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# NINDS COMMON DATA ELEMENT PROJECT – APPROACH AND METHODS

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## INTRODUCTION

In clinical research studies, much time and effort are devoted to deciding what data to collect and developing data management systems to capture the data. The data collection forms developed by the investigators often have inadequate definitions and idiosyncratic permissible values. When the studies are completed, it is often a challenge for the investigators to combine data from individual studies or to share their data since data have been stored in various formats which do not foster aggregation.

In an effort to assist investigators and accelerate clinical research in neuroscience the National Institute of Neurological Disorders and Stroke (NINDS), the National Institutes of Health (NIH), Department of Health and Human Services, embarked upon the Common Data Element (CDE) Project. The rationale of the CDE Project is to develop standard data items with accompanying tools for rapid implementation of data collection by clinical researchers in the neuroscience community, in particular those funded by NINDS, and to harmonize data collection across clinical studies. The goal of the NINDS in sponsoring this effort is to eliminate “reinventing the wheel” as often occurs with the funding of a new study.

The goals of the Project are to:

- **Disseminate standards** for the collection of data from participants enrolled in studies of neurological diseases.

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- ***Create easily accessible tools*** for investigators to collect study data. These tools should be especially helpful to new investigators and others working with limited budgets.
- ***Encourage focused and simplified data collection*** to reduce burden on investigators and practice-based clinicians to facilitate their participation in clinical research.
- ***Improve data quality*** while controlling cost by providing uniform data descriptions and tools across NINDS-funded clinical studies.

The anticipated benefits of the CDE Project include accelerating study start up and facilitating data sharing and aggregation. The standard definitions, measures, and templates should help researchers more rapidly assemble their data collection materials. When studies which have used the CDEs are complete, less effort should be required to transform the data into a common format for aggregation and to perform meta-analyses, as much of the data are defined the same way.

## BACKGROUND

Over the past several years, a number of efforts have been initiated by both government agencies and private associations to improve the quality of data collected in clinical research. Before initiating its CDE Project, the NINDS explored other data standardization efforts at NIH by accessing Web sites and speaking to Institute representatives from the National Institute on Drug Abuse, the National Cancer Institute (NCI), and the National Institute of Allergy and Infectious Diseases. Of note, the NINDS closely reviewed several pertinent components of the NCI cancer Biomedical Informatics Grid (caBIG®) project, including the Cancer Data Standards Registry and Repository (caDSR), the CDE Browser tool, and the Enterprise Vocabulary Services (EVS) that provides controlled terminology as the semantic base for the NCI CDEs.[1, 2, 3] The Institute also examined international efforts in neurological diseases that have had NINDS input (e.g., Brain Monitoring with Information Technology [BRAIN IT], National Electronics Clinical Trials and Research [NECTAR], International Mission for Prognosis and Analysis of Clinical Trials in TBI [TBI-IMPACT]).

Beyond NIH initiatives, the NINDS reviewed the Clinical Data Interchange Standards Consortium (CDISC) standards. Especially relevant to the Institute were the CDISC Study Data Tabulation Model (SDTM), the CDISC Clinical Data Acquisition Standards Harmonization (CDASH) standard, and the CDISC terminology standards that go along with these models.[4, 5] Also reviewed were efforts at core data set standards emerging for the Electronic Health Record, including those by the Accredited Standards Committee. The Accredited Standards Committee is developing standards for electronic data interchange primarily for insurance and other healthcare related businesses.[6]

Ultimately the decision to develop CDEs for the NINDS was made because the existing efforts were not yet extensive enough to meet the data collection needs of neurological studies. The NINDS began planning its CDE Project in March/2005; the Project intended to address the need for tools that NINDS investigators, as well as investigators conducting research funded through other mechanisms, could implement immediately in their neuroscience clinical research studies.

## METHODS

The NINDS CDE tools have been developed through an iterative process, beginning with a focus on a critical core of CDEs and later expanding to CDEs for specific neurological

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diseases. The NINDS Program Directors and personnel of the contractor, KAI Research Inc., continue to work together to realize the Project's goals. They are referred to jointly as the NINDS CDE Team (NCT).

## Development of the Critical Core CDEs

The CDE effort began with the identification of data elements and forms that transcend studies and disease areas. To develop the critical core CDEs, we began with the identification of:

1. Data elements, forms, and definitions used in completed and ongoing studies funded by NINDS;
2. Data commonly referenced in published primary study papers; and
3. Other standardization efforts within the NIH and greater health community.

The result was the development of a critical core set of data elements, structures and forms relevant across neurological studies that were vetted through a Steering Committee.

The NCT was asked by the Project Officer to focus on stroke, epilepsy, Parkinson's disease, and traumatic brain injury for the initial critical core CDE development. Investigators conducting studies in these disease areas were contacted and asked to send current copies of study case report forms (CRFs) or "forms" and manuals of procedures (MOPs). Materials were received from 20 studies, listed in Table 1 (Web only), which the NCT then used to begin the process of identifying common data items, forms, and data definitions. The CDEs identified from these initial studies were included in a draft set of core forms reviewed by NINDS staff. The NCT also reviewed the standard forms used to submit phenotypic information to the NINDS Human Genetics DNA and Cell Line Repository and the forms available on the NCI CDE Browser.[31, 2] Thus, the CDE Project emanated from clinical research that investigators have conducted and the data and forms used in these NIH-funded studies.

To document the data reported in publications, the NCT searched the literature to identify clinical trials of treatments for neurological diseases that enrolled more than 300 participants. A review of studies in Neurology and the New England Journal of Medicine yielded a sample of primary papers for 49 clinical trials. Additionally, four studies were identified through a Medline search of large, simple studies. The NCT reviewed the primary papers from these 53 studies and cataloged by domain the type of data reported in the articles. The informative results of this review are shown in Table 2 (Web only). The ways in which data were used in the articles further guided the initial identification of CDEs and provided the rationale for including the selected items. The literature review also pointed out that much of the data collected in NINDS trials had not been published in primary papers. Therefore, the NINDS CDE effort encourages investigators to collect only the data they need to test their hypotheses and protect research participants.

Based on forms in use in the neurological studies, the literature review, potential uses of the data, and consideration of federal policies related to clinical research (e.g., NIH Policy on Reporting Race and Ethnicity Data - http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm), the NCT proposed a critical core set of CDE modules. The list of CDE modules, along with a comment to the relevance to the NINDS CDE Project, is shown in Table 3. In addition to these modules, the critical core CDE materials also include template "administrative" forms, which are important for study management but typically are not entered in the study database. An example of an administrative form is the Screening Log, which documents all individuals screened for a study as well as the reasons for failing the screening process.

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The critical core CDE development steps produced the following:

- Generic data elements and items in a structure that facilitates data independence;
- Data dictionary with definitions and permissible values;
- Template study forms in Microsoft Word format;
- Logic and range checks;
- Data collection and form completion instructions for a MOP; and
- Web site (http://www.commondataelements.ninds.nih.gov/) that facilitates access to all the CDE materials.

To obtain reaction to the critical core CDEs from clinical investigators investigating treatments for neurological diseases and to ascertain whether the Project would meet an unmet need, the NINDS assembled a Steering Committee. The Steering Committee is composed of senior clinical investigators, statisticians and data managers who are experienced in the conduct of multi-site clinical studies. In April/2006 the NCT asked the Steering Committee to review the first version of the CDEs, forms, definitions, and the Web site. The NCT was able to implement the Steering Committee's specific suggestions for revisions to improve the CDE products. More globally, the Steering Committee advised the NINDS to continue to support the CDE Project as the members believed that the CDE products were needed and that the anticipated benefits of the effort were clear. The Steering Committee continues to provide ongoing review and guidance about the NINDS CDEs.

## Validation and Refinement of the Critical Core CDEs

To establish a "proof of concept," the NCT developed a data model or data sharing framework that uniquely incorporates and categorizes the recommended CDEs and data collection forms. The data model allowed the NCT to apply the CDEs to completed neurological studies to ensure the definitions were robust enough to be applied retrospectively and to facilitate meta-analysis. The NCT tested the data model with five historical NINDS-sponsored clinical trials listed in Table 1 (Web only). Applying the CDEs and data model iteratively to each legacy data set as the tools were revised permitted refinement of both data collection (i.e., the content of the critical core CDEs) and data sharing activities (i.e., the data model or data sharing framework) of the Project.

The comparison of the NINDS critical core CDEs to the data elements of two other data standardization efforts also helped to validate the critical core CDEs. The NCT compared the critical core CDEs to the CDISC SDTM and the CDISC CDASH standards as well as to the NCI caBIG CDE standards accessible through the CDE Browser.[4,5,2] These comparisons helped to identify gaps in the critical core CDEs and also informed the NCT where definitions and permissible values could be improved.

## Development of Disease-specific CDEs

After organizing and gaining acceptance on the critical core, the next series of steps have focused on developing CDEs and data collection products for specific neurological diseases. The NCT learned several valuable lessons from the development of the critical core CDEs and applied them to the disease-specific CDE development process, including:

- Ensure the CDEs are identified, developed, and vetted by experts in the scientific community.
- Establish a "hands off approach" by the NCT while the working groups develop CDEs, but provide support and guidance as needed.

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- Make the development process as transparent and inclusive as possible.

The process of developing disease-specific CDEs began with epilepsy and the same development model has been and is being used to create CDEs for many other neurological diseases. While the specific development steps may differ slightly across the diseases, the basic process implemented for the disease-specific CDEs parallels and improves upon the one used for the critical core. Importantly, the process is flexible enough so that each clinical research community is able to customize it to fit its needs. The ten key steps are outlined below:

1. ***Identify a working group of experts*** – to define the CDE content. The NCT identifies experts in clinical research (i.e., clinical investigators, study coordinators, statisticians, and data managers) who can participate in a disease-specific CDE working group; the NINDS identifies Chairperson(s) to lead the working group.
2. ***Divide working group into smaller subgroups*** – to focus on a specific domain or topic of data relevant to the disease area (e.g., imaging, neuropsychology/ cognition, biospecimens, etc.). A chair is selected for each subgroup.
3. ***Review study materials and literature*** – to inform the working group and NCT.
    a. The NCT identifies clinical studies (usually those funded by NINDS) in a disease area and contacts the investigators to request copies of the protocols, forms, and MOPs. The NCT reviews these materials to develop matrices to tabulate data elements collected across studies.
    b. The NCT also reviews the literature to determine what data have been published and produces similar matrices that present the results of the literature search quantitatively.

    These matrices provide the rationale for the inclusion of particular elements in the CDEs. The NCT provides the working group with summary counts of the elements that currently are collected across studies to help ensure the disease-specific CDEs are grounded in the data commonly collected and analyzed by clinical researchers.
4. ***Convene working group kick-off meeting*** – to familiarize the working group members with the overall CDE Project and the CDE development process, inform them of the proposed timeline, and review next steps. The NCT provides a presentation about the NINDS CDE Project; the matrices of data elements collected and reported across studies; a list of study forms and publications reviewed; and sample CRF templates from the critical core CDEs.
5. ***Commence subgroup teleconferences*** –to identify and develop CDE recommendations. The NCT provides the logistical and administrative support for teleconferences of the working groups, which are held every four to six weeks, as well as guidance to each subgroup to limit duplication of efforts and streamline the recommendations.
6. ***Produce draft CDE recommendations***. Each subgroup produces a data dictionary of CDEs that characterizes each CDE and provides operational definitions to guide collection; template data collection forms; and a list of recommended standard instruments. The NCT assists in drafting the CDE materials once the group makes content decisions.
7. ***Conduct internal working group review*** – to refine the draft CDEs. The internal review, which typically lasts one month, allows the working group members to review and provide feedback about the materials drafted by all subgroups.

Following the internal working group review period, each subgroup reviews the comments it received and revises or refines the draft CDEs as necessary.

8. ***Reconvene working group at a national meeting*** – to critique the package of draft CDE materials and to discuss plans for soliciting feedback about the CDE materials from the larger clinical research community.

9. ***Hold public open comment period*** – to improve the quality of the CDE materials and to encourage buy-in from the research community regarding their use. After the NCT posts version 0.0 of the CDEs on the Web site, a public review period commences, typically lasting 6 to 8 weeks. During the public review period, organizations, associations, pharmaceutical companies, and researchers identified by the working group and NINDS, are invited to review the CDE materials and to provide feedback.

10. ***Release version 1.0 of disease-specific CDEs*** – to make CDE materials available for use. Upon conclusion of the public review, the NCT collates the comments received and provides them to the appropriate subgroups. The subgroups review the feedback and make additional modification to the CDEs. The initial development process ends with the NCT posting version 1.0 of the disease-specific CDEs on the Web site (http://www.commondataelements.ninds.nih.gov/).

## RESULTS

A review of published NINDS-funded clinical trials formed the basis for a definition of core elements common to most clinical trials in neurology. A retrospective recoding of data from completed and published clinical trials showed wide variance in the implementation of the same data elements. One simple example is the data element of sex, some studies called this element sex while others called it gender. The coding of the sex/gender data also varied across the studies: some studies used the codes Male and Female; others used the codes 1 and 2; others 1, 2, and 99; others M and F; and still others 0 and 1. The review also revealed that large amounts of data were collected but not reported in the primary results and sometimes never published.

The NINDS CDE Web site currently includes the critical core (a.k.a., general) CDEs as well as version 1.0 of several disease-specific CDEs; many more will be published there through the first half of 2012 as shown in Table 4. Researchers are encouraged to visit the Web site, select data elements appropriate for their study from the general modules and the relevant disease-specific modules. Investigators, clinical coordinators, data managers and other members of the research team are advised to view the CDE modules as menus from which to carefully select only those CDEs required to either answer the questions their studies are designed to answer or protect the safety of study participants.

Use of the CDEs is not required by NINDS but the Institute is strongly encouraging investigators of Phase III and exploratory clinical trials to use the CDEs in their CRFs and data managements systems (PAR-11-173 and PAR-10-199).[32, 33] In addition, the NINDS is introducing investigators who have been awarded funding to conduct a clinical trial to the NCT so that the NCT can provide the research teams with training on how to access and use the CDEs in their studies. CDE training sessions also are planned for upcoming national conferences and meetings, such as the Annual Meeting of the American Epilepsy Society. The NCT is optimistic that such initial CDE training workshops will help to establish relationships with the research teams who are using or will use the CDEs so that they are more forthcoming with advice and suggestions for refining the CDEs and related tools. The NINDS views the early adopters of the version 1.0 disease-specific CDE packages as pilot



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testers of the usability and feasibility of the CDEs and therefore integral to the success of the CDE Project.

## DISCUSSION

The NCT recognizes the CDE Project must be dynamic and continue to involve the clinical research community if it is to demonstrate its contributions and benefits. As a result, the NCT is tracking those research teams who are using the CDEs and is contacting them proactively to solicit their feedback about the CDEs and related tools so that their proposed revisions and additions can be incorporated into future versions of the CDE products. Research teams also have the ability to submit their comments about the CDEs through the Web site at anytime (http://www.commondataelements.ninds.nih.gov/Feedback.aspx). Advances in medicine, clinical research, and medical informatics are also likely to require revisions and additions to the NINDS CDEs. Thus, it will be important for the Project to continue to use clinical research experts to evaluate the CDEs periodically to ensure that the CDEs evolve and accurately reflect current research practices.

The CDE Steering Committee has played and will continue to play a key role in helping the NCT to ensure the CDE Project continues to meet its goals and evolves with the needs of the clinical research community. The NCT recently appointed new members to the Steering Committee as the Project had grown significantly since the Steering Committee originally was formed. The current Steering Committee convened in March 2011 and again in February 2012.

One issue the CDE Project currently is dealing with is how to ensure consistency across the critical core and all the disease-specific CDEs. The disease-specific CDEs have thus far been developed in waves; each wave consists of the development of CDEs for three to five diseases in parallel. This parallel development has made it challenging to ensure the consistency of CDEs developed within the same wave until after the version 1.0 CDE recommendations of each are released. For CDEs currently being developed, ensuring consistency with the critical core CDEs and the available disease-specific CDEs is somewhat easier, as the NCT has developed a database for its internal use that allows team members to search for existing CDEs and recommend them to the working groups for reuse. The NCT currently is working to improve the consistency amongst the available CDE packages (Table 4); this work will continue as the next wave of disease-specific CDEs is released in 2012.

As the NCT strives to increase the consistency amongst the NINDS CDEs and also to address shortcomings in the version 1.0 disease-specific packages identified by CDE users, it will require the expertise and buy-in of clinical investigators, research coordinators, data managers, and statisticians. Thus, the NCT currently is assembling oversight committees for each of the publically available disease-specific CDEs. The oversight committees, which include a subset of members from the original working groups as well as researchers new to the CDE Project, will work with the NCT to maintain assigned CDEs by making revisions to version 1.0 after sufficient feedback has been gathered from users, after approximately one year. The timeframe for evaluating future versions of CDEs will be assessed by each oversight committee. The CDE Steering Committee will serve as the adjudicator whenever the oversight committees' recommendations and decisions introduce inconsistencies among the CDEs.

As in the NINDS CDE Project, some other efforts underway to create data standards for clinical research have also begun to develop data standards for specific therapeutic areas. The NCT will continue to observe other data standardization efforts and will consult with



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the CDE Steering Committee and/or the oversight committee for the disease to determine to what extent the CDEs should align with a particular effort. The NINDS certainly does not want to "reinvent the wheel" with its CDEs and strives to align itself with similar data standardization efforts when prudent and feasible; the ultimate goal being the creation of a global data content standard that can be used across the entire clinical research community. Thus far the NCT's collaborative work with other data standardization efforts has focused on those with a large amount of overlapping content with the NINDS CDEs and significant adoption within the clinical research community. For example, the NCT currently is collaborating with the Biomedical Data Standards division of the NCI Center for Biomedical Informatics and Information Technology and recently conducted a pilot project to register the NINDS critical core CDEs and a subset of the NINDS stroke CDEs into NCI's caDSR.[1] The pilot project enabled the NCT to improve its CDEs by reusing existing vocabulary standards and metadata. It also helped to disseminate the NINDS CDEs to various other NIH institutes and research organizations (e.g., CDISC) who use the caBIG tools to create and manage their data standards.

The NCT also currently is conducting a pilot project with CDISC. Since April/2009 CDISC has worked to develop data standards for specific therapeutic areas and has already released Cardiovascular and Tuberculosis Data Standards.[34] CDISC SDTM standards have been widely adopted throughout the world. The NCT and CDISC are working together to align the NINDS Parkinson's disease (PD) CDEs with existing CDISC SDTM standards to develop a PD-specific data standards specification and implementation guide. The CDISC PD Data Standards are expected to be released in early 2012. The NCT and CDISC teams may collaborate again on other therapeutic area when their data standards development work intersects.

In the last few years the use of electronic health records (EHRs) has been widely discussed as a method to improve health care and reduce health costs. While interaction with EHRs has not been a goal of the CDE Project, CDE data standards eventually may facilitate the linking of EHR systems and NINDS clinical research. The NCT is tracking the progress of the CDISC Healthcare Link Initiative and other projects that seek to fully realize the interoperability between healthcare and clinical research.[35] Of note, the NCT recently initiated discussions with the Lister Hill National Center for Biomedical Communications of the National Library of Medicine to determine how better to incorporate into the NINDS CDEs standard clinical vocabularies (e.g., SNOMED CT) that can be used by both clinicians and researchers.

## CONCLUSION

There are numerous actual and potential contributions of the NINDS CDE Project to the clinical research enterprise. The Web site (http://www.commondataelements.ninds.nih.gov/), master CDE Data Dictionary, and modules are existing products. The process that evolved for the CDE development is important as it provides a mechanism for research community participation and adoption, a structure for decision-making, and a technical support team. The actual CDEs and forms should provide time and cost savings for the NINDS and its grantees embarking upon clinical studies. Additionally, the data from related studies will be comparable. Similar benefits are anticipated for researchers in academia and industry who use the CDEs in studies that are not sponsored by the NINDS. As more research teams use the CDEs, the NINDS program staff look forward to the comments from users to improve the CDE materials and tools and to ensure that the Project continues to achieve its goals.

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## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 3**

Critical Core CDE Modules

| |
|---|
| ***Demographics*** – to characterize study populations |
| ***Inclusion/Exclusion*** – to document participants' eligibility for a study |
| ***Medical History*** – to identify co-morbidities |
| ***Physical Examination*** – to record current health status, severity at baseline and outcome |
| ***Concomitant Medications*** – to document ongoing prescriptions and ad hoc medications that may interact with treatment/ intervention |
| ***Treatment Log*** – to record compliance with intervention |
| ***Adverse Events*** – to describe safety issues |
| ***Outcome Measures or Study Endpoints*** – to address study hypotheses |
| ***Study Discontinuation/Completion*** – to document patient status |
| ***Genetic Elements*** – based on the required fields of the NINDS Human Genetics DNA and Cell Line Repository |

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**Table 4**

Current and Future Contents of the NINDS CDE Web Site (http://www.commondataelements.ninds.nih.gov/)

| Status | Name of CDE Package *Listed in the order of actual/ expected publication* | Year of Publication on Web site | Total CDEs | Total CRF Templates and Guidelines |
|---|---|---|---|---|
| **CDEs Currently Available** | Critical core/ General | 2007 | 181 | 24 |
| | Epilepsy | 2010 | 498 | 37 |
| | Spinal cord injury | 2010 | 607 | 13 |
| | Traumatic brain injury | 2010 | 602 | 44 |
| | Stroke | 2010 | 1,130 | 53 |
| | Parkinson's disease | 2010 | 1,103 | 60 |
| | Congenital muscular dystrophy | 2011 | 579 | 30 |
| | Friedreich's Ataxia | 2011 | 373 | 21 |
| **CDEs in Development** | Amyotrophic lateral sclerosis | 2012 | *TBD* | *TBD* |
| | Multiple sclerosis | 2012 | *TBD* | *TBD* |
| | Huntington's disease | 2012 | *TBD* | *TBD* |
| | Headache | 2012 | *TBD* | *TBD* |
| | Neuromuscular diseases* | 2012 | *TBD* | *TBD* |

*Including, but not limited to: Duchenne Muscular Dystrophy, Facioscapulohumeral Muscular Dystrophy, Myasthenia Gravis, Myotonic Dystrophy, and Spinal Muscular Atrophy.