element as determined by the NINDS project teams. There are currently nine “Core” CDEs that are required for all diseases in NINDS. Figure 7 provides a summary overview of the CDE structure

3.5 Veterans Administration Research Environment

The United States Department of Veterans Affairs Veterans Administration Health Care System (VAHCS) provides a centralized hub for TBI rehabilitation treatment services. From an experimental perspective, VAHCS presents the most ideal setting currently available for post-acute TBI rehabilitation due to the alignment of services, payment, and expertise and level of coordinated care. In non-military rehabilitative health systems, payment and reimbursement often drive the delivery of treatment services, confounding CER (141). The rehabilitation treatment process is mature and generally well-regarded by clinicians and other stakeholders (Lamberty G, personal communication, 2013). Finally, the VAHCS patient base is diverse as they admit service members who suffer insults in both non-military and military settings.

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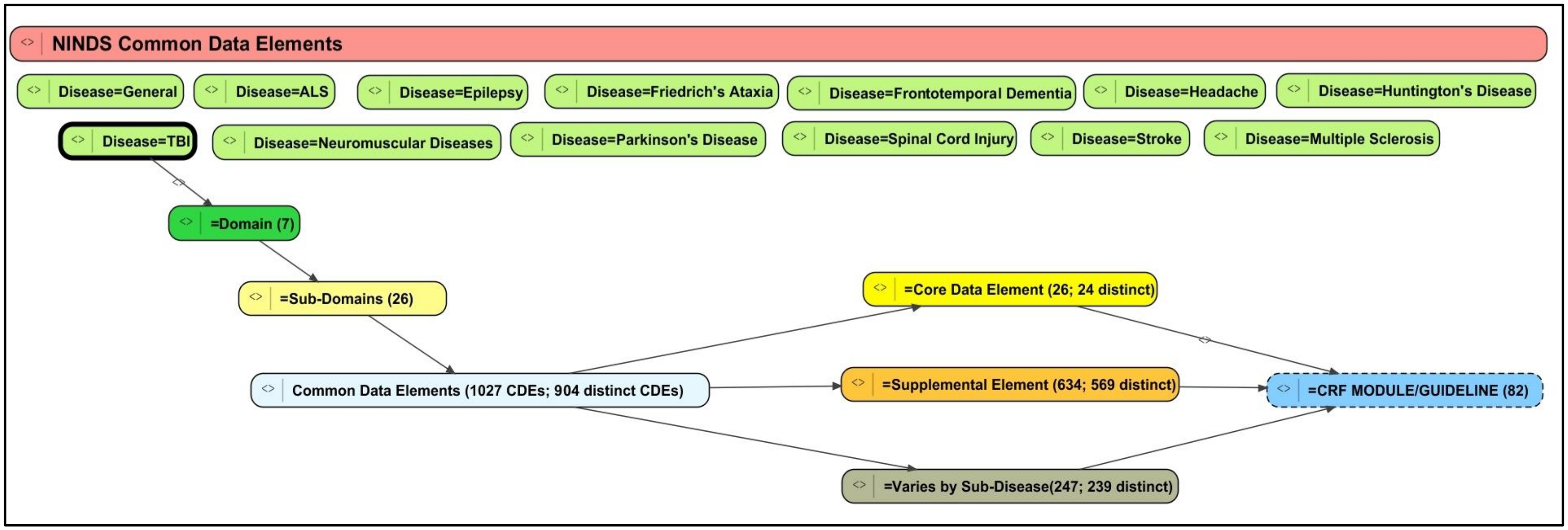

Figure 7. Traumatic Brain Injury Common Data Elements Structure Overview.
Portrays the structure of the TBI Common Data Elements. Domains include Patient Characteristics, Patient History, Injury Related Events, Assessments & Examinations, Treatment/Intervention Data, Protocol Experience, Outcomes & Endpoints, and Safety Data. Core Elements are elements common to all disease areas. Case Report Forms (CRF) Modules are templates comprised of CDEs for use in clinical research.

3.5.1 Veterans' Administration Hospital Traumatic Brain Injury Patient Pathway

The Minneapolis, Minnesota VAHCS is a 279 inpatient bed facility that has been in operation since 1921 and reports 750,485 outpatient visits and 89,822 Community-Based Outpatient Clinic visits over the course of its existence. The Minneapolis VAHCS is a teaching hospital and provides "a full range of patient care services with state-of-the-art technology, as well as education and research" that includes primary care, tertiary care, long-term care, surgery, psychiatric services, physical medicine and rehabilitation, neurology, oncology, dentistry, geriatrics and extended care (225).

The Minneapolis VAHCS is one of four Polytrauma VA Medical Centers in the United States and the rehabilitation programs are accredited by the Commission on Accreditation of Rehabilitation Facilities. The centers provide services for active-duty service members and Veterans for TBI rehabilitation, amputations, blindness and other injuries. The rehabilitation unit at the Minneapolis VAHCS for Polytrauma and TBI is a 10-bed transitional and community re-entry unit known as "4J." Patients come from active-duty and community referrals based on injury type and veteran status. Referrals generally follow geographical catchment areas but can be made outside of this in the case of the need for particular specialty services (225). Due to the reduction in active military theaters, referrals from the private sector are increasing (Lamberty G, personal communication, 2013).

A Licensed Clinical Social Worker (LCSW) manages referrals to the unit, coordinates care plans for patients, and reports centralized data to the VA Central Offices. A patient entering 4J at the Minneapolis VAHCS has typically been discharged from an acute care setting and is considered post-acute as quantified by a Rancho Los

Amigos score ≥4. This threshold designates that a patient has stabilized following an initial insult and acute care and demonstrates a minimal "readiness for rehabilitation" (226). Upon receipt of referral, the social worker assigns patients based on level of care needed to acute inpatient status for severe diagnosis or admittance to the Polytrauma Transitional Rehabilitation Program (PTRP) for mild/moderate diagnosis. The PTRP is an inpatient residential "time limited, goal oriented, residential rehabilitation program that partners with Veteran and Service member participants to improve their physical, cognitive, communicative, behavioral, psychological, and social functioning after significant injury or illness" (227). The Physical Medicine and Rehabilitation (PM&R) unit houses the interdisciplinary PTRP and Polytrauma Rehabilitation Center programs, which constitutes the physical medicine rehabilitation setting. Treatment notes used in the research presented here originate from PM&R.

The social worker consults with a physician and nurse to determine a patient's readiness for entry to a specific program. Considerations are given to the Rancho Los Amigos score, initial diagnosis, and likelihood for success in rehabilitation. Patient and staff safety are also considered in referrals. Census is considered as the PTRP has 18 beds, 12 of which are open to TBI patients (Tepper S, personal communication, 2013). The average length of stay for a 4J patient is 49.9 days (n=15; SE, 8.8; range, 8-105) (Lamberty G, personal communication, 2013).

Upon admission, a patient receives a standard set of services which includes physical therapy, occupational therapy, recreational therapy, social work, dietary consultation, nursing, and vocational and psychological therapies. Specialist consultations are made for orthopedic issues and infections. Coordination of services is performed by a physiatrist and social worker who lead weekly care team meetings where treatments are discussed, coordinated, and evaluated (Tepper S, personal communication, 2013).

3.5.2 Patient Data Collecting and Reporting

Rehabilitation from the clinical standpoint is rounds-oriented with daily and weekly team meetings to discuss patient progress, plans, and to align efforts. Typically, a physiatrist leads these sessions and a social worker records information into a Progress Note (daily) or an Interdisciplinary Note (weekly).

The VISTA electronic medical record system includes the Computerized Patient Records System (CPRS). The Functional Status Outcomes Database (FSOD) is the reporting system used by the rehabilitation units to generate reports for the VA Central Office. The LCSW coordinates with the Program Support Assistant for reporting. There are 15 standard weekly reports and quarterly census required for the VA Central Office. Reporting the FIM is a mandate of the VA as is the Mayo-Portland outcome measure. Reports are submitted via the FSOD at the Austin Information Technology Center in Austin, Texas, a large government information technology and data services center (Tepper S, personal communication, 2013). A separate rehabilitation data research coordinator performs a clinical data management and reporting function for the TBI Model Systems databases, a consortium of TBI rehabilitation research centers that have no official affiliation with the VA.

Clinicians treating 4J patients record treatment plans in semi-structured clinical notes in the CPRS system. Data is not recorded at the time of care but following treatment sessions or at intervals of clinician availability. The structure and content of the data recorded in notes is guided by the particulars of the professional discipline, the overall coordinated patient treatment plan, and the localized departmental characteristics (Lamberty G, personal communication, 2013).

3.5.3 VA Computerized Patient Record System Treatment Notes

From a data collection and reporting standpoint, patient data is coordinated through the CPRS. Each clinician involved in treatment completes a progress note according to their discipline department standard after an individual treatment session. Notes are generally based on 30 or 60 minute sessions unless otherwise noted (Lamberty G, personal communication, 2013). Recording is typically performed using a free-text document within the CPRS system or copied and pasted from an external word processing program. This results in semi-structured notes with high content variability. The one data reporting standard used across notes is the reporting of Functional Independence Measure (FIM) sub-scale relevant to a specific clinical domain. Typically notes are narrative in style and may contain some discipline specific scales.

Chapter 4 Methodology

4.1 Introduction

There currently is no consistent, validated biomedical ontology development or testing model to guide ontology design. In fact, the nature of biomedical domain ontologies inherently requires a customized approach in order to identify and represent the concepts and relationships unique to a particular domain (81). Therefore, the methodological steps are derived from a variety of literature and tools. The basic framework for the methods presented here was informed through best practices of previous biomedical ontology design processes, from key sources in the biomedical ontology literature, and by using the knowledge resources provided by the NCBO and the *Protégé* development group. The methods used here are informed through engagement with authoritative ontology development projects that are also guiding projects such as the World Health Organization's development of the next version of the International Classification of Diseases (ICD-11) (83).

Biomedical ontology development processes are typically collaborative, iterative, and ongoing (228). Though the efforts here represent the work of a single author, the TBI ontology has been designed to promote engagement with other biomedical ontology development projects and the TBI clinical domain. The TBI ontology developed in this study is foundational, extensible, and will require ongoing collaboration and curation to "age gracefully" (39).

4.1.1 Qualitative Methods

Qualitative methods were used in this ontology development project. Qualitative methods are systematic, subjective ways "to gain insights through discovering meanings" by "exploring the depth, richness, and complexity inherent in phenomena" (229), p.61. In contrast to quantitative methods (which require numerical data that are used to test and measure a hypothesis) qualitative methods often employ language and understanding as a means to explain social phenomena. Particular to health research, qualitative methods are concerned with how social processes and practices in health care are created and what meaning they have for people within specific contexts (230).

The methods for this project were designed to reflect a "saturation" of domain source material to inform the creation of a domain conceptualization that was used to build the foundational TBI ontology. As such, the methods are classified as "philosophical inquiry" ("research using intellectual analysis to clarify meanings, make values manifested, identify ethics, and study the nature of knowledge"). More specifically, the methods are classified into the sub-area of "foundational inquiry," which is defined as "research examining the foundations for a science…that provide analysis of the structure of a science and the process of thinking about and valuing certain phenomena held in common by the science" (229), p.75.

4.1.2 Methods Overview

The four steps to building a domain ontology include (84):

1. Capture knowledge of a given domain and develop requirement specification.
2. Conceptualize knowledge in a set of Intermediate Representations (IR).
3. Implement conceptual model in a formal language or description logic.

4. Evaluate the ontology with respect to frame of reference during each phase and between phases of their life-cycle.

These steps were used in this project. The first step was conducted by gathering knowledge about the domain from published literature, domain metadata, and domain experts. The second step was accomplished by systematically extracting domain information into a series of tables from which a visual conception of the domain was created. Third, this conceptualization was mapped into a formal ontology language (Protégé OWL) and fourth, evaluations were executed within and between each of the steps. Gathering domain understanding is referred to as "knowledge management" which is aimed at identifying, codifying, structuring, and validating information artifacts. The ontology will allow "knowledge integration" through interaction with the clinical domain. Figure 8 presents the methods overview.

4.1.3 Methodological Validity

Validity is "an integrated evaluative judgment of the degree to which empirical evidence and theoretical rationales support the adequacy and appropriateness of interpretations and actions based on test scores or other modes of assessment. The principles of validity apply to...inferences based on any means of observing or documenting consistent behaviors or attributes" (231), p. 5.

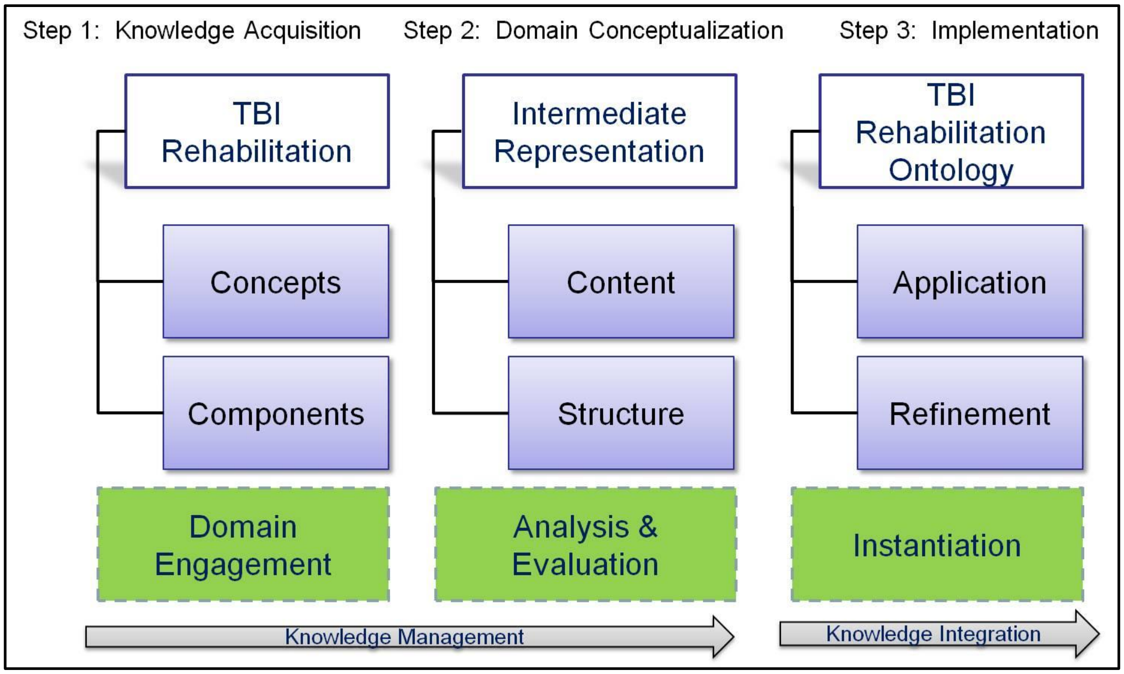

Figure 8. TBI Rehabilitation Ontology Methodology Overview.
The methods entailed analyzing the clinical domain and developing a conceptualization to bridge between the domain and the ontology. Engaging and analyzing TBI rehabilitation domain are described as "knowledge management" steps. Design of the TBI rehabilitation ontology and implementation are described as "knowledge integration."

Validity of methods verifies that the process and interpretations of the research consist of "systematic and self conscious research design, data collection, interpretation, and communication" (232), p. 110. Given the lack of standardization of biomedical domain ontology methods, establishing methods validity here is warranted.

There are three types of validity: Content (based on expert feedback, does the artifact contain what it purports to contain?), Criterion (the connection between the artifact and what it represents in reality), and Construct (the ability of an artifact to answer a question it is supposed to be able to answer) (231). Face validity is a subjective form of content validity, appropriate for qualitative methods used to engage domain clinicians. Criterion validity of the methods is satisfied through the use of sources that build off of vetted work, which in this project includes of the “domain metadata” source types and several Open Biological and Biomedical Ontology (OBO) principles. Finally, construct validity will be substantiated by the use-case categories that recommended as next steps outlined in Chapter 6.

To assure veracity of results, a “triangulation” of data sources, types, and collection activities is employed (233). Triangulation refers to data collection in which evidence is deliberately sought by different means from a wide range of different, independent sources (234). Second, multiple levels of validation, including engagement with clinical domain experts, use of competency questions, and use of an ontology reasoner were performed. Finally, the methods, use-case, and discussion sections explain the connection between the data, the phenomenon (ontology), and its relevance (232).

4.2 Sources

Defining the ontology’s scope and purpose at the outset of a project is a key step that demarcates the first classification decision by determining domain parameters (56). The scope of this project was defined as post-acute, multi-disciplinary, non-surgical, non-pharmaceutical, physical medicine rehabilitation for moderate-to-severe-diagnosed TBI rehabilitation. The TBI rehabilitation ontology is a “conceptualization of a world view from a particular perspective” therefore the methods describe a means to understand and represent the clinical domain of TBI rehabilitation as things, relationships, and constraints (91), p. 13.

The first aim of this project was to conceptualize the domain using domain knowledge sources which comprised the “Knowledge Acquisition” step of the methods overview (Figure 7). A strategy for identifying, selecting, and analyzing sources was developed. Several areas of domain knowledge were explored to determine resource availability. Several TBI rehabilitation systematic reviews were identified and led to an exploration of more general rehabilitation literature and identification of two projects in neurological rehabilitation taxonomy development. The Common Data Elements (CDE) TBI data standardization project was identified through literature scanning. Two clinicians were interviewed for domain content understanding. Finally, consultation with an ontology expert emphasized the utility of analyzing clinical treatment notes to ground the ontological choices in the clinical setting.

4.2.1 Source Selection

Sources were identified and grouped into one of five source type categories. The first was coded as "general rehabilitation literature" and included key commentary articles that discuss the approaches to and challenges of physical medicine post-acute rehabilitation research. These sources were selected as a theme characterized as "How can [condition-independent] post-acute, rehabilitative services be measured and compared?" Second, systematic reviews of TBI rehabilitation research provided knowledge of TBI rehabilitation interventions and the research elements considered meaningful to clinicians. These reviews were collected and grouped as "TBI rehabilitation literature." Literature source selection and analysis was based on the purpose of the source and the authors' potential motivations. Titles, abstracts, headings, and conclusions were scanned for initial inclusion.

The TBI Common Data Elements were analyzed to determine data standards, organization of information types, and level of codification. These were grouped as the "clinical data standard" source type. Taxonomic works in spinal cord injury (SCI) and stroke were referenced for typification of upper level groupings, granularity, and terminological structure. This source type was grouped as “TBI-related conditions.” Finally, TBI rehabilitation treatment notes from the VAHCS were included to satisfy practice-based evidence of in a rehabilitative setting and to understand the information and data structures employed by clinicians (158). Institutional Review Board (IRB) approval was received to review the notes and these approved documents appear in the Appendix. Descriptions of the source types and their contents were presented in Chapters 2 and 3 and are summarized in Table 4.

4.2.3 Source Analysis and Framing Questions

A systematic approach to analysis was developed that consisted of a set of questions applied across all source types. Questions were designed to reflect the aims and objectives of this project.

1. How are rehabilitation interventions described in the source type?
2. How are rehabilitation interventions measured and compared in the source type?
3. What are the critical components/themes/concepts concerning rehabilitation research in this source type?

These questions guided data extraction from source types and informed the initial domain conceptualization. The diversity of source types assured domain knowledge saturation. Since the conceptualization was meant to be broad enough to capture high-level, coarse domain knowledge which can further subsume granularity through future iterations, the questions were delineated in a similarly broad manner. The framing questions are thus an analog of the project aims and objectives.

Table 4. TBI Rehabilitation Domain Conceptualization Source Types.
These sources were processed using the methods portrayed in Figure 8.

Knowledge Source Type	Description	Use	Examples
General rehabilitation literature	Journal articles, conference proceedings framing rehabilitation research issues	Characterization of rehabilitation research	Kane, 2007(7); Whyte, 2012(30)
TBI rehabilitation literature	TBI clinical research articles, commentaries, and manuals describing treatment or research	Components/characterization of TBI rehabilitation research	Systematic Reviews(31); Treatment Manuals(32)(33)
TBI clinical data standard	Domain-aligned clinical research data standard set	Framework and data structure of TBI rehabilitation; integration of relevant elements	NINDS TBI Common Data Elements (CDEs)(35)
TBI- related conditions	Journal articles discussing characterization and data standardization in similarly complex condition treatments	Knowledge structure and levels of granularity	Spinal Cord Rehabilitation (SCIRehab) taxonomy project(34)
TBI rehabilitation treatment notes	Patient progress notes from VAHCS inpatient rehabilitation program	Context and content of programmed services	Occupational Therapy Progress Note

Answers to the framing questions were compiled as sources were analyzed and categories were subsequently developed to begin to extract and organize common summary terms, phrases, or concepts. For example, from the "general rehabilitation literature" source type, such phrases as, "treatment theory" appeared in multiple publications indicating this was an important domain concept. Authoritative source choices were selected for source each type to assure relevance. For example, a seminal paper by Kane (141) and a NIH consensus report on rehabilitation (128) were included as sources of "general rehabilitation" type. The "TBI rehabilitation literature" sources were comprised of systematic reviews of 363 studies and the "clinical data standard" source is the NIH and international TBI data standard.

4.2.4 UMLS MetaMap Analysis

The summary terms and phrases from all source types were collected and analyzed using the Unified Medical Language System (UMLS) MetaMap concept analysis tool. Processing of the summary terms and phrases for each source type was performed through the UMLS Semantic Knowledge Representation "Batch MetaMap" tool. Only concepts receiving a MetaMap score >800 were used to develop the final set of terms (34).

Terms and phrases were de-duplicated per source type. Frequency weighting is not measured by the MetaMap process. Terms and phrases were initially processed through the MetaMap batch program by submitting a *.txt* file for each source type and were submitted in the syntactic form presented in the "Summary Term Grouping" column in Tables 8-12. Terms and phrases that were unnecessarily parsed by the processer were further normalized to eliminate prepositions or articles. For example, "Frequency of Service" yielded two separate mappings, one for "Frequency" and one for "of Service." These terms were flagged and re-processed to mitigate gaps due to input phrases and to determine if processing as a single phrase improved mapping. Other phrases such as "global outcome" could not be normalized further and were processed as individually parsed terms, yielding a MetaMap summary score for the parsed phrase components (34).

The UMLS concept mapping was repeated for each source type and terms were collected into a master table representing all five source types. Any terms or phrases scoring <800 were eliminated from consideration (34). Next, selected terms or phrases were coded as either "Session" if its context as used in the domain source was in regard to a discrete rehabilitation encounter, or as "Program" if the source referred to the larger collection of services in a program. "Both" was applied to terms used in both contexts. Terms coded only at the "Program" level were eliminated as the scope of this work was aimed at rehabilitation sessions. For example, "intensity" was a term extracted from multiples sources. From a programmatic level, intensity describes the volume of services. From a session level, intensity describes the level of activity. Instances of both appeared in multiple sources.

These terms comprised the entities of the domain which were used to inform the Intermediate Representation (IR) and subsequently the ontology. Terms were incorporated into the IR visualization either directly (i.e, "setting") or through a concatenated structure of relationship ("treatment"→"theory"="treatment theory"). Finally, as the IR was assembled with primitive ontological relations, terms were coded as either an "explicit" inclusion, meaning they directly fit into the context of the model or "implicit" meaning they were implied through the structure and relationships. For example, the phrase "Polytrauma social worker" was not literally included in the final term set as it could be implied through the "Clinician" entity and represented a too-detailed level of instantiation for this foundational step.

4.2.5 General Rehabilitation Literature Methods

The search strategy employed to identify general rehabilitation literature sources included searching in *PubMed, PsychINFO,* and *Web of Science* databases using inclusive terms such as "rehabilitation research." Additionally, manual searches of the *Archives of Physical Medicine and Rehabilitation* were conducted to identify titles and authors with potential relevance. Inclusion criteria included a general physical medicine and rehabilitation focus, research methodologies, commentaries, and reviews.

4.2.6 TBI Rehabilitation Literature Methods

Six literature reviews were identified using *PubMed*, *Web of Science,* and *PsychInfo*. MeSH index terms were used and included "Brain Injuries; Injury, Brain, Traumatic; TBI; Traumatic Brain Injury; moderate/severe TBI; multi-disciplinary rehabilitation; post-acute; interventions; TBI outcomes" and all study designs (RCT, observational, etc.) were included. Articles were limited to English, 1990-present. Studies identified as surgical or pharmaceutical interventions or as pediatric were excluded.

4.2.7 Common Data Elements Methods

The CDEs were analyzed to determine the current state of TBI research data standardization (235) and to identify possible ontological classification groups and semantic relationships. A two-step process was performed. First, the full set of 908 TBI CDEs, v2.0, was extracted from the NINDS CDE website and visualized using Visualized Understanding Environment (VUE) (http://vue.tufts.edu/). The set of 44 "Treatment/Intervention" elements was extracted and analyzed for content coverage to determine adherence to controlled clinical coding systems. Finally, the "CDE Name" and "Definition/Description" fields were extracted from the TBI and Stroke "Treatment" CDE sets and processed in UMLS MetaMap.

4.2.8 Stroke & SCIRehab Taxonomy Methods

These projects were conducted to classify rehabilitation interventions in closely related neurological disease areas, similar to TBI. Their contents (taxonomies) were extracted and analyzed through the framing questions and MetaMap processing. Additionally, the levels of organization in these taxonomies was considered to inform hierarchy and granularity of entities in the IR.

4.2.9 Treatment Note Methods

Historical patient treatment notes for five modal patients (moderate/severe TBI) in the Minneapolis VA PTRP in-patient rehabilitation program were analyzed. The patient set had been previously vetted in Yamada et al., 2012 (236). Access to the VA Vista CPRS program was gained as were VA and UMN IRB approvals to view these records. A summary of patient characteristics is presented in Table 5 and the extraction table for the manual review follows in Table 6.

Framing questions were applied to the results of the extractions and the terms/phrases were processed in UMLS MetaMap.

4.2.9.1 Comparative Effectiveness Review Components & Entity Mappings

To demonstrate alignment with CER, the set of entities processed in UMLS MetaMap was subsequently mapped into one or more of the CER categories, and PICOTS (Population, Intervention, Comparator, Outcome, Timing, and Setting). This mapping was performed to validate linkage from grounded domain source material to CER component. Links were determined using the UMLS Semantic Type attached to the MetaMap output terms and by the context of the domain sources.

Table 5. Clinical Treatment Notes Patient Summaries.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	21	22	19	23	23
Injury	IED blast injury	IED blast injury and building collapse	Penetrating brain injury due to indirect mortar fire	Penetrating brain injury due to IED blast	IED blast injury and vehicle rollover with anoxic injury due to cardiac arrest
GCS/PTA/LOC	Initial GCS = 13, but 2 weeks of PTA, duration of LOC unknown	Initial GCS = 7	Admit GCS = 11	Initial GCS = 8	Initial GCS = 3
FIM/Total Mean at Admission	116 / 6.0	75 / 4.0	59 / 3.0	27 / 2.0	19 / 1.0
FIM/Total Mean at Discharge	124 / 7.0	120 / 7.0	97 / 5.0	98 / 5.0	109 / 6.0
Length of Stay	37 days	66 days	81 days	124 days	122 days

IED – Improvised Explosive Device; GCS – Glasgow Coma Scale; PTA – Post-Traumatic Amnesia; LOC – Loss of Consciousness; FIM – Functional Independence Measure (236)

Table 6. Clinical Treatment Note Extraction Criteria.
Local Title and Standard Title are headings provided by the note templates. Discipline, Completer Discipline, Type, and Structure were headings developed by this researcher.

	Local Title	**Standard Title**	**Discipline**	**Completer Discipline**	**Type**	**Structure**
Criteria	Standard VA title of note	Secondary VA note title	Discipline of note	Discipline of note author and signer (may be different than "Discipline" of note)	Criteria for note occurrence	Assessing level of note structure & standardizat ion
Extraction/ Tag	Local title as appeared in note	Standard title as appeared in note	Particular discipline or "interdisciplinary" if disciplines >1	Discipline/role of author	PRN, progress, consult, event, admission, discharge	Free text; semi-structured; SOAP

4.3 Intermediate Representation as Domain Conceptualization

The TBI rehabilitation domain conceptualization was informed by the source extractions and analysis described above. Selected terms and phrases comprised the entities used to create the IR, which visualized primitive ontological relationships as a means to inform potential ontological relations. This is Step 2 of the Methodology Overview, "Domain Conceptualization," the creation of an Intermediate Representation (IR) which bridges domain source data to ontologies (84).

4.3.1 Donabedian Framework and Rehabilitation Encounter

To frame the IR, three levels of context were considered. First, the definition of TBI post-acute rehabilitation demarcated the clinical domain to be represented and accounts for the knowledge gained from sources and UMLS. Second, a foundational model was used as framing to assure alignment within a well-validated model of healthcare delivery (237). Finally, an encounter-based model nested within the foundational model was used to portray the entities derived from the domain analysis. Using this nested framework:

1. Provided context to "unpack" the components of an individual rehabilitation session.
2. Provided a testable use-case model environment.

The foundational model, Donabedian's "Structure-Process-Outcome," classified the operational characteristics or "things" of rehabilitation (patient, condition, clinician, etc.) as "Structure." "Process" classified the interaction of services in care delivery and "Outcomes" classified the measureable results of the Structure-Process interaction. The entities from the domain analysis were tagged according to whether they were determined to be a component of Structure, Process, or Outcome, respectively, and structure within groupings was initially agnostic.

The second level of IR organization was constructed using an encounter-based model as the central hub entity. A clinical encounter is defined as "an instance of direct provider/practitioner to patient interaction, regardless of the setting, between a patient and a practitioner vested with primary responsibility for diagnosing, evaluating or treating the patient's condition, or both, or providing social worker services" (238). An encounter serves as a focal point linking clinical, administrative and financial information and can occur in different settings. This encounter-based model was consistent with literature that discussed the importance of "unpacking" the events of rehabilitation encounters in order to perform effectiveness comparisons.

4.3.2 Intermediate Representation Development

Based on the "encounter" hub, five major classes (or axes) of entities were determined to be necessary and sufficient to constitute a rehabilitation encounter, including: Participant, Setting, Treatment, and Discipline, and Outcome. Terms and phrases from the source type analysis were mapped to an appropriate axis and then organized using a basic ontology relation such as an *is_a* relation, or other simple OBO relations.

4.3.3 Face Validity of Intermediate Representation

A first-draft IR was informally evaluated by two clinicians to determine "face validity." One clinician was a neuropsychologist in the VAHCS TBI rehabilitation system and the other was a clinical professor and researcher of stroke rehabilitation. The goal was to validate content (entities) and structure. The clinicians were asked five questions regarding the nature of the representativeness of the IR.

Questions asked:

1. Does it represent a communicable model of a rehabilitation encounter?
2. Are the present entities valid?
3. Is the present structure valid?
4. What should not be included?
5. What is missing?

The model was consequently refined based on feedback (239).

4.4 Protégé Ontology Modeling

Results of the IR informed ontology development in Protégé. The IR provided a domain conceptualization from which the TBI rehabilitation ontology was assembled.

An intermediate representation is not an ontology but rather an iterative knowledge artifact which contains much of the information needed to create an ontology (84). The VUE IR visualization is not coded in a formal ontology language, an ontology develop in Protégé was needed to formalize the entities and relations into OWL which allows for computation (240).

4.4.1 Class Hierarchy and Definitions

The IR entity terms were imported into *Protégé* into as an *is_a* hierarchy to establish an initial ontology structure consistent with OBO principles. Term definitions were included for each of the classes and were derived from the NCI Metathesaurus concept terms from MetaMap processing. The NCE Metathesaurus is the standard source for International Neuroinformatics Coordinating Facility (INCF) terminologies, thus aligning the TBI ontology definitions with an international standard. To derive definitions, terms were entered into the NCI Metathesaurus Browser. Parameters were set to "exact match" for the initial search. If no results were generated, the parameters were changed to “contains.” The "Semantic Type" feature was used to refine result sets. The semantic type "Therapeutic or Preventive Procedure" was selected since it is related to rehabilitation. Classes were labeled in accordance with the parlance of the domain and through source analysis (241).

4.4.2 Leveraged Ontologies

BioPortal, the OBO Foundry ontology library, and Ontobee were evaluated to determine feasibility for use in this study (43). Leveraging of existing ontologies was conducted by using the “Recommender” tool in BioPortal to search for the eight parent classes. Manual searching of individual ontologies was also conducted in OBO Foundry and Ontobee. Criteria for class label selection were 1) consistent term definition (synonymous) with TBI rehabilitation ontology class definition and 2) source ontology of selected match term was mapped to the Basic Formal Ontology (BFO). The BFO was imported into the Protégé environment and merged with the TBI rehabilitation ontology environment. The TBI rehabilitation entities were then mapped to BFO "SPAN" and "SNAP" entity types to assure adherence to the OBO design principle of assured interoperability between biomedical ontologies (44). Leveraged entities identified through other ontologies were given the name and identification number of the reference ontology entity and the IR name (95).

4.4.3 Relations

While *is_a* relations were applied initially to develop a simple taxonomic class hierarchy, further OBO Formal relations were applied to represent the nature of relationships as portrayed in the IR. An ontology relation "best practice" is to maintain simplicity of relations (90). The OBO Relations Ontology provides 167 relations for potential leverage, a sub-set of which was used in the TBI rehabilitation IR (Table 7).

Table 7. Ontology Relations Selected for the TBI Rehabilitation Intermediate Representation. OBO relations used in the Intermediate Representation (Available from: http://obofoundry.org/ro/).

Relation	Definition	Inverse Property/Other Properties
is_a	C is_a C' if and only if: given any c that instantiates C at a time t, c instantiates C' at t	transitive, reflexive, anti-symmetric
actively_participates_in	x actively participates in y if and only if x participates in y and x realizes some active role	has_active_participant
developmentally_contributes_to	(OBO definition pending)	has_developmental_contribution_from
functionally_related_to	grouping relation that collects relations used for the purpose of connecting structure and function	n/a
happens_during	X happens_during Y if: (start(Y) before_or_simultaneous_with start(X)) AND (end(X) before_or_simultaneous_with end(Y))	n/a
has_active_participant	x has participant y if and only if x realizes some active role that inheres in y	n/a
has_input	Pending	input_of
has_output	Pending	output_of
occurs_in	Pending	n/a
part_of	C part_of C' if and only if: given any c that instantiates C at a time t, there is some c' such that c' instantiates C' at time t, and c *part_of* c' at t	transitive, reflexive, anti-symmetric
participates_in	Pending	n/a

4.4.4 Ontology Design Patterns (ODP)

Literature and OBO Foundry tools were explored to discover relevant design patterns. The use of OBO Principles and competency questions are considered design patterns. Further examination of possible technical patterns of class relations was considered.

4.5 Evaluation

Multiple levels of evaluation were conducted. Hoehndorf et al. (242) have classified the areas of evaluation methods that correspond with the particular domain, goal, development stage, use, and/or scope of an ontology.

1. Direct – evaluation of the ontology structure and content.
2. Application-based – evaluates the results from an application that uses the ontology.
3. Analysis-based – evaluates the use of the ontology as tool in scientific data analysis.

The evaluation for this foundational project occurs primarily in the first level, "Direct," through the domain conceptualization and ontology class identification. Chapter 6 will describe some of the next steps beyond this work that will evaluate the ontology in the other two areas.

4.5.1 Levels of Evaluation

Each of the Brank et al. (106) evaluation approach levels (Chapter 2) was addressed using either triangulation (lexical/conceptual, semantic relations), *Protégé* tools (hierarchy/taxonomy, syntactic, architecture), or through expert review described below (lexical/conceptual, semantic relations, context/application). No gold standard for comparison exists as this is foundational domain ontological work. Similarly, the domain source data is not normalized to a degree that could provide a standardized comparison. Thus, the approach for this work falls into the categories of application and human assessment.

The informal competency questions guided the domain conceptualization and terminology. These questions were general and aim to relate the methods and results to the research question. They were applied to each of the source types and are portrayed as conclusions in each of the subsequent source-type analyses (62).

4.5.2 Protégé Reasoner

Two examples of types of class relationships demonstrable with reasoning (243):

1. Disjoint - two classes, an instantiation can only be a member of one.
2. Equivalent - membership in one class triggers membership in another class.

Additionally, "satisfiability" validates whether a class can be instantiated. If not, results of inferencing will be inconsistent (244). Accordingly, the Pellet reasoner in Protégé was configured to perform the following class inferences:

1. Unsatisfiability
2. Equivalent classes
3. Disjoint classes

Checking for these three criteria ensures that the classes are distinct, structured correctly, and can subsume eventual granularity.

Chapter 5 Results

Brief descriptions of results are presented in the following sections, with full results tables appearing in the Appendix. Tables contain the extracted information from the source type and how it was summarized to inform MetaMap processing to create the Intermediate Representation. A large-scale overview visualization of the IR follows, with a link to an archived, permanent digital storage location for further reference. Tables 8-10 portray the evaluation results.

The project aims as described in chapter one:

1. Develop a domain conceptualization of post-acute Traumatic Brain Injury (TBI) rehabilitation.
2. Codify foundational classes and properties for a TBI physical medicine rehabilitation ontology.
3. Align domain conceptualization and ontology entities with comparative effectiveness review (CER) process.

5.1.1 Source Summary Tables

Results of the term/phrase extractions from each source type are portrayed in Appendix tables. Tables are constructed with source, framing questions, and resulting summary term/phrases determined to be representative of the source.

5.1.1.1 General Rehabilitation Literature

Table 8. General Rehabilitation Literature Source Results.

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary term grouping
Hart, 2009(129)	Content and process levels	Theoretically and empirically	Treatment theory; clinician actions linked to knowledge artifacts	manualization; treatment theory; granularity of treatment descriptions; treatment delivery
Kane, 2007(141)	Identification of treatment components	Effectiveness equation: f(baseline, patient clinical characteristics, demographics, treatment); Program vs. session; Partitioning effects from other influencing factors	Study design; measuring interventions; outcomes; timing; common metric; "ascertainment bias" - subjectivity of measurement	timing; therapist skills; setting; context; multi-discipline team organization; outcomes measurement; medical case-mix; treatment role; granularity
Hart & Whyte, 2003(7)	Theory-supported treatment actions	Multiple levels; program-level to specific actions; “nested doll”	Global; intensity of particular treatment; problem-based treatment; therapy content and process	manualization; setting; engagement; motivation; participation; intensity; clinician skill; therapist behavior; treatment theory; case-mix; mechanism of action
Bellg et al., 2004(143)	Treatment fidelity; manualization; treatment delivery; treatment receipt; enactment of treatment skills	Treatment fidelity; manualization; treatment delivery; treatment receipt; enactment of treatment skills	Measurement of nebulous concepts	treatment fidelity; manualization; treatment delivery; treatment receipt; enactment of treatment skills

Table 8 (continued).

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary term grouping
Whyte & Barrett, 2012(142)	ICF (Impairment) + (Activity/Participation)	Participation/global	Confounders; generalizability	Treatment theory; treatment object; enablement theory; mechanism of action; activity; participation
Hart, 2012(144)	Treatment theory groupings and consequent actions	Study design dictates measures, outcomes	Study design; sample size; multiple/composite outcomes	Therapeutic alliance; participation; engagement; team; treatment theory; fidelity/manualization
Prvu-Bettger and Stineman, 2007(145)	Multidisciplinary rehabilitation services delivered after acute hospitalization that are given either in institutional (inpatient, skilled nursing, or long-term care facilities) or in community-based (outpatient or home health) settings. services provided by multidisciplinary teams	By condition (stroke, TBI, rheumatoid arthritis, hip fracture, older adults)	Study design; selection bias; TREND and CONSORT provide guidance for these but more guidance needed since RCTs not possible; outcomes; intersection of mind-body-social-environment (ICF); consider patients without access; transition between levels of care; disseminating results	Patient demographics; study design; setting; timing of services; timing of follow-up

5.1.1.2 TBI Rehabilitation Literature

Table 9. TBI Rehabilitation Literature Source Results.

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary term grouping
Gordon, Zafonte et al., 2006(245)	Comprehensive-holistic; cognitive; intensive; milieu-based; programmatic; remediative; compensatory	Return to work/military/school; community integration; productivity; quality of life; family engagement	Standard protocols; population	Intensity; timing; mobility
Cicerone, Langenbahn et al., 2011(194)	Cognitive; attention; vision; visual-spatial functioning; language and communication skills; memory; executive functioning; problem solving and awareness; comprehensive-holistic cognitive; computer-based	Practice standard (highest); practice guidelines (medium); practice option (lowest); class I-III designation of selected studies	Study design	Group therapy; individualized; remediation; compensation; intensity; computer-based
Turner-Stokes, 2008(185)	Typology: community multi-disciplinary; specialist inpatient; intensity	Return to work; functional; independence/social activity; cost impact; family; NSF typology: strong evidence, moderate evidence, limited evidence, indicative evidence	Study design	Intensity of services; information provision; treatment plan; timing; coordination of services; supported-work; holistic; case-mix; early; intense; specialist; behavioral; community; vocational; late; ongoing

Table 9 (continued).

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/ intervention components critical to CER from the source type?	Summary term grouping
Lu, Gary et al. 2012(246)	Cognitive-comprehensive; cognitive/academic/ communication; compensatory; computer-based; psychotherapy & behavior modification; physical; pharmaceutical; nutrition; alternative	Functional; global; Multi-disciplinary intensive/ comprehensive vs. standard of care; overall "positive effect; adverse effect; no effect"	Study design	Multi-disciplinary; intensity of services; goal; compensatory; remediation; individual; group; exercise
Brasure, Kane et al., 2010(195)	Multi-disciplinary; setting (inpatient, outpatient, combination, home/community, residential transitional); model of care (holistic day, outward bound, cognitive-didactic, functional, cognitive and community adaption); delivery (group, individual); program duration (weeks/months)	Productivity; community integration; Strength of evidence (SOE) score	PICOTS; primary outcomes, secondary outcomes; risk of bias; sample size; subject demographics; minimal clinical importance; sustainability of outcomes; external validity	Group; individual; multi-disciplinary; setting; duration
Wilde, Whiteneck et al., 2010(175)	12 CDE outcome domains	By outcome domain	Units, parameters of units; standardized tools; agreement of researchers; clinical significance	Global outcome; functional outcome
Ragnarsson, 2002(128)	Cognitive; compensatory; psychotherapy; pharmacotherapy; behavior modification; vocational; comprehensive interdisciplinary; nutritional; recreational; music; art; alternative medicine	Restorative; compensatory	Patient demographics; study design; outcomes	Setting (school/ workplace, residential, specialized care); timing of services

5.1.1.3 Data Standard - Common Data Elements Results

Table 10. Common Data Elements Source Results.

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary term grouping
TBI Common Data Elements	"Treatment"/ "Intervention"/" Therapies" CDEs (11)	Functional outcomes; global outcomes; standardized assessment tools (FIM, Mayo-Portland, etc)	Domains (7): Patient/Subject Characteristics; Patient/Subject & Family History; Disease/Injury Related Events; Assessments & Examinations; Treatment/Intervention Data; Protocol Experience; Outcomes & Endpoints; Safety Data; possibly Sub-Domains and/or all CDEs from Rehabilitation	Patient characteristics; patient history; family history; disease event; injury event; assessment; examination; treatments; intervention; protocol; outcomes; endpoint; safety; intensity level; ICD-9-CM; frequency of service; session duration; program duration; ongoing
Other CDEs (Stroke)	"Treatment"/ "Intervention"/" Therapies" CDEs (31)	n/a	Domains (6): Patient/Subject Characteristics; Patient/Subject & Family History; Disease/Injury Related Events; Assessments & Examinations; Treatment/Intervention Data; Protocol Experience; Outcomes & Endpoints	smoking; weight-loss; diet; data collection date; location after discharge; mobility device; durable medical equipment; follow-up; primary care physician

5.1.1.4 Stroke & SCIRehab Results

The stroke taxonomy modeled the physical therapy domain, somewhat limiting the scope in contrast to a multi-disciplinary rehabilitation program. Accordingly, they organized the contents around 1) Functional Activities and 2) Body Systems and identified 12 classes subsuming 63 terms. Term definitions and relations were not included.

The occupational therapy (OT) area of the SCIRehab project was analyzed. Similar to the Stroke taxonomy, multiple levels of classification were identified. At the upper level of the taxonomy, “Program,” “Session,” or “Activity” provided parent groupings. Three levels of increasing granularity were arranged below these classes and 26 OT activities were identified. Table 11 shows results.

Table 11. Stroke and SCIRehab Source Results.

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary Term Grouping
Stroke (9)	Functional; Body Systems; (12 areas total)	Multiple-levels; granularity	Patient physical functioning status	(Structural); Assistive devices; pet therapy; neuromuscular intervention; education; equipment; modality; musculoskeletal intervention; cognitive intervention;
SCIRehab (156,247)	Disciplines	Session Level; Activity Level	Detailed activity of rehabilitation session	(Structural); Assistive devices; physical therapy; occupational therapy; speech therapy; recreation therapy; psychology; social work; case management; nursing education

5.1.1.5 VA Clinical Treatment Note Results

A total of 495 progress notes describing five patients were reviewed. Notes were primarily semi-structured with domain-specific headings, filled in with natural language free text summarizing session activities and patient performance. Level of note standardization or templates appeared low, and use of controlled terminologies and/or coding systems was minimal. The primary clinical code used in the notes was Current Procedural Terminology (CPT). Other coding systems were virtually absent from these notes.

There were 59 “Note Types” (per VA note designation), 17 different treatment disciplines represented, 6 distinct discipline specialty consultations, and 23 distinct roles of completers. Seven note types contained interdisciplinary/summary treatment information. Details of the note extraction can be found in the Appendix. Table 12 shows results of the note term/phrase extraction.

5.2.2 MetaMap Results

From the source types and through MetaMap processing, 156 terms/phrases were derived. Phrases that did not yield a match in the first run were flagged and re-processed using lexical variants. Five term/phrases scored <800 or did not have a match. Terms/phrases scoring ≥800 consisted of 16 distinct UMLS Semantic Types. These steps are portrayed in Figure 9.

Table 12. Clinical Treatment Notes Source Results.

Source	How are rehabilitation interventions described in the source type?	How are rehabilitation interventions measured/compared in the source type?	What are the issues/intervention components critical to CER from the source type?	Summary Term Grouping
VA Progress Notes; 5 Mod-Severe patients from previous "Intensity of Services" project (Mayor, Yamada, et al., 2012). Manual review of >500 notes.	Free text, semi-structured discipline notes; summary Physiatry notes; specific goals, actions of session; recommendations for subsequent sessions	Summarized in weekly and discharge Physiatry notes; largely free text; some FIM scores with discipline-specific scores aggregated in summary reports	(not explicit)	Goal; participation; activity; intensity; frequency; duration; engagement; Occupational Therapy; Social Work; Psychology; Nursing; Physical Medicine; Physical Therapy; Psychiatry; Speech Language Pathology; Recreational Therapy; Spiritual; Interdisciplinary; Dietician; Physiatry; Optometry; Nutrition; Military; Family; Clinical psychology; Vocational Therapy; Ophthalmology; Neuropsychology; Podiatry; Audiology; Social Work Supervisor; Occupational Therapist; Polytrauma Social Worker; Psychologist; Social Work Case Manager; Nurse; Physician; Physical Therapist; Social Worker; Psychiatrist; Speech Pathologist; Recreational Therapist; Chaplain; Optometrist; Clinical Psychologist; Ophthalmologist; Neuropsychologist; Podiatrist; Case Manager; Ophthalmic Photographer; Optometry Resident; Audiology Supervisor

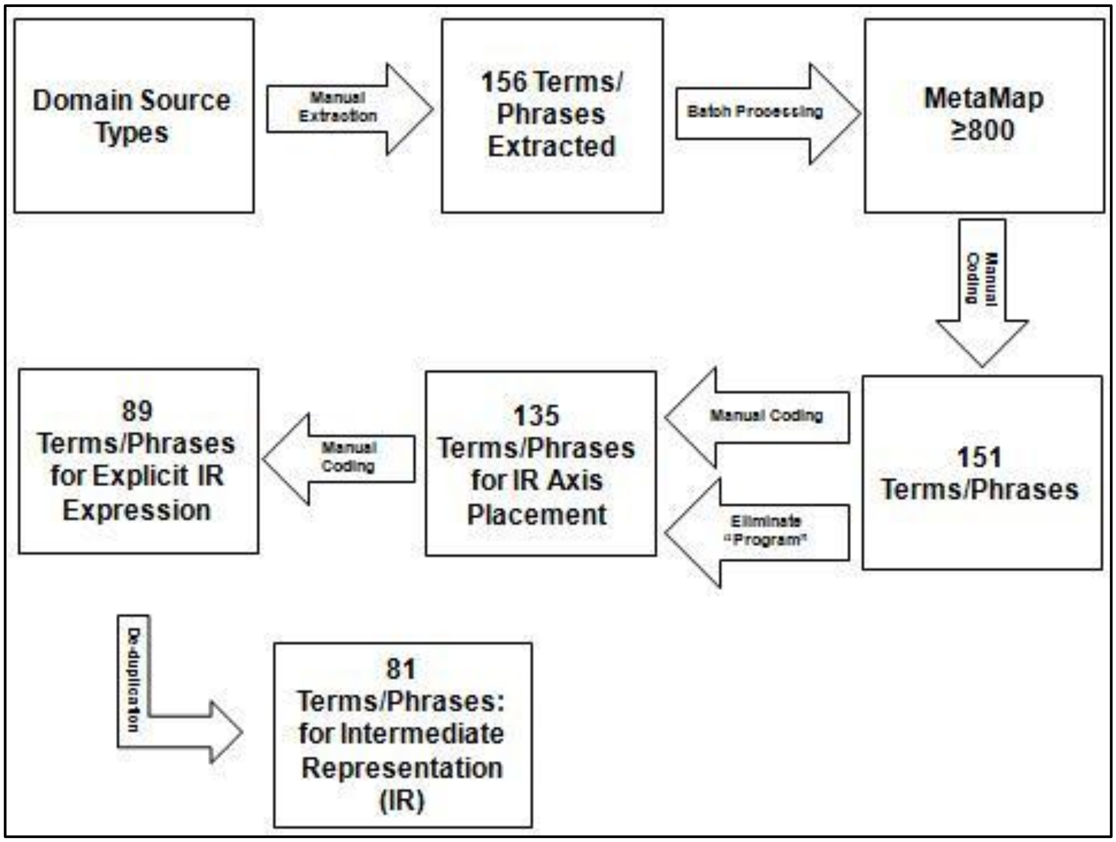

Figure 9. TBI Rehabilitation Source Types to Intermediate Representation.
Portrays the steps from domain source data extraction through UMLS MetaMap processing to IR. This is the path of term/phrases from the domain to an informational resource to develop the domain conceptualization.

5.3 TBI Rehabilitation Intermediate Representation

The IR aligns with the Davis (100) criteria for an Intermediate Knowledge Representation role as both a domain conceptualization and an underlying information source for the TBI rehabilitation ontology. Table 13 portrays the criteria and alignment and Figure 10 portrays the IR as developed in VUE. This figure is available in archived format for more detailed exploration at http://conservancy.umn.edu/handle/156978.

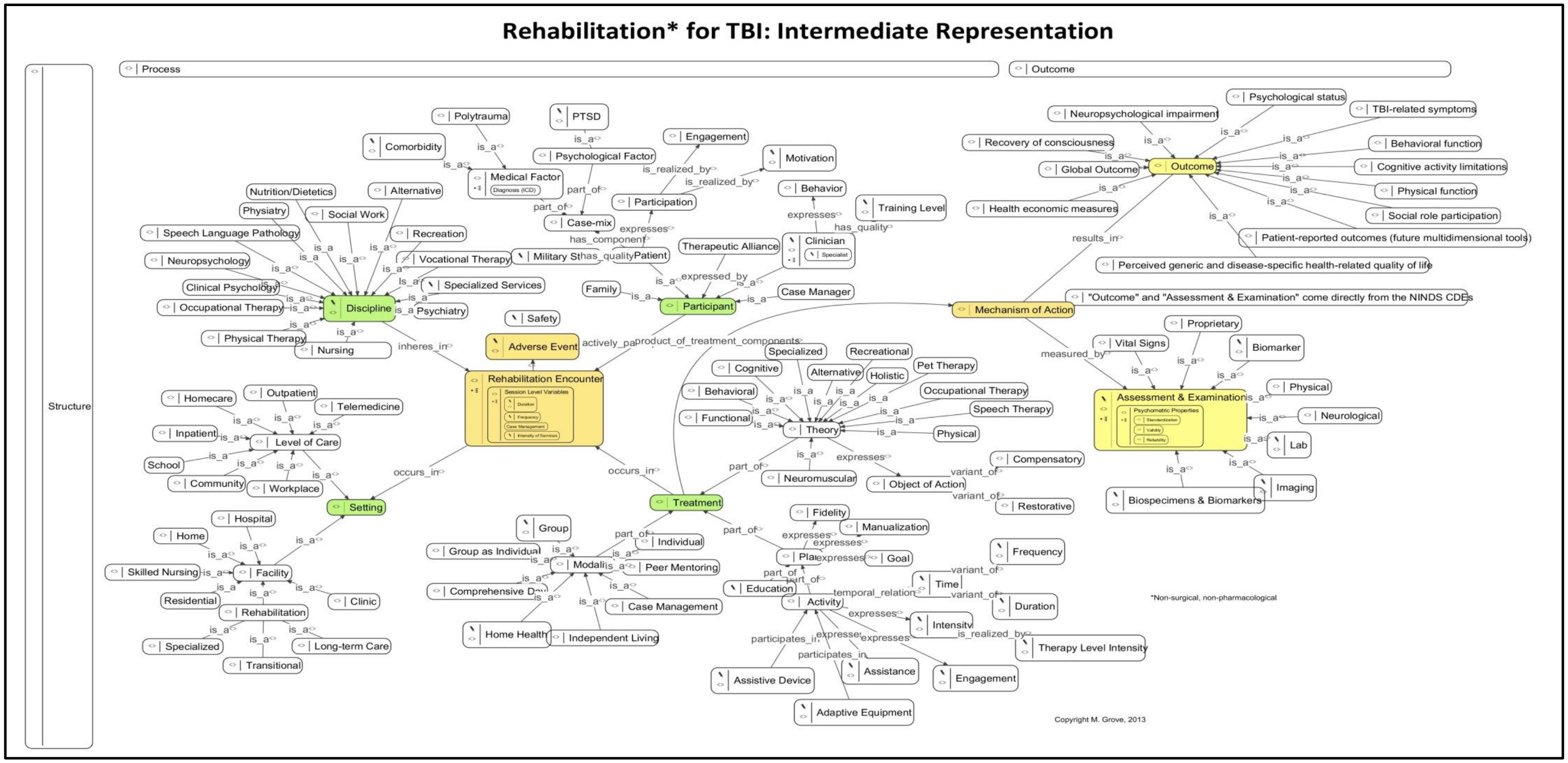

Figure 10. TBI Rehabilitation Domain Conceptualization (IR).
"Outcomes" and "Assessments & Examinations" parent and children levels were taken directly from the CDEs. "Mechanism of Action" and "Object of Action" were included as important concepts referenced in recent literature as keys to understanding the complex mix of variables in the domain. Digital version of this figure is available at (insert link) for detailed examination. An archived version of this figure is available for detailed exploration at http://conservancy.umn.edu/handle/156978. Figure is modeled using Visual Understanding Environment (VUE) (248).

Table 13. Intermediate Representation (IR) as Domain.
Conceptualization and Underlying Ontology Informational Model. Left column states the various roles a KR serves as informational resource. Right column portrays how the TBI rehabilitation IR matches these roles.

Intermediate Knowledge Representation Role (100)	**TBI Rehabilitation IR**
Serves as a surrogate for a thing	Named and visualized components of domain
A set of ontological commitments describing how a part of the world can be considered	Primitive ontological relations applied between components
Medium for computation	Candidate classes and properties for ontology
Medium for human expression	Human-understandable terms and definitions
A fundamental theory of intelligent reasoning in terms of three components:	(see below)
Fundamental conception of intelligent reasoning	Structure-Process-Outcome framework
Set of inferences that the representation sanctions	Relations
Set of inferences it recommends	“Mechanism of Action;” “Object of Action”

5.3.1 Intermediate Representation Face Validity Results

Iterative feedback from two rehabilitation clinicians provided face validity. They reviewed periodic lists of the candidate entities from the various source types and noted whether these were important to rehabilitation and rehabilitation research. An example of their input included the differentiation between a discipline administering a particular rehabilitation session and the basis of the theory administered within the session.

5.4 TBI Rehabilitation Ontology

Seventy-seven classes were created in Protégé (65 BFO “Continuant” and 12 “Occurrent”) based on the IR and translation to ontology. Twenty classes in the “Assessment” (8) and “Outcome” (12) parent categories were directly leveraged from the CDE structure, meaning 57 classes were identified and modeled from the source saturation. Figure 11 portrays the complete term steps from domain source types to ontology classes as carried out through the Methods overview presented in Chapter 4. Additionally, seven properties were included as listed in Table 14. The ontology is not a direct translation of the IR but is rather an interpretation, as will be discussed in Chapter 6. A full table of the entities, definitions, properties, and instances are in an Appendix table. A permanent archived version of the ontology can be viewed at https://conservancy.umn.edu/handle/156931. Screen shots of the ontology in Protégé are presented in Figures 12 and 13.

Table 14. TBI Ontology Properties.
OBO relations and hierarchy selected for the TBI rehabilitation ontology.

Parent Property	SubProperty
topObjectproperty	**modifier_property**
	has_quality
	measured_by
	relational_property
	expressed_by
	occurs_in
	part_of
	participates_in
	variant_of

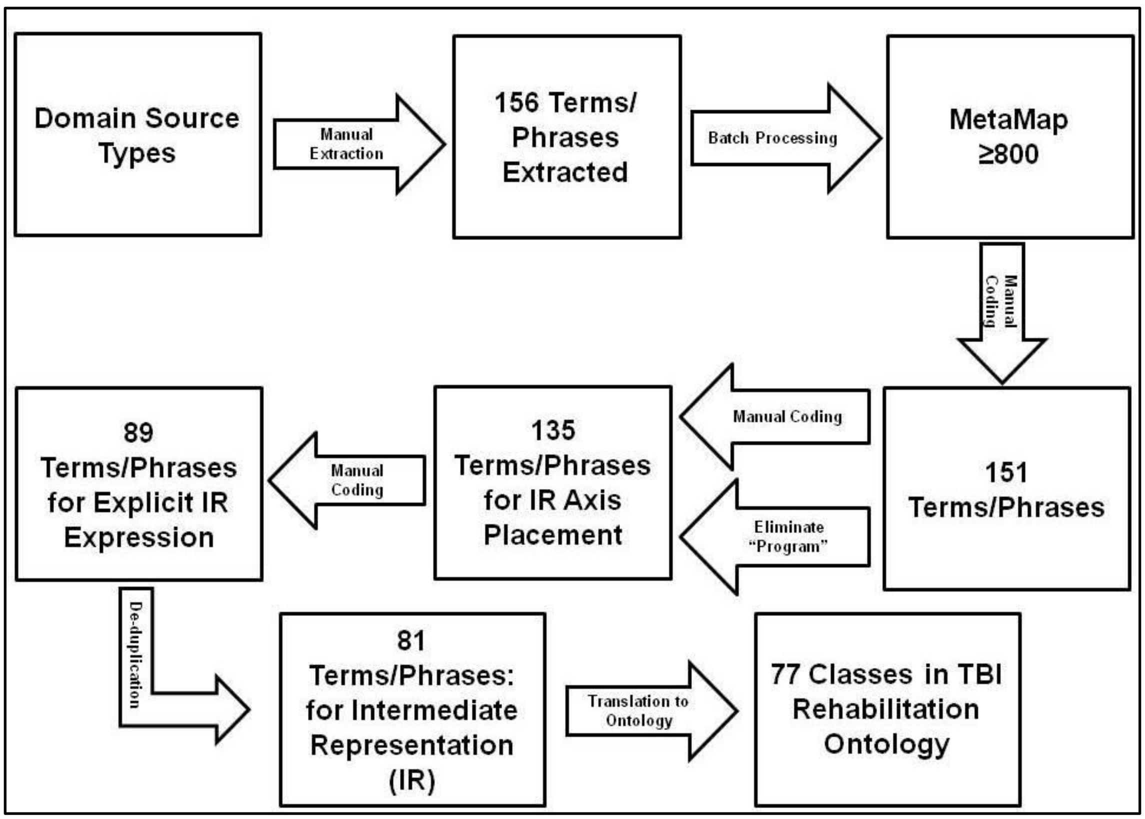

Figure 11. Intermediate Terms/Phrases to Ontology Classes.
Shows the results of source type analysis to ontology class development.

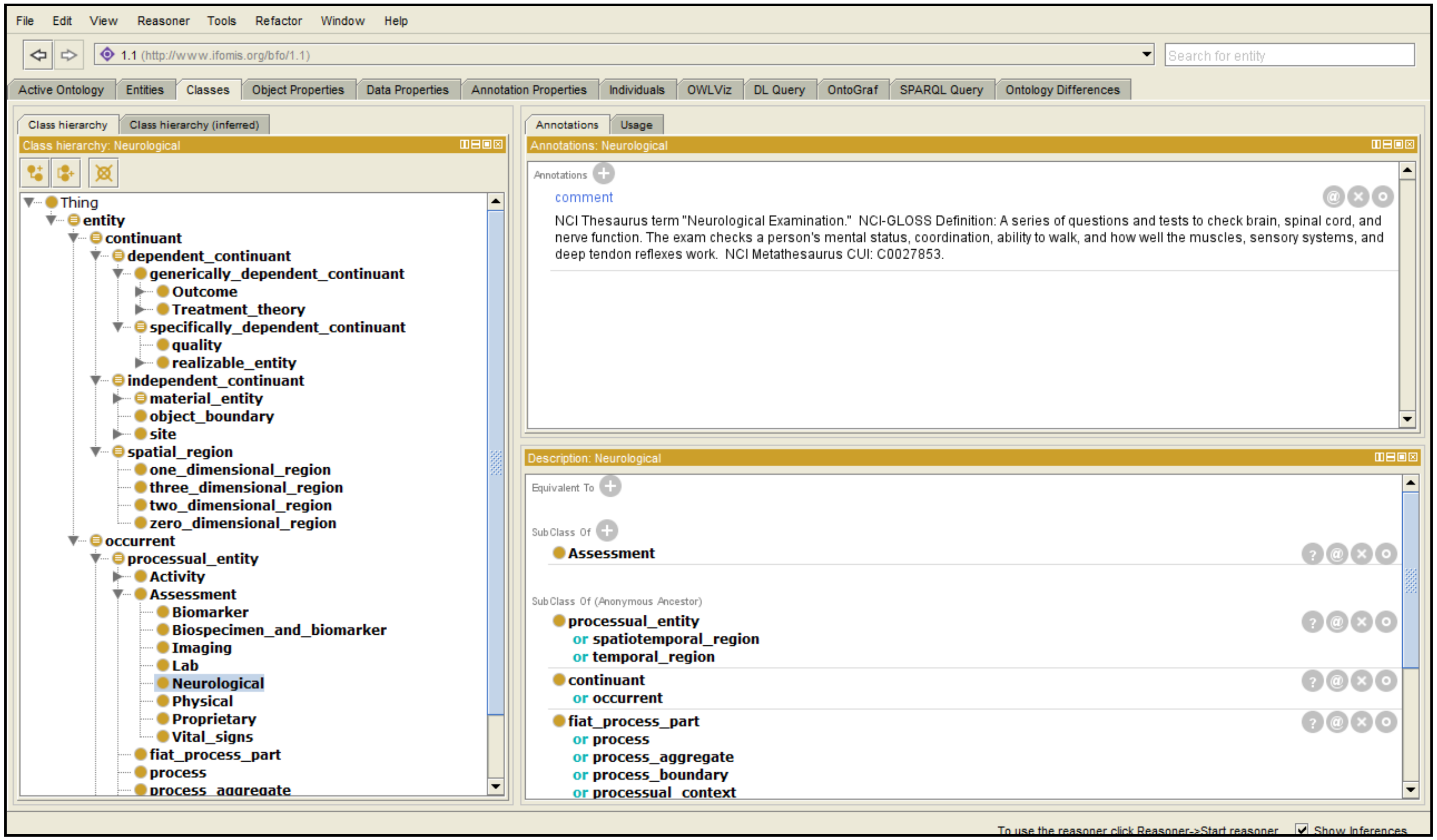

Figure 12. TBI Rehabilitation Ontology Viewed in Protégé (249).

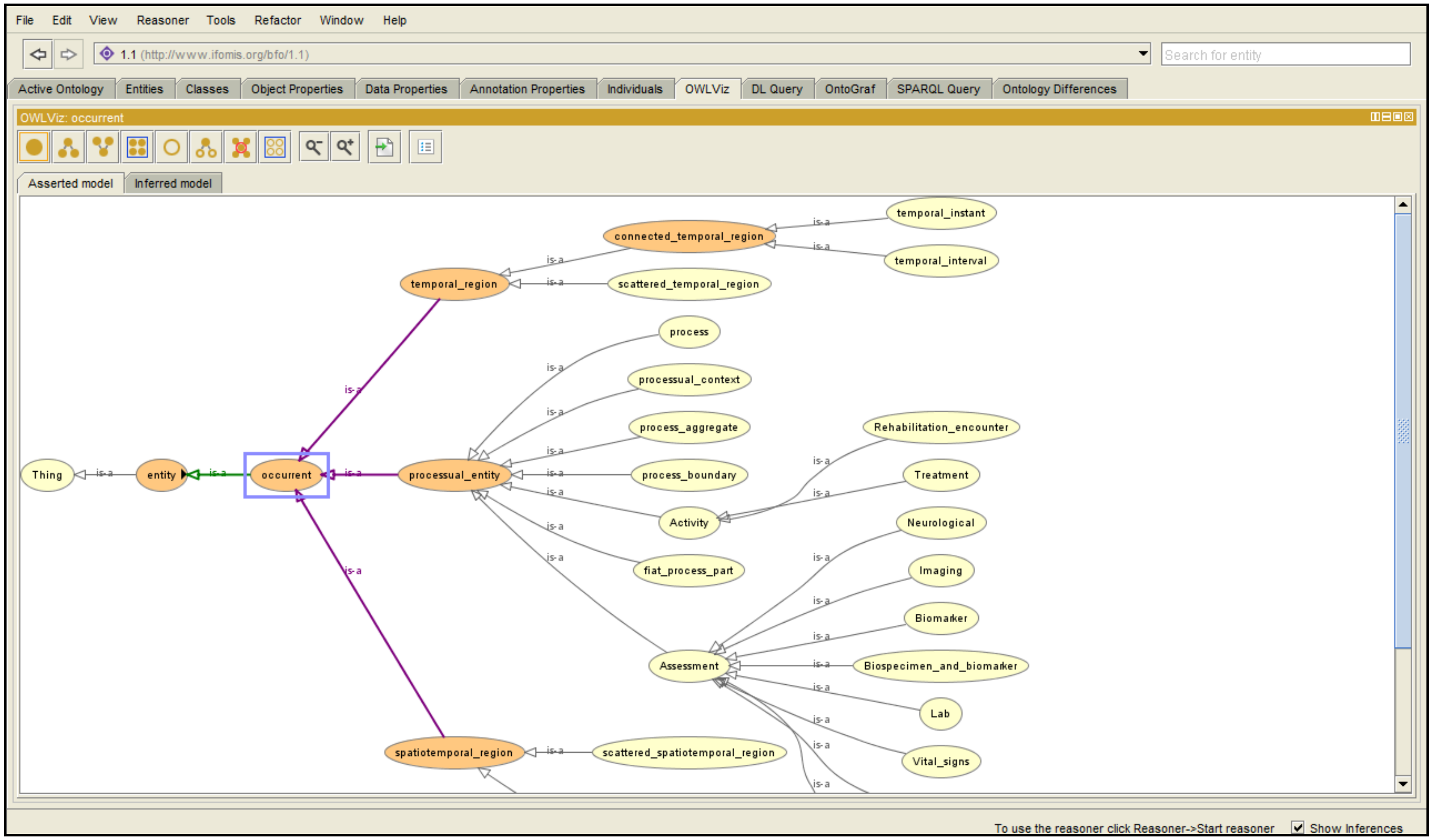

Figure 13. TBI Rehabilitation Ontology Viewed in Protégé (249)**.**

5.4.1 Leveraged Ontology Summary

Six ontologies were used for leveraging. The upper-level Basic Formal Ontology (BFO) was imported and integrated into the TBI rehabilitation ontology Protégé environment. The eight parent-level classes were mapped to existing biomedical ontologies and given the respective class name, identifier, definition, and synonyms, where available. Minimum criterion for inclusion of an entity was its ontology's upper-ontology alignment (BFO). This step assures interoperability between biomedical ontologies (92). Results of the mappings are portrayed in Table 15 and Figure 14.

Table 15. Listing of Leveraged Ontologies.

Source	Scope/Terms	Description	Data Type
Basic Formal Ontology (BFO)*(94)	39 categories	Upper-level ontology that can be used in support of domain ontologies; assures connection to other biomedical ontologies	Controlled terminology/ontology
BIRNLex(80)	3,580 classes	Entities for data and database annotation covering anatomy, disease, data collection, project management and experimental design	Controlled terminology/ontology
Ontology for General Medical Science (OGMS)*(250)	132 classes	Entities involved in a clinical encounter	Controlled terminology/ontology
NIFSTD*(251)	59,168 classes	Set of modular ontologies to describe neuroscience data and resources	Controlled terminology/ontology
Translational Medicine Ontology (TMO)(252)	300 classes	High level patient-centric ontology for the pharmaceutical industry	Controlled terminology/ontology
NCI Thesaurus*(253)	>34,000 concepts	Ontology-like vocabulary that includes broad coverage of the cancer domain	Controlled terminology

*OBO Foundry Candidate Ontology

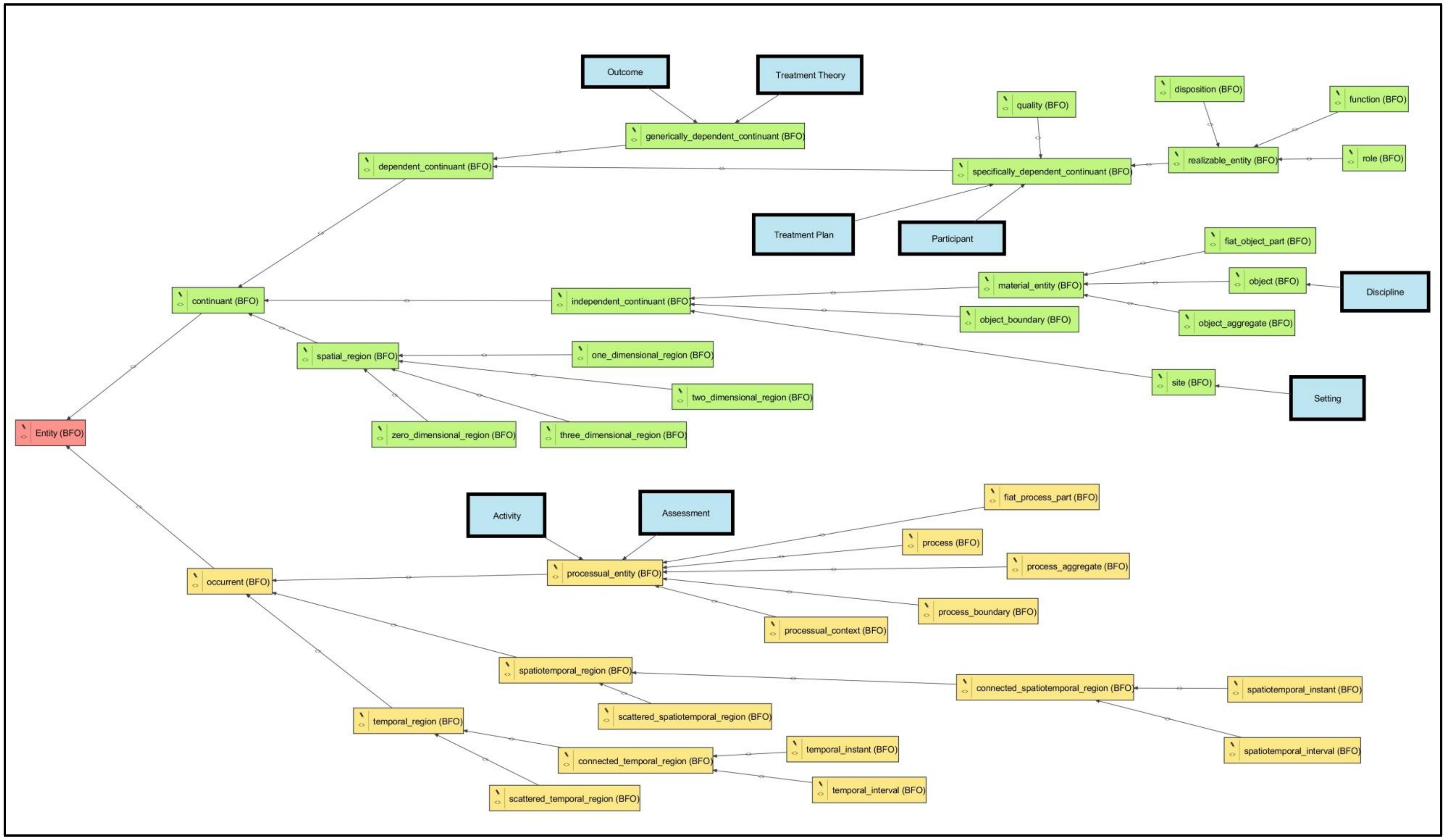

Figure 14. Mappings from Basic Formal Ontology (BFO) to TBI Rehabilitation Ontology.
TBI rehabilitation ontology entities are outlined in black and are shown mapping directly to their respective BFO entity types.

5.5 Evaluation Results

Evaluation was performed for the domain conceptualization and for the ontology according to the methods in chapter five. The following tables describe adherence to the sets of competency questions that checked content and structure.

5.5.1 OBO Design Principles and Competency Questions Results

OBO design principles were followed where possible. While all were considered throughout data collection, analysis, and evaluation, not all principles remained relevant to the final set of ontological classes. Two sets of "Formal Competency Questions" were applied, with some moderate redundancy of coverage between them. The first set, portrayed in Table 16, are the OBO Design Principles, and the second set, Table 17, are general recommendations for formal competency questions from Spear (51). Table 18 portrays the Informal Competency Question results.

Table 16. TBI Rehabilitation Ontology Adherence to OBO Principles.
These are the answers to the "Formal Competency Questions." "FP"=Foundational Principle.

OBO Design Principles			TBI Ontology Adherence to OBO Criteria	
OBO FP ID	**Principle Name**	**Description**	**Rationale**	**TBI Rehabilitation Ontology**
FP 001	Open	The official OWL version of the ontology must have two annotations using the properties "dc:license" and "rdfs:comment"	The ontology must be open and available to be used by all without any constraint	Protégé OWL generates automatically
FP 002	Common Format	Common formal language in an accepted concrete syntax	Ontology is in, or can be expressed in, a common shared syntax so the same tools can then be usefully applied	Protégé generates OWL, OWL2, RDF, XML, all accepted syntaxes
FP 003	Identifier space	Each class and relation (property) in the ontology must have a unique URI identifier	The source of a term (i.e. class) from any ontology can be immediately identified by the prefix of the identifier of each term	Protégé generates unique URIs for all entities
FP 004	Versioning	Metadata for changes	The ontology provider has procedures for identifying distinct successive versions	Protégé versioning
FP 005	Clearly delineated content	Coherent natural language definitions of top-level term(s) incorporating cross-product links to other OBO Foundry ontologies	The ontology has a clearly specified and clearly delineated content. The ontology must be orthogonal to other ontologies already lodged within OBO to allow for combination of multiple ontologies	Domain is "TBI MD PM Rehabilitation" and is currently unique among OBO ontologies; natural language used for terms, definitions
FP 006	Textual definitions	Textual definitions for a substantial and representative fraction, plus equivalent formal definitions	Many biological and medical terms may be ambiguous, so terms should be defined so that their precise meaning within the context of a particular ontology is clear to a human reader	NCI Thesaurus, CDISC, CDEs, leveraged ontology, or research literature provided definition for each term
FP 007	Relations	Clearly defined relations (currently being redefined to reflect class-level, not just instance-level)	Uses relations which are unambiguously defined following the pattern of definitions laid down in the OBO Relation Ontology	Use of OBO Relations Ontology (RO)
FP 008	Documented	The ontology is well-documented	Publications for users and developers	Dissertation publication; subsequent article publications

Table 16 (continued).

OBO Design Principles			TBI Ontology Adherence to OBO Criteria	
OBO FP ID	**Principle Name**	**OBO FP ID**	**Principle Name**	
FP 009	Plurality of users	The ontology has a plurality of mutually independent users	URIs used in variety of projects	Engagement with domain through CDE project
FP 010	Commitment to collaboration	OBO Foundry ontology development is carried out in a collaborative fashion	Ensure consistency with neighboring OBO Foundry ontologies and ensure use of relevant content from these neighboring ontologies	Adherence to OBO criteria; BioPortal publication; publication and conference presentations
FP 011	Locus of authority	There should be a single person who is responsible for the ontology, for ensuring continued maintenance in light of scientific advance and prompt response to user feedback	Maintain integrity and further development	M. Grove to be listed as contact in BioPortal and publications
FP 012	Naming conventions	4 areas for adherence: Convention, Univocity, Reduce String Variance, and Typography http://www.biomedcentral.com/1471-2105/10/125	Enhance communication, simplify, support integration, facilitate automated tools	Naming of entities consistently follows criteria in all four areas
FP 016	Maintenance in light of scientific advance	Ontology reflects domain developments	Ensure the improvement of ontology over time	Domain engagement and update schedule

5.5.2 Formal & Informal Competency Question Results

Table 17. Formal Competency Question Results.
Adapted from Spear, 2006(51) and description as to how the TBI rehabilitation ontology addresses the questions.

Competency Question Domain	Competency Question (241)	TBI Rehabilitation Ontology
Formal & Material Ontologies	Formal categories: what formal ontological categories are important for the domain?	Basic Formal Ontology (BFO)
	Formal Relations: what formal ontological relations are important for the domain?	*is_a; part_of; instance_of*
Granularity	What is the appropriate maximum and minimum level of granularity or complexity that the ontology requires?	1.0: Comparative Effectiveness Review (CER) components 2.0: Activities of rehabilitation session
Relevance	What is necessary for inclusion given the domain?	Multiple disciplines subsumed
	What is necessary for inclusion given the intended use?	Linking treatment theories, activities, and outcomes
Gathering Information	What are the important general terms and relations dealt with in the domain?	Literature & clinical notes; key informants
Scientific Investigation	How do the terms and relations function in scientific theories of the domain being represented?	Components to develop evidence supporting theory
	Are the terms and relations that have been collected an adequate reflection of what is most crucial for understanding the truth about this domain of reality as reflected in current scientific knowledge?	High-level classifications linking rehabilitation to CER will yield granular evidence through instantiations in practice and refinement of the ontology
Thought Experiments and Imaginative Variation	What are the essential or defining features of the domain as a whole?	Goals, activities, outcomes
	What are the essential or defining features of the particular entities and relations that have been selected as crucial?	Multiple disciplines, multiple roles, multiple theories
Logical, philosophical, and scientific coherence	Terminology & definitions	NCI terminologies (CDISC standard); domain literature
	Taxonomy	*is_a* principles of sub-sumption
	Categories and relations, align the domain information with relevant formal ontological categories and relations	Mapped to BFO categories
Coherence and compatibility with other relevant ontologies	Harmonization with terminologies	UMLS validation; NCI terminologies; mapped to other OBO ontologies
Human understandability	Plain language and definitions	KR and simple terms and definitions

Table 18. Informal Competency Questions Results.
Describes how the TBI rehabilitation ontology addresses the informal competency questions used to guide development. These questions are analogous to the project aims.

Informal Competency Question	TBI Rehabilitation Ontology
What are the essential-for-CER components associated with post-acute, multi-disciplinary TBI treatment programs?	Treatment, theory, encounter, discipline, participant, setting, treatment plan (ontology classes)
Can these components be parsed and codified in an ontology?	Instantiated reasoner results
Can a combination of codified components from multi-discipline programs across settings be aligned into a shareable ontology environment (Protégé) to answer a comparative effectiveness research question?	Mappings of terms to PICOTS; Protégé model of terms

5.5.3 Protégé Reasoner Results

Pellet identified no inference class violations for equivalency or unsatisfiability. Table 19 portrays the disjoint coding applied in the ontology design and the results from Pellet.

Table 19. Pellet Reasoner Disjoint Class Results.
TBI rehabilitation ontology parent classes and results of disjoint reasoning testing.

Parent Class	Coded as disjoint (Y or N)	Pellet Result
Discipline	Y	No violations
Setting	N	No violations
Activity	Y	No violations
Role	Y	No violations
Treatment_plan	N	No violations
Treatment_theory	N	No violations
Assessment	Y	No violations
Outcome	Y	No violations

Chapter 6 Discussion

6.1 Introduction

The purpose of this study was to develop a domain conceptualization and ontology for post-acute, traumatic brain injury rehabilitation. The results provide an understanding of the domain and an information model that standardizes a subset of TBI rehabilitation research. The black box of rehabilitation requires informatics tools so it can be unpacked and compared. Standardization normalizes variability of practice, facilitates the Chute interoperability model, and ultimately improves delivery of evidence-based care. The following sections summarize the results and discuss the applicability of this work.

6.1.1 Contributions

The contribution of this project is twofold: 1) process, establishing a validated, repeatable method for biomedical domain ontology design, and 2) content, providing an intermediate TBI rehabilitation information model and ontology for further development. Application of methods and results are viewed as applicable to other domains of rehabilitation and to further development within TBI rehabilitation. Use of the ontology will contribute to improved clinical decision-making in TBI rehabilitation by facilitating domain knowledge interoperability.

6.2. Process and Content

Methods of TBI ontology construction were consistent with those of Uschold and Gruninger's (62) ontology design model. The motivating scenario from their model is TBI research complexity. Their "Informal Competency Questions" were the framing questions used to analyze TBI and rehabilitation domain sources. A "Formal

Terminology" was developed from domain sources, the NCI Metathesaurus, and the UMLS. Adherence to OBO principles and the contribution of Spear's (51) principles informed the deployment of "Formal Competency Questions." The "Formal Axioms" were modeled using Protégé and based on first-order logic. The "Completeness Theorems" are the demonstration of the ontologies ability to answer one of the "Informal Competency Questions" (framing questions) as demonstrated by the results of the Protégé Pellet reasoner. Table 20 summarizes the Uschold and Gruninger steps used in the TBI rehabilitation ontology development.

Table 20. TBI Rehabilitation Ontology Development Process and Results Summary.

Uschold and Gruninger Steps(62)	**TBI Rehabilitation Study Process Elements**	**Application of Study Contributions**	**Outcomes**
Motivating Scenario	NIH Roadmap, black box, Chute Model	Clinical setting, interoperability, reduced complexity for research	Domain conceptualization
Informal Competency Questions	Framing questions	Interventions identified and compared; discovery of domain sources; application of domain conceptualization using CER and Donabedian framework.	Interventions described
Formal Terminology	Domain sources, NCI Metathesaurus, UMLS	Ontology class identification and definition.	Class set with terms and definitions
Formal Competency Questions	Protégé modeling	Hierarchy assembled, relations identified, leveraging of other ontologies.	Validated class hierarchy; Spear (241)informal competency adherence
Formal Axioms	Protégé first order logic	Alignment to formal upper ontologies	Alignment with other formalized ontologies
Completeness Theorems	Competency questions; Protégé reasoner	Use of ontology in clinical research	PICOTS alignment; use-cases areas

Use of qualitative methods and diverse domain sources provided grounded evidence to address the problem statement and meet the project aims and objectives. The domain conceptualization of TBI rehabilitation provides a standardized model which can be applied to other complex rehabilitation domains. The modeling of the TBI rehabilitation components within a rehabilitation encounter gives structure to assist unpacking the treatment black box. Linking “treatment” and “theory” classes to assessment and outcome classes provides a logical pathway for identifying causative agents to provide an enhanced understanding of treatment theory, care delivery, and healthcare information across settings. Use of the UMLS MetaMap and the NCI Metathesaurus aligns the ontology with existing clinical terminologies and information retrieval systems, creating a link between the ontology and research literature. Finally, by providing entity mappings to a comparative-effectiveness model (PICOTS), the ontology demonstrates potential for formal reviews of treatment effectiveness.

6.3 Findings - Source Types

The framing questions used in the study were standardized to evaluate source types from the perspective of clinical research. A clinical comparative effectiveness review in practice would not include such disparate sources but would in fact deliberately seek analogous datasets. The belief here is that the use of a breadth of sources yields generalized domain meaning. Asking standard questions and collecting responses into a single conceptualization created a model that represents the overlapping unified content of the source types. The following sections present discussions of the findings from each source type area and their applicability to the results.

6.3.1 General Rehabilitation Literature

Articles from general rehabilitation were seminal, foundational, and authoritative. The TBI sources included reviews of 363 clinical research articles. The two bodies of literature illustrated the challenges of complex intervention delivery and research. Challenges published in the TBI literature were typically more specific than those identified in the general rehabilitation literature. There was a discernible lack of informatics recommendations as to how to deal with research complexity from both bodies of literature. This likely reflects the clinical nature of the articles but also demonstrates a need for discussions of the role of information technology in these clinical domains.

Both literature sets included discourse around the theme of complexity and its effect on research. Many authors recognized the difficulty of performing rehabilitation clinical research and the consequent effect on external validity of results. Difficulty in study design was addressed frequently and difficulty in unpacking the “black box” of treatments was at minimum implied in all articles. The challenge of treating comparable patient groups, the lack of standardized treatment delivery, and vague descriptions in clinical research publications was noted by several investigators. Patient stratification will be improved by collecting instances of the patient class in the TBI rehabilitation ontology across treatment settings and therefore allow creation of patient cohorts. Treatment communication will become increasingly standardized through the use of various combinations of TBI rehabilitation ontology classes such as discipline, treatment theory, and activity.

Subjective concepts such as therapeutic alliance and patient engagement were mentioned frequently as important to assessing the effect of rehabilitation. However, measurement of these concepts remains a challenge due to lack of definition and scales. Their ontological classes in the TBI rehabilitation ontology will collect instances which can then be further analyzed for characterization through property refinement. Improved understanding of these concepts will lead to identification of proper metrics and scales for measurement. By providing a hub for data collection and definition, this shows how the TBI rehabilitation ontology will serve as a domain communication tool.

The multiple-levels of treatment programs were also a common theme. This was best exemplified by the “Russian Doll” analogy made by Whyte and Hart (7) who frame rehabilitation as a nested doll of treatments, measurements, and outcomes. The importance of this informed many choices in the IR modeling and ontology class selection. The ontology fits into several levels of the ICF model, therefore representing short- and long-term effects, and distal and multiple levels of effect. Entity selection for the IR entailed eliminating post-MetaMap processing terms/phrases if they were contextually applicable only at the program level. Reasoning for this decision was that this project was aimed at unpacking the elements of rehabilitation treatments occurring in a session. However, an orthogonal program-level classification system can be designed to subsume the classes in this current encounter-based model for a more coarse representation. This will allow for program-level classifications for measurement and comparison. Through the ICF linkage, the encounter, and the program models, the TBI rehabilitation ontology is positioned to operate at multiple levels of characterization.

The TBI rehabilitation reviews discussed clinical complexity which motivated the undertaking of this project. Study design, generalizability, and identification of the “active ingredient” of rehabilitation were common themes, similar to the general rehabilitation literature. The diversity of study types, interventions, and levels of measurement across these studies demonstrates the heterogeneity in data and consequent need for standardization efforts.

Included among the reviewed studies were those ranging from very specific interventions for visuo-spatial deficits(194) to comparisons of “specialist” care versus “standard” care programs (185). The latter comparison reflects the problem of treatment description discussed in all the reviews and in the rehabilitation literature. By naming clinical research treatment arms using terms such as “standard care” and providing very little in the way of detailed description, repeating or comparing is impossible. Manualization of treatments is therefore very limited in TBI rehabilitation and contributes to localized variability in rehabilitation programs. Using the ontology to assemble a knowledge base comprised of TBI rehabilitation instances from many treatment centers, treatment manuals can be assembled that reflect broad acceptance and use by clinicians in the field.

As in the general rehabilitation literature, study design was seen as the biggest challenge for improving the TBI rehabilitation evidence base. An emerging approach espoused by some authors is to modify the research process itself either by allowing increased acceptance of observational design or through “practice-based evidence” efforts (254,255). Collectively, authors propose a sort of triangulation of evidence types that can be assembled to drive hypothesis testing and clinical treatment (142). The TBI rehabilitation ontology can be used to tag and consequently parse activities in observational studies that essentially make them comparable at the ontology classification and property levels. This can be accomplished through post-hoc annotation in knowledge bases or by using the ontology to inform template design in practice-based evidence data collection. Therefore, it is suggested that use of the ontology mitigates the need to modify study design and instead proposes that clinicians engage with the ontology to complement their current efforts and to allow their data to conform to comparable datasets.

Development of treatment theory summarizes many of the problems for TBI rehabilitation researchers. Validated and accepted domain theories ideally guide treatment delivery, creation of knowledge bases and clinical decision support systems, and drive research. Without standardized means of capturing and communicating the particular characteristics of rehabilitation, identifying and validating theory is challenging. The ability of the TBI rehabilitation ontology to standardize communication addresses part of this problem, but it also presents a new opportunity to identify emerging hypotheses for treatments. In reality, observational data and anecdotal evidence frequently contribute to treatment plans for TBI rehabilitation. By inferencing a knowledge base using the ontology, a researcher will be able to explore data and identify relationships that are not readily apparent to the naked eye. For example, a SPARQL query could be designed to generate all instances of compensatory speech-language pathology interventions delivered by clinicians with an audiology license, occurring in an inpatient setting for a mild-TBI patient that resulted in a clinically-significant improvement on the Participation Index of the Mayo-Portland Adaptability Inventory over a 12-month incremental period. Based on these results, the researcher could hypothesize a connection between these variables and design a study to test the theory. Not only is a new treatment theory identified, but a shareable evidence base is also begun.

6.2.1.3 Common Data Elements (CDEs)

Analyzing the CDEs differed from analysis of other sources because the CDEs presented an objective data model. Using the CDEs to inform the development of the ontology was a challenge due to depth and context problems. A relatively small set of elements currently exists in the rehabilitation domain and therefore details of a patient encounter are not present. The overall structure of the CDEs was informative and consistent with the PICOTS categories. The CDEs could serve as a framework for linking the demographic, surgical, and pharmaceutical aspects of the condition to create a holistic portrait post-acute TBI rehabilitation.

The “Therapies” sub-domain of the “Treatment/Intervention” CDEs represents physical medicine rehabilitation and showed low match rates to existing clinical standards. The “Surgical” and “Drugs” elements showed higher match rates due to standardization within these clinical domains. However, in the case of TBI CDEs, alignment with the Clinical Data Interchange Standards Consortium (CDISC) has been undertaken and eventually all CDEs will be closely aligned with existing standards (NINDS/INCF, personal communications, 2013).

The overall structure of the TBI CDE set is consistent with ontology design principles (*is_a* hierarchy, fewer than seven levels) and were used to inform the TBI IR and ontology. The “Assessments and Examinations” and “Outcomes and End Points” CDE domains were directly leveraged to develop the IR under the Donabedian framework category “Outcome.” The Treatment/Intervention CDEs lack content and relationships to fully inform a semantic model for TBI rehabilitation and have limited ability to portray the realities of a rehabilitation encounter. For example, rehabilitation is often driven by payment and reimbursement yet payment coding systems (CPT codes and DRGs) are virtually absent from the CDEs.

The CDEs' strength as a domain source is implied by the clinical domain experts and international standards group collaborating on their development (216). The requirement that all NINDS-funded research use the CDEs in reporting ensures refinement and domain consensus. Further, the 17 TBI rehabilitation centers that comprise "TBI Model Systems" use the CDEs in their collaborative research and the Federal Interagency Traumatic Brain Injury Registry (FITBIR) is based on the CDE platform (220). Use of FITBIR gives researchers "the ability to observe caseload and population characteristics over time, which might facilitate the evaluation of disease incidence, disease etiology, planning, operation and evaluation of services, evaluation of treatment patterns, and diagnostic classification" (256), p. 87.

Inferencing aggregated data sets also yields new knowledge and generates new hypotheses about treatment theory. Clinicians or researchers may interact with registries to contribute data, retrieve data, or to generate new knowledge. One of the FITBIR recommendations is to "[d]evelop "matchmaking" strategies to promote collaboration" (257). "The future impact of registries…will depend on… global cooperation to achieve consistent data (via standards)" (258), p.233.

For the TBI rehabilitation ontology, alignment with the CDEs is an important step to assure that researchers using the CDEs can also use the ontology and to assure interoperability with registries such as FITBIR. Further, 806 candidate Instances from the "Outcome" and "Assessment" nodes in the CDEs are candidates for inclusion in the next steps of development for the TBI rehabilitation ontology.

6.2.1.4 Stroke & SCIRehab

Referencing work from a related condition that is supported by a developed information structure is informative for content, structure, and process of biomedical domain ontology development. The challenges of defining the rehabilitation setting, the nature of what is to be represented and how it can be structured, optimizing the levels of granularity to create data structures useful for research and quantification all contributed to the IR and ontology. Based on experiences here, exploration of work in similar domains is a recommended step for any biomedical ontology development project.

Granularity of treatment descriptions was the biggest difference between these and other sources and the strength of their contribution to the ontology. The "Program-Session-Activity" parent classes informed the "encounter"-based structure of the IR model and helped to address issues related to rehabilitation measurement described by the Whyte and Hart (7). The "Activity" level components were too detailed for the TBI rehabilitation conceptualization and ontology, and "Program" levels were conversely too coarse (247). Though not directly leveraged, they provided informative framing for development of the encounter-based model of the IR.

The practice-based evidence (PBE) methods reported in the SCIRehab and Stroke taxonomy projects provided significant value as validated models for future use and development of the TBI rehabilitation ontology. These methods identified very specific elements of a rehabilitation session (i.e., assistive device). As referenced previously, PBE methods to gather detail can identify the components of rehabilitation and in turn, enhance the evidence base. The TBI ontology provides a referential data structure for PBE template design. The sheer size of the studies (SCIRehab enrolled 1,500 patients) provided substantial grounded evidence and therefore modeled an approach that could greatly contribute to the generalizability problem for TBI research.

6.2.1.5 Clinical Treatment Notes

The VA clinical treatment demonstrated the heterogeneity and complexity of treatment delivery and their review was necessary to understand the TBI rehabilitation information ecology. Literature described clinical and process complexity of treatment but very little consideration of the informatics ramifications was found. Therefore, clinical treatment notes were viewed as a means to bind together source types and to gain understanding of the representation and flow of information within treatment settings. Choosing TBI treatment notes from the VA was especially important because of the service alignment and treatment environment.

The VA rehabilitation treatment note process, the multiple roles, disciplines, and systems, and the variance in note structure and content lead to the difficulty in interoperability. Treatment notes at the VA are used for interdisciplinary communication with colleagues and are recorded in an unstructured, free-text manner. Data reporting requires a manual extraction from the notes and is tedious and inconsistent. Information is entered into a record in an unstructured manner but extracted from the record by a different user to meet a structured data need. Treatments were defined with a great deal of variability in terms of detail and were coded to billing and reporting systems (ICD and CPT). Notes thus often present anecdotal evidence of treatment effectiveness without providing the standardized granularity of description to determine the particular active ingredient in a causal pathway (156).

Manual extraction of the notes highlighted many of the issues described in the literature as extraction was time consuming and challenging. Interacting with them was challenging for an independent researcher unfamiliar with the note environment but the need for standardization was very apparent. In the context of clinical research, use of the notes would be difficult as automated extraction and computation is nearly impossible. Inefficient manual extractions introduce potential for human error and subjectivity. The ability to parse information from the notes could be enhanced by using the TBI rehabilitation ontology. Clinical treatment note templates could be informed by the ontology and therefore increasing the level of standardization within the VISTA CPRS. This would permit annotations that could be easily extractable for clinical research (259). The treatment notes were most useful to help build an understanding of the information ecology of TBI rehabilitation and provided further evidence for the need of domain standardization.

6.2.2 Domain Conceptualization/Intermediate Representation

The IR domain conceptualization and framework was translated into a formalized ontology environment by applying OBO principles and ontology development best practices. The IR was directly modeled and edited using Protégé. This involved examining the granularity, class hierarchy, potential ambiguities, and integrating leveraged ontology entities. The IR therefore served as the underlying informational resource for the ontology (81).

Conceptualizing the TBI rehabilitation domain was shaped by thematic research problems. For example, a theme identified in systematic reviews of TBI rehabilitation was generalizability of results, which was primarily attributed to small sample sizes.

Systematic reviews included this point, as well. Because statistical calculations of power or Bayesian models were often missing, extrapolating results for a particular patient profile or across populations was weak.

A second theme included the lack of agreement on outcomes measures. Historically, short-to-medium term outcomes have been common in TBI rehabilitation research but during the past several decades, longer-term, global outcomes have been increasingly proposed (175). However, the validity of using which measures for which interventions contributes to the difficulty in determining treatment effectiveness. Use of the ICF model helps address this as is the work of consortia such as the Model Systems' Center for Outcome Measurement in Brain Injury (COMBI) which is developing more rigorous measurement (260).

Finally, the ambiguity of program description theme was apparent when categorizing the services delivered in a program. Usage descriptions, as identified in literature, refer to a set of services as "Holistic, Intensive, Meta-Cognition" and compare it to "Standard Care" without further explanation. The analogy of a black-box of rehabilitation becomes quite appropriate when studies use similarly vague level of descriptors.

These themes not only summarize the experience of conceptualization, but also indicate the problem that motivated this project. It is challenging for an investigator to achieve a satisfactory level of standardization in a field where these types of vagaries exist. In informal conversations, clinicians make stronger statements about what works or does not work in TBI rehabilitation but they admit that linking interventions to outcomes requires far more rigor before they can become part of standard care.

"When a designer [of an ontology] can come to understand the domain knowledge needed to solve an application task in terms of a predefined problem-solving method, it becomes clear how each element of the domain knowledge might ultimately contribute to the problem-solving behavior of the system" (261), p.231. In this study, the problem was the "unpacking" of rehabilitation encounters and the solution is the classification of the components and development of their relationships and instances. Conceptualizing the domain contributed to a method for understanding its own complexity.

6.2.3 Foundational Ontology

An initial set of ontological classes and relationships informed by the domain conceptualization provides a foundational ontology for TBI rehabilitation. The classes and relations are a relatively high-level, coarse set which will be refined through subsequent studies. The ontology's use of NCI Metathesaurus definitions, mappings to BFO, use of Relations Ontology properties, leveraging of other biomedical ontologies, and publication to a shareable environment (BioPortal) will allow it to evolve as a hub in a larger set of harmonized ontologies. At this early stage, the ontology has application value as "[s]imple ontologies (e.g., limited to subsumption hierarchies) are useful for data aggregation and clustering" (73), p.6.

The entities from BIRNLex, OGMS, and NIFSTD link the ontology to larger, established neuro-anatomical and biomedical ontologies. All leveraged ontologies are part of the interoperable BioPortal repository, are linked through the BFO, and most are candidate OBO Foundry ontologies. Aligning the TBI ontology to the Basic Formal Ontology ensures harmonization with other formalized BFO-compliant ontologies.

The development of the IR and ontology required exploration of many data sources and informational models. Adhering to the informal and formal competency questions suggests a degree of foundational validity. Most biomedical ontologies are typically developed by large groups of experts over long periods of time. Because this ontology was developed by one investigator over a relatively short time period, it likely will undergo refinement as more domain engagement occurs. The ontology does not represent a completed artifact but rather a foundation upon which to build a more robust and complete domain ontology.

Some challenges encountered in this project reflect the relatively nascent state of validated biomedical domain ontologies. Most existing biomedical ontologies model "things" such as genetic material, anatomy, or other informational artifacts. While these things are clearly important to biomedical research, they reflect characteristics of specific biomedical domains. Things that objectively exist in nature and can be encountered through the human senses lend themselves well to previous human-developed organizational structures such as the classification of living things. None of these established ontologies were easy to develop because of scope, rigor, and philosophical debate about whether objectivity can even truly exist. Nature, through evolution, seems to provide a certain level of organization that has in fact only been re-purposed by humans in attempts to understand the elements of nature itself. Classification schemes such as ontologies are human tools that mimic structures of the natural world. This emphasizes the importance of letting the domain characteristics serve as informational sources for artifacts such as the TBI rehabilitation ontology.

Smith and others espouse "universality" over concepts, as concepts are subject to change over time based on human understanding(64,74). Universality allows for knowledge to be added to an informational structure as understanding evolves, but maintains a foundational connection to "that which exists." Using nature as example, biologists may discover a new insect, but if it is determined to bear the qualities of the scientific Class "Pauropod," then it *de facto* belongs to the Subphylum "Myriapoda," the Phylum "Arthropoda," and the Kingdom "Animalia." Membership criteria to these classes did not change, but rather the minimum characteristics required of each class allowed the insect membership, due to its observable, objective qualities. Applying a similar approach to human-generated domains such as TBI rehabilitation introduces significantly less developed definitions, membership criteria, and rigor of qualities for class membership and relations. Clinical terminologies such as SNOMED have contributed a great deal to information organization but their concept base relies on evolving knowledge of a term or set of terms rather than universal criteria of observation. Considering it has taken nature billions of years to manifest its structural system, it is no wonder that it is challenging to accomplish rigorous classification structures in clinical domains that are still developing foundational knowledge.

The models consulted for this project represented efforts in biomedical areas close to the natural world. They provided systematic approaches and presented rich experiential knowledge describing the motivations, challenges, and uses for biomedical ontologies. However, it was difficult to find integrated models in the literature that describe the classifications of the activities of healthcare such as rehabilitation, particularly in the case of temporal concepts. This project referenced a use-case scenario of comparative-effectiveness research to illustrate a clinical problem and to propose a solution. In this regard, the "Ontology of Clinical Research" (OCRe) was examined as a potential leveraged ontology. However, the OCRe is essentially an information ontology that classifies the "things" needed for clinical researchers in general. Alternatively, the Gene Ontology (GO) classifies biological and genetic chemical processes occurring at a molecular level, a higher level of granularity than systems used to classify human physical medicine rehabilitation activity. The OCRe and the GO are successful for facilitating biomedical research, but they also represent some of the difficulties in this project, including the challenge of finding validated, applicable information classification systems of human healthcare activity modeling. Another ontology of note, the Omaha System, shows promise in representing these types of concepts and deserves further consideration as a model for ontology development.

Both the GO and OCRe, along with the officially leveraged ontologies used in this project, present exciting possibilities for linkage with the TBI rehabilitation ontology. Interoperability of these ontologies could allow inferencing between the activities of a physical medicine rehabilitation program and the GO, thus potentially illuminating the "mechanism of action" for rehabilitation. Also, linking with standardized clinical research methods and large patient-treatment databases could help address the problem of small sample size in TBI research literature.

In consulting the literature, clinicians, and informaticians, there is an inconsistent understanding of ontologies and their applications. As is true with many areas of informatics, tools and processes developed and validated through research are only as valuable as the willingness of users to employ them. So it is with ontologies. A clinician's primary concern is delivering care and administrative mechanics are sometimes viewed pessimistically as less-than-desirable realities of modern healthcare. Further, the field of Informatics is becoming specialized to the degree that experts in other areas may not have an understanding of what ontologies are and how they can complement their domain. The issue may be characterized as one of understanding and one of willingness to adapt. A future work use-case demonstrating linkages between biomedical ontologies and clinical utility is therefore needed to demonstrate proof-of-concept and create clear models for use of ontologies in biomedicine.

6.2.4 Ontology Evaluation

Multiple levels of evaluation occurred during the assembly of the domain conceptualization. Conceptual veracity was achieved through the triangulation of sources, the use of clinician feedback for face validity, and competency questions that guided entity and relation choices. Formal evaluation of the ontology followed a similar multi-level approach as outlined by Brank et al. (106). Matching their evaluative steps included the use of formal and informal competency questions of ontology design, MetaMap scoring of class terminology, and the use of the Protégé Pellet reasoner. Matching the competency question areas ensured harmonization of the ontology with other biomedical ontologies. MetaMap assessment ensured alignment with biomedical information resources and reasoner results demonstrated the functionality of the ontology for use cases. Table 21 shows how these steps were accomplished.

Table 21. Ontology Evaluation Levels and Methods for TBI Rehabilitation Ontology. (Adapted from Brank et al.) "x" denotes a level of evaluation is achieved through the respective method. "n/s" denote that the method does not apply for that level. Grey columns denote the specific criteria used to meet these levels in the TBI rehabilitation ontology.

Brank et al. Evaluation Levels			TBI Rehabilitation Ontology Evaluation	
Level	**Application based**	**Assessment by humans**	**Method**	**Criteria**
Lexical, vocabulary, concept, data	x	x	UMLS	MetaMap scores
Hierarchy, taxonomy	x	x	Stroke; SCIRehab; reasoner	Match depth of *is_a* hierarchy
Other semantic relations	x	x	Informal competency questions	Adherence to OBO design criteria (formal competency questions)
Context, application	x	x	Formal competency questions; reasoner	Informal competency questions; reasoner output; use-case categories
Syntactic	n/a	x	Protégé – OWL	Successful output format and exchange
Structure, architecture, design	n/a	x	OBO Principles	Adherence to OBO design criteria

6.3 Further Implications

Development of the TBI rehabilitation ontology will address problems within the clinical domain by facilitating interoperability of data within and across systems. The use of an ontology connects the domain to a wider information structure within medicine and across the network of the World Wide Web. Predicting all of these interactions is impossible but establishing a link provides a foundation for growth and exploration in these areas.

6.3.1 Interoperability

The motivation for this project was the need for standardization and interoperability in TBI rehabilitation research. Complex conditions such as TBI with multiple levels of treatment and assessment have organically birthed idiosyncratic systems of data collection (35). Rehabilitation treatment information has shown to be highly localized in terms of tools for collection and codification. This results in limited interoperability between systems, across settings, and in human communication and languages for communicating the best evidence-based medicine to TBI rehabilitation patients need improvement.

The translational healthcare model of accelerating the bench-to-bedside process was also a significant underlying part of this work. Researchers clearly understand the need to leverage the exponential growth in computing power for biomedical research. In some ways, it appears as if the computing power has grown more rapidly than our biomedical information classification structures. Considering Chute's interoperability framework, we can imagine the millions of healthcare encounters that occur every day of every year around the world. Biomedical data is created in each one of these encounters, but we are limited by the processes and the vehicles by which we transfer these data into interoperable computable environments. There is a rich level of interactions that occur in these settings that we currently only capture in extremely limited types and formats.

Chute's framework presents an aspirational model of healthcare data and knowledge interoperability where treatment contributes to research, which in turn, contributes back to putatively improved treatment through iterative cycles. The cyclic identifies healthcare data creation nodes and models translation processes between them.

The creation nodes are critical informatics application points where solutions to avoid "silo-effects" of data are implemented. Standards and semantics are lubricant applied to facilitate the flow between nodes, culminating in elevated states of knowledge. The TBI rehabilitation ontology is a data standard and semantic model that can improve the function of this cycle

The TBI rehabilitation ontology is anchored in a "patient encounter," recognizing informative healthcare data is being generated by the very nature of the encounter. Ontologies can be used for indexing and annotating and are often used for information retrieval providing another link to the Chute model. In fact, indexing clinical documents is often called coding, and ontologies are considered as tools for use in coding (262). Adding the information exchange capabilities of ontologies and the ability to codify, store, retrieve, and share data becomes apparent (71).

The informatics challenge consequently is to align information technology tools and processes, in this case the standards and semantics, to best facilitate capturing, processing, and sharing these data. The TBI ontology is designed to meet this challenge as a model that enhances data capture in clinical encounters and classifies it in a standardized, computable manner. Figure 15 shows how the TBI rehabilitation ontology fits into the Chute Clinical Interoperability Framework.

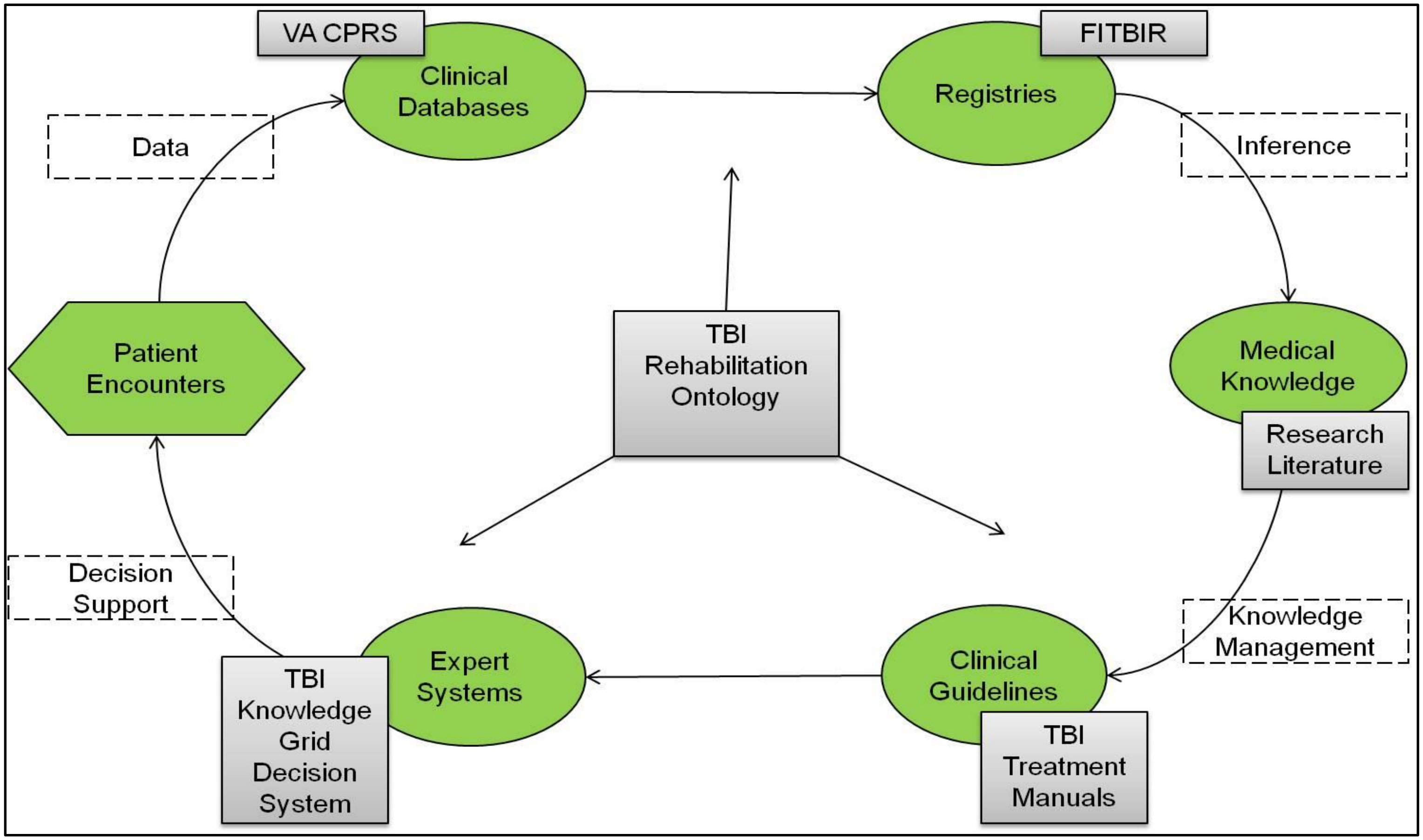

Figure 15. Modified Chute Interoperability Framework.
Modified to show the specific data creation nodes for TBI rehabilitation research. The VA CPRS is the Computerized Patient Record System of the VA Hospital System. FITBIR is the Federal Interagency Traumatic Brain Injury Registry. TBI Knowledge Grid Decision System is a query-able, point-of-care software architecture. The TBI rehabilitation ontology facilitates the capture, storage, retrieval, and sharing within and between nodes (6).

6.3.2 Semantic Web

The TBI rehabilitation ontology adheres to the W3C standards to ensure interoperability, use of multiple syntaxes, and optimize expressiveness. Its development is consistent with the "Open World Assumption" which posits that "anyone can say anything about anything" and this is the foundational approach for the future of information technology and the Web. Broadening the thinking beyond the disciplines related to TBI rehabilitation, the ability to share information with any discipline has the potential to identify far-reaching relations of effectiveness. "Each ontology instance is a resource in the Semantic Web and different instances can be connected with one or more properties from ontologies" (243), p.23. For example, connections which allow biomedical ontologies to interact with ontologies in geographic information systems (GIS) permit exploration of relationships between variables of rehabilitation and those of physical location (263). The graph-structure created by exponential URI-coded triplets from any domain results in the creation of a true "web" of asserted and inferred knowledge.

Finally, new variables derived from data collection and analyses carry their own provenance (264). Data provenance is simply describing how data came to be through the concepts of lineage and pedigree. Using neuroimaging, an example of provenance can be described by looking at "[k]nowledge about the origin and history of an image is crucial for establishing data and results quality; detailed information about how it was processed, including the specific software routines and operating systems that were used, is necessary for proper interpretation, high fidelity replication and re-use" (265), p.178.

6.4 Limitations

Scoping was a challenge in every step of this project. The decision to omit drug, surgery, and imaging aspects of TBI clinical care was made during the early stages of research to reduce complexity, though Psychiatry was included as a discipline subclass. Each of these is vital to TBI treatment and research and will require assessment and eventual inclusion. Further, a certain level of granularity was achieved during this study but additional work remains to develop ontologies that fully represent the TBI rehabilitation processes. The ontology will also need instantiation to further develop relations which are currently primitive and somewhat limited. Also, broader domain engagement is needed to ensure the generalizability of the ontology.

A specific aspect of the ontology that needs consideration is discussion of the ambiguous concepts presented in the literature. For example, activities class types of patient encounters were very difficult to map to BFO class types. This will require a deep philosophical analysis by inter-disciplinary teams. For example, temporal concepts such as time intervals and time points are difficult to represent and capture. Also, though they are modeled in the ontology, more exploration to characterize "therapeutic alliance," "patient engagement," and "mechanism of action" is needed to satisfy the needs of clinical researchers.

From a clinical standpoint, the treatment notes were limited by a lack of longitudinal data and outcomes. Also, the strength of using the Veterans Administration Hospital System as experimental environment may in fact compromise the translation of data gleaned from this source as it is not representative of many treatment environments. The role of nurses in rehabilitation is under-emphasized due to a clinical role that reflects a convergence of disciplines. More exploration of the unique relationship of nursing practice in the domain is needed and will need to be added to this ontology.

Finally, issues of cost and usability have not been addressed in this study. Exploration of the resources needed to access and engage with the TBI rehabilitation ontology need consideration, as does exploration of specific Application Programming Interfaces (APIs) and use in other information systems.

6.5 Next Steps and Future Work

Recommended next steps include use case demonstrations, domain clinician engagement, and usability studies. Extensions of TBI ontologies are needed for imaging, drugs, and surgery that can fully model the TBI disease process. Continued development of intervention ontological model which complements the other NINDS areas is needed. The qualitative methods used here described as “foundational inquiry” provide the basis for subsequent quantitative studies (229).   Bridges have been built for interoperation with other ontologies and these connections need to continue to be explored. Establishing measurements of adoption will be needed to evaluate the utility and contribution to other ontologies (35). Specific areas of next steps include:

1. Ontology knowledge bases
2. Curation plan
    - Continued engagement with the domain to instantiate and refine the ontology (Collaborative Protége; BioPortal & OBO Foundry)
    - Ontology refinement/integration with clinical research/map to OCRe
3. Clinical content

- API development
- Quantified evaluation (applying to corpus and instantiating)
- CDE/NINDS/IHTSDO/OneMind4Research groups
- Employ "practice-based evidence" methods
- Usability research
- Templates and tool suites for clinicians and researchers
- Use cases; cost-benefit analyses
- Longitudinal data (FITBIR)

6.5.1 Use Cases

Use cases are recommended to facilitate further domain engagement. According to Musen, "[t]he merits of a particular ontology can be measured only in terms of how well that ontology supports development of the application programs for which it was designed, and of how easy it is for developers to reuse that ontology to build new applications" (50), p.233. Indeed, the success of an ontology requires at least one purpose or use-case defined to demonstrate its utility (35). In terms of the ongoing evaluation of the TBI rehabilitation ontology, use cases can serve to validate (clinical or research applications) and refine (instantiation, granularity, harmonization, and iterations) classes and properties.

Smith provides specific examples of biomedical ontology use-case domains (74):

1. Reference for naming things.
2. Representation of encyclopedic knowledge.
3. Specification for information models.

4. Specification of data exchange formats.

5. Representation of semantics of data for information integration.

6. Computer reasoning with data.

Steps for a use-case using the TBI rehabilitation ontology to facilitate a comparative effectiveness review (CER) (202):

1. Formulate a focused (clinical) question.

2. Develop a method of locating relevant evidence, including explicit criteria addressing content and methodological quality.

3. Develop methods for abstracting, summarizing, and synthesizing the evidence.

4. Locate the relevant studies and assess their methodological validity and quality.

5. Abstract and synthesize the relevant information. This may be done qualitatively, or quantitatively, in which case the systematic review is a meta-analysis.

6. Draw conclusions for practice, policy, or future research, which are based narrowly on the evidence, taking into account its quantity, quality, and consistency.

Using the TBI rehabilitation ontology in steps 2, 3, 4, and 5 of the CER use-case gives the investigator a data extraction tool to classify and analyze data. Collecting the data with the ontology allows the investigator to explore relationships between the studies that may not be apparent. Results in Step 6 can be presented partly in terms of the ontology to provide a future investigator with a leveragable dataset.

Chapter 7 Conclusion

Traumatic brain injury (TBI) post-acute rehabilitation is complex and presents difficulty for clinical research. Determining effectiveness of interventions is challenging due to patient heterogeneity, injury etiology, disease pathology, heterogeneous treatments, and variability in outcomes. From an informatics standpoint, data sharing is difficult as a consequence of the clinical complexity and the lack of standardization. The Chute framework for clinical interoperability proposes that standards be developed to allow information technology to learn from and subsequently inform healthcare delivery.

Interoperability in the Chute framework consists of degrees of interaction between humans and machines. Interoperability can be simply described as the fact that one person enters knowledge into a system and another retrieves it (52) and for this process to operate best, users need to understand both the inputs and the outputs while systems need to understand the same knowledge as expressed in a different language. Ontological standards can simultaneously serve both purposes.

A foundational ontology for TBI rehabilitation has been developed. A triangulation of sources informed a domain conceptualization which provided an intermediate model on which the ontology could be developed. Seventy-seven ontological classes representing TBI rehabilitation have been formalized and tested in Protégé. Domain engagement to enhance and expand the ontology is needed, as are use-case demonstrations. However, the ontology has been designed according to foundational biomedical principles to assure it can serve a useful and growing role in TBI rehabilitation research. The methods and model presented here also serve as informative guides for other biomedical ontology projects which may benefit from the lessons learned. The immediate candidates for consideration are the rehabilitative areas of other neurological diseases in the research purview of the National Institute of Neurological Disorders and Stroke (NINDS). It is designed to serve as a communication model and as the foundation for technical models. Table 22 restates the project Aims and results.

Table 22. TBI Rehabilitation Project Aims and Results.

Aim	Result
Develop a domain conceptualization of post-acute Traumatic Brain Injury (TBI) physical medicine rehabilitation	Intermediate Representation (IR)
Codify foundational classes and properties for TBI physical medicine rehabilitation ontology	Class set and hierarchy in Protégé
Align domain conceptualization and ontology entities with comparative effectiveness review (CER) process	Ontology entities map to CER categories. Model is integrated with Chute Interoperability model. Use-cases areas.

The results of this project fit within the seminal Donabedian healthcare quality framework, the Chute Clinical Data Interoperability Framework, and the International Classification of Function Disability Model, three foundational healthcare models. It also addresses a need discussed widely in literature, as called for by the National Institute on Disability and Rehabilitation Research (NIDRR) and NINDS, and through United States federal legislation.

Considering that "[a] well-formed ontology will be built in a modular way using a mixture of generic domain, generic task and application ontologies," the TBI rehabilitation ontology is on a firm foundation (87), p.401. The ontology will help unpacking the black box of rehabilitation, improve the clinical research process, and contribute to translational medicine. Final success will be measured by the degree to which this project helps to unify the domain of TBI research and aligns it with the NIH Roadmap as ultimately, “comparable patient data are the key to improved effectiveness and efficiency in healthcare” (8), p.300.

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Appendix Table of Contents

Appendix University of Minnesota Institutional Review Board

TO : lael@umn.edu, grov0013@umn.edu,

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

Study Number: 1305E32601

Principal Investigator: Michael Grove

Title(s):
Post-Acute TBI Rehabilitation Ontology
This e-mail confirmation is your official University of Minnesota HRPP notification of exemption from full committee review. You will not receive a hard copy or letter. This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature.

The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested.

If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged.

This exemption is valid for five years from the date of this correspondence and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date.

Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654.

You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study.

The IRB wishes you success with this research.

We have created a short survey that will only take a couple of minutes to complete. The questions are basic, but will give us guidance on what areas are showing improvement and what areas we need to focus on:
https://umsurvey.umn.edu/index.php?sid=94693&lang=um

Appendix Veterans Administration Health Care System Institutional Review Board

ENTERED MAY 1 9 2013

ADD NEW PERSONNEL
AMENDMENT FOR IRB REVIEW
Minneapolis VA Health Care System

Date	5/10/2013
IRB Study Number	Pending 4463 - B
Principal Investigator	Gregory J. Lamberty Ph.D.
Study Title	The Nature and Frequency of Clinical Interventions for Comprehensive Inpatient Rehabilitation at the Minneapolis VA Polytrauma Rehabilitation Center (PRC): A Model

Contact Person	Phone	Mail Code	Email
Susan G. Sauter, RN	612-629-7489	4K-TBI	Susan.Sauter@va.gov

Role on study	First Name	Last Name	Mail Code	Phone	Pager	Email	Training Date	Off-site?	Degrees	Department	Employment Status	Consenting subjects?	Exposed to hazards?*
Staff	Michael	Grove	4K-TBI	916-852-9589	None	grov0013@umn.edu	2-13-2013	No	MS	Health Informatics	Intern	No	No

☒ Conflict of Interest form attached. (required for all personnel)

*Indicate whether this person will be working with any hazards to research staff (drawing or shipping blood, etc.) that have been identified for this study.

Principal Investigator signature ____________ Date 5-13-2013

For IRB Use Only

This study was initially reviewed: ☒ Expedited ☐ Full

Expedited IRB Review & Approval (if applicable)

Having reviewed this request and accompanying materials I have determined that the request:

☒ Meets criteria for expedited review and is approved

☐ Meets criteria for expedited review, but full IRB review is recommended.

☐ Does not meet criteria for expedited review and requires full IRB review

Reviewer signature ____________ Date 5-21-13

Full Committee IRB Review & Approval (if applicable)

This amendment was reviewed by the Institutional Review Board A B on ________ and was:
☐ Approved with no modifications required.
☐ Modifications required to secure approval were received ________, and were reviewed and approved by: ☐ Primary reviewer ☐ IRB A B Full committee

IRB Chair or designee signature ____________ Date ________

☐ This approval includes consent version date ________ and/or HIPAA version date ________

If a co-investigator has equal responsibility with the principal investigator, they should be designated as a co-principal investigator.

Change in principal investigator. If the study was initially reviewed by expedited review, then the change in principal investigator may be reviewed by expedited review; if initially reviewed by the full IRB Committee, then the change will be reviewed by the full IRB Committee.

What is your reason or justification for changing the principal investigator?

Off-site personnel address(es)

Version date April 5, 2013

Appendix Table 1 Common Data Element (CDE) TBI Treatment/Intervention Sub-Domain Content Coverage Results

	ICD-9-CM	UCUM	CDISC SDTM	RxNORM	caBIG	No Reference
Drugs (n=12)	0	2	0	3	6	1
Surgeries & Other Procedures (n=21)	2	0	0	0	0	19
Therapies (n=11)	2	0	1	0	0	8

Appendix Table 2 Common Data Element (CDE) Treatment/Intervention Strength of Match by Data Standard

(0=No Match, 1=Partial Match, 2=Complete Match)

	Drugs (n=12)			Surgeries & Other Procedures (n=21)			Therapies (n=11)		
	Score (%)			Score (%)			Score (%)		
	0	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**
SNOMED-CT	100%	0%	0%	42.9%	23.8%	33.3%	45.5%	45.5%	9.1%
ICD-9-CM	100%	0%	0%	90.5%	0%	9.5%	81.8%	0%	18.2%
LOINC	0%	0%	0%	90.5%	9.5%	0%	45.5%	36.4%	18.2%
RxNORM	75%	0%	25%	0%	0%	0%	0%	0%	0%
CPT	100%	0%	0%	0%	0%	0%	0%	0%	0%
UCUM	83.3%	0%	16.7%	0%	0%	0%	0%	0%	0%
caBIG	50%	0%	50%	0%	0%	0%	0%	0%	0%
CDISC SDTM	100%	0%	0%	0%	0%	0%	90.9%	0%	9.1%

Appendix Table 3. TBI Rehabilitation Classes and Definitions.

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Discipline	A grouping of occupations and fields of study	NIF Standard Ontology	generically_ dependent_ continuant
Alternative	Any medical substance or procedure not generally accepted by orthodox western medicine or an unorthodox application of an otherwise accepted substance or procedure	n/a	n/a
Clinical_psychology	The branch of psychology that deals with the diagnosis and treatment of psychological and behavioral problems	n/a	n/a
Neuropsychology	The study of how the physiology of the brain and central nervous system are related to behavior	n/a	n/a
Nursing	Nursing encompasses autonomous and collaborative care of individuals of all ages, families, groups and communities, sick or well and in all settings. Nursing includes the promotion of health, prevention of illness, and the care of ill, disabled and dying people. Advocacy, promotion of a safe environment, research, participation in shaping health policy and in patient and health systems management, and education are also key nursing roles	n/a	n/a
Nutrition	The science of food, the nutrients and other substances contained therein, their action, interaction, and balance in relation to health and disease	n/a	n/a
Occupational	The promotion and maintenance of physical and mental health in the work environment	n/a	n/a
Physiatry	A medical specialty focused on restoring functional ability and quality of life to people with physical impairments or disabilities	n/a	n/a
Physical_therapy	The use of exercises and physical activities to help condition muscles and restore strength and movement. For example, physical therapy can be used to restore arm and shoulder movement and build back strength after breast cancer surgery	n/a	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Psychiatry	The medical science that deals with the origin, diagnosis, prevention, and treatment of mental disorders	n/a	n/a
Recreation_therapy	A type of therapy that uses activities to help meet the physical and emotional needs of patients with an illness or disability and help them develop skills for daily living. These activities include arts and crafts, music, spending time with animals, sports, and drama. Recreational therapy is being studied as a way to relieve distress in cancer patients who are being treated for pain	n/a	n/a
Social_work	A community resource that helps people in need. Services may include help getting to and from medical appointments, home delivery of medication and meals, in-home nursing care, help paying medical costs not covered by insurance, loaning medical equipment, and housekeeping help	n/a	n/a
Specialized_service	Developed or designed for a special activity or function	n/a	n/a
Speech_language_ pathology	A field of study concerned with the diagnosis and treatment of disorders of speech and voice	n/a	n/a
Vocational	Training of the mentally or physically disabled in work skills so they may be returned to regular employment utilizing these skills.	n/a	n/a
Setting	A position, site, or point in space where something can be found	NIF Standard Ontology	Site
Facility	Services and space and equipment provided for a particular purpose; a building or place that provides a particular service or is used for a particular industry	n/a	n/a
Clinic	A health care facility where patients are admitted to get treatment provided by a group of physicians practicing medicine together	n/a	n/a
Home	A person's permanent place of residence	n/a	n/a
Hospital	An institution that provides medical, surgical, or psychiatric care and treatment for the sick or the injured	n/a	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Residential	Facilities which provide supervision and assistance in activities of daily living with medical and nursing services when required, generally for those not needing hospital services but still in need of medical assistance	n/a	n/a
Skilled_nursing	The patient will be admitted into a medical center equipped with a trained nursing staff that is eligible to receive Medicare funding	n/a	n/a
Specialized_ rehabilitation_ center	Facilities which provide programs for rehabilitating the mentally or physically disabled individuals	n/a	n/a
Long_term_care	The patient will be admitted into a Medicare funded (or other type of) medical center for a considerable length of time	n/a	n/a
Level_of_care	Describes general program of care approach; author supplied definition	n/a	n/a
Transitional	Support given to patients when they move from one phase of disease or treatment to another, such as from hospital care to home care. It involves helping patients and families with medical, practical, and emotional needs as they adjust to different levels and goals of care	n/a	n/a
Community	NCIt Definition: A set of people with some shared element. The substance of shared element varies widely, from geography to a situation to interest to lives and values. The term is widely used to evoke sense of collectivity. CSP Definition: interacting population of individuals in a common location; a group of people with a common characteristic or interest living together within a larger society	n/a	n/a
Homecare	Care of a patient at home, by family members and/or health personnel	n/a	n/a
Inpatient	The patient will be admitted full time into a free standing rehabilitation center or a rehabilitation center within a general medical facility	n/a	n/a
Outpatient	A patient who comes to a healthcare facility for diagnosis or treatment but is not admitted for an overnight stay	n/a	n/a
School	An educational institution	n/a	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	**Definition (NCI Metathesaurus unless otherwise noted)**	**Leveraged Ontology**	**Basic Formal Ontology Class**
Telemedicine	The delivery of healthcare from a distance using electronic information and technology such as computers, cameras, videoconferencing, the Internet, satellite, and wireless communications	n/a	n/a
Workplace	Place or physical location of work or employment	n/a	n/a
Participant	Someone who takes part in an activity	Ontology for General Medical Science	realizable_entity
Case_manager	Case management includes nursing activities of coordination, advocacy, and referral. These activities involve facilitating service delivery on behalf of the client, communicating with health and human service providers, promoting assertive client communication, and guiding the client toward use of appropriate community resources	n/a	n/a
Clinician	An individual, such as a physician, nurse practitioner or other health care professional, who takes responsibility for a subject's care	n/a	n/a
Family	A domestic group, or a number of domestic groups linked through descent (demonstrated or stipulated) from a common ancestor, marriage, or adoption	n/a	n/a
Patient	Person under a physician's care for a particular disease or condition. NOTE: A subject in a clinical trial is not necessarily a patient, but a patient in a clinical trial is a subject. See also subject, trial subject, healthy volunteer. Often used interchangeably as a synonym for subject but healthy volunteers are not, strictly speaking, patients	n/a	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Treatment_plan	A document outlining the essential treatment issues which will be addressed. This may include the problem to be addressed, the proposed treatment, the treatment goal, the time frame to meet goals, and an estimate of the costs	Ontology for Biomedical Investigations	realizable_entity
Activity	An active process; excludes processes and mechanisms which fulfill biological functions	Ontology for General Medical Science	processual_entity
Rehabilitation_ encounter	A clinical encounter that encompasses planned and unplanned trial interventions, procedures and assessments that may be performed on a subject. A visit has a start and an end, each described with a rule. NOTE: For many domains each visit results in one record per visit	n/a	n/a
Treatment	An action or administration of therapeutic agents to produce an effect that is intended to alter or stop a pathologic process	n/a	n/a
Theory	A well-substantiated explanation of some aspect of the natural world	Translational Medicine Ontology	generically_ dependent_ continuant
Alternative_treatment _theory	A well-substantiated explanation of some aspect of alternative treatment	n/a	n/a
Behavioral_theory	A well-substantiated explanation of some aspect of behavioral treatment	n/a	n/a
Cognitive_theory	A well-substantiated explanation of some aspect of cognitive treatment	n/a	n/a
Functional_theory	A well-substantiated explanation of some aspect of functional treatment	n/a	n/a
Holistic_theory	A well-substantiated explanation of some aspect of holistic treatment	n/a	n/a
Occupational_theory	A well-substantiated explanation of some aspect of occupational therapy treatment	n/a	n/a
Pet_therapy_theory	A well-substantiated explanation of some aspect of pet therapy treatment	n/a	n/a
Physical_therapy_ Theory	A well-substantiated explanation of some aspect of physical therapy treatment	n/a	n/a
Specialized_service_ Theory	A well-substantiated explanation of some aspect of specialized service treatment	n/a	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Speech_language_ pathology_theory	A well-substantiated explanation of some aspect of speech-language pathology treatment	n/a	n/a
Assessment	In healthcare, a process used to learn about a patient's condition. This may include a complete medical history, medical tests, a physical exam, a test of learning skills, tests to find out if the patient is able to carry out the tasks of daily living, a mental health evaluation, and a review of social support and community resources available to the patient	Ontology for General Medical Science	processual_entity
Biomarker	A variation in cellular or biochemical components or processes, structures, or functions that is objectively measurable in a biological system and that characterizes normal biologic processes, pathogenic processes, an organism's state of health or disease, likelihood of developing a disease, prognosis, or response to a particular therapeutic intervention. Biomarkers include but not limited to such phenotypic parameters as specific enzyme or hormone concentration, specific gene phenotype, presence or absence of biological substances	Common Data Elements	n/a
Biospecimen_and_ biomarker	Any material sample taken from a biological entity for testing, diagnostic, propagation, treatment or research purposes, including a sample obtained from a living organism or taken from the biological object after halting of all its life functions. Biospecimen can contain one or more components including but not limited to cellular molecules, cells, tissues, organs, body fluids, embryos, and body excretory products	Common Data Elements	n/a
Imaging	Any technology or method that aids in the visualization of any biological process, cell, tissue or organ for use in screening, diagnosis, surgical procedures or therapy	Common Data Elements	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Lab	A medical procedure that involves testing a sample of blood, urine, or other substance from the body. Tests can help determine a diagnosis, plan treatment, check to see if treatment is working, or monitor the disease over time	Common Data Elements	n/a
Neurological	A series of questions and tests to check brain, spinal cord, and nerve function. The exam checks a person's mental status, coordination, ability to walk, and how well the muscles, sensory systems, and deep tendon reflexes work	Common Data Elements	n/a
Physical	A systemic evaluation of the body and its functions using visual inspection, palpation, percussion and auscultation. The purpose is to determine the presence or absence of physical signs of disease or abnormality for an individual's health assessment	Common Data Elements	n/a
Proprietary	Proprietary or locally owned method	Common Data Elements	n/a
Vital_signs	The name given to the test that analyzes a particular set of vital signs including temperature, respiratory rate, heart beat (pulse), and blood pressure	Common Data Elements	n/a
Outcome	A specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumor size, and improvement of disease	Translational Medicine Ontology	generically_ dependent_ continuant
Behavioral_function	Behavioral dysfunction commonly is reported after TBI and may contribute to difficulties in return to work/school, personal relationships, and social functioning	Common Data Elements	n/a
Cognitive_activity_ limitation	Cognitive activity measures describe the impact of neuropsychological impairments on cognitively loaded real-world tasks, such as instrumental ADLs, functional communication, and health and safety-related behaviors	Common Data Elements	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Global	Global outcome measures summarize the overall impact of TBI, incorporating functional status, independence, and role participation	Common Data Elements	n/a
Health_economic_ measure	Health economic measures assess the magnitude of benefit in relation to costs spent; e.g., they identify the most cost-effective therapeutic procedure in terms of cost per QALY	Common Data Elements	n/a
Neuropsychological_ impariment	Objective measures of neuropsychological functions, such as attention, memory, and executive function, are very sensitive to effects of TBI and often affect everyday activities and social role participation	Common Data Elements	n/a
Patient_reported_ outcome	No single measure to date can adequately capture the multiplicity of difficulties that people with TBI may face. This domain includes emerging large-scale measurement tools for patient-reported outcomes across several domains for generic medical populations, neurologic compromise, and TBI-related symptoms	Common Data Elements	n/a
Physical_function	People with TBI (particularly severe TBI) may manifest difficulties in physical or neurologic functioning, including cranial or peripheral nerve damage; impairment in motor functioning, strength, and/or coordination; or impairment in sensation. These impairments may contribute to difficulties performing day-to-day activities safely and independently	Common Data Elements	n/a
Psychological_status	Psychological issues associated with TBI that affect outcomes include adjustment problems, personality changes (e.g., impulsivity), or mood disturbances. In addition, substance use disorders are prevalent in persons with TBI and can have a substantial impact on long-term outcomes	Common Data Elements	n/a

Appendix Table 3 (continued).

Class (parent classes in bold)	Definition (NCI Metathesaurus unless otherwise noted)	Leveraged Ontology	Basic Formal Ontology Class
Quality_of_life	TBI may create significant limitations in multiple areas of functioning and well-being, often reducing perceived quality of life with regard to multiple generic and disease-specific dimensions	Common Data Elements	n/a
Recovery_of_ consciousness	Duration of coma, level of consciousness, and rate of recovery contribute significantly to functional outcome and have a key role in treatment and disposition planning	Common Data Elements	n/a
Social_role_ participation	Participation is defined by the WHO as "involvement in life situations" and commonly includes engagement in endeavors within one's community. TBI affects many areas of participation, including work/productive activity, recreation and leisure pursuits, and social/family role function	Common Data Elements	n/a
TBI_related_ symptom	TBI-related symptoms include somatic (e.g., headaches, visual disturbances), cognitive (e.g., attention and memory difficulties), and emotional (e.g., irritability) symptoms. They commonly are reported after TBI or concussion and may persist in some cases at all levels of TBI severity	Common Data Elements	n/a