Patient-Reported Outcomes Measurement Information System (PROMIS) Mid-Course Review Report

September 12, 2007

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ACRONYMS

APHO – Advisory Panel on Health Outcomes
CAT – Computer Adaptive Testing

CFR – Code of Federal Regulations
CHF – Congestive Heart Failure

COPD – Chronic Obstructive Pulmonary Disease

CORE – Northwestern University Center on Outcomes, Research and Education
DHHS – Department of Health and Human Services

DIF – Differential Item Functioning
EC – Executive Committee

FDA – Food and Drug Administration
HAQ – Health Assessment Questionnaire
IRB – Institutional Review Board

IRT – Item Response Theory

IVRS – Interactive Voice Recognition System
KAI - KAI Research, Inc.

NIAMS – National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH – National Institutes of Health

OPASI – Office of Portfolio Analysis and Strategic Initiatives
PDA – Personal Data Assistant

PHS – Public Health Service

PRO – Patient-Reported Outcome(s)

PROMIS – Patient-Reported Outcomes Measurement Information System

PRS – Primary Research Site(s)

RFA – Request for Applications

RIC – Rehabilitation Institute of Chicago

RICC – Roadmap Implementation Coordination Committee

SAB – Scientific Advisory Board
SC – Steering Committee

SCC – Statistical Coordinating Center
UBC – United BioSource Corporation

UCLA – University of California, Los Angeles
WHO – World Health Organization

GLOSSARY

Computer Adaptive Testing (CAT) Score – Scores which represent a person's standing on a domain (e.g., physical functioning, depression). Questions are selected so researchers may estimate scores with the minimal number of questions without a loss in measurement precision. CAT integrates the advances in measurement theory and the power of computer technology to administer a patient-reported outcome (PRO) instrument that selects questions on the basis of a patient's response to previously administered questions (or possibly other prior information).

Ceiling Effects – The clustering of individuals' scores at the top of a scale.

Differential Item Functioning (DIF) – A procedure used to determine if test questions interact with sample characteristics to cause response differences. Scales containing DIF items may have reduced validity for between-group comparisons because their scores may be indicative of a variety of attributes other than those the scale is intended to measure.

Domain Framework – A map that portrays the structure of each domain and its conceptual framework or, where applicable, hierarchical structure.

Floor Effects – The clustering of scores at the bottom of the scoring scale.

Item – A question (including its response choices) in a survey.

Item Bank – A collection of items measuring the same underlying latent trait or construct on a common metric.

Item Response Theory (IRT) – A body of psychometric theory in which mathematical models are used to analyze data from questionnaires, relating the probability of a certain response to an underlying trait.

Short Forms – A parsimonious subset of items selected from a full item bank to yield an accurate estimate at a targeted range of the measured domain.

T-scores – Scores that have a mean of 50 and standard deviation of 10 in a reference (e.g., general) population.

Theta Metric – The underlying (latent) construct estimated from the responses individuals give to the items in a scale. These items have been previously calibrated by an IRT model.

Use Cases – Short summaries describing how certain features of the CAT system will function.

ACKNOWLEDGEMENTS

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) organized the PROMIS Mid-Course Review on behalf of the National Institutes of Health (NIH). In addition, personnel from the Office of Portfolio Analysis and Strategic Initiatives (OPASI) participated in key Mid-Course Review activities, including the orientation teleconference and the face-to-face meeting between the Review Panel and the PROMIS Principal Investigators.

The Mid-Course Review Panel provided the expertise and guidance necessary to complete the Mid-Course Review. The NIH Science Officers provide technical assistance, advice and program stewardship for the PROMIS grants. Appendix 1 lists the Review Panel members and the NIH Science Officers.

EXECUTIVE SUMMARY

The PROMIS Initiative and Mid-Course Review

The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative, one of the NIH Roadmap efforts designed to re-engineer the clinical research enterprise,[1] establishes a collaborative relationship between NIH and individual research teams through a cooperative agreement (U01) mechanism.

PROMIS is developing new ways to measure patient-reported outcomes (PRO) such as pain, fatigue, emotional distress, physical functioning, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases. The focus and assessments of the PRO items, thus far, has been on the following clinical populations: cancer, chronic obstructive pulmonary disease (COPD), heart disease, osteoarthritis, psychiatric conditions, rheumatoid arthritis, and spinal cord injury.[2]

The broad objectives of the PROMIS Network (the Network) are to:

- develop and test a large Item Library measuring PRO;
- create a computerized adaptive testing (CAT) system that allows for efficient, psychometrically robust assessment of PRO in clinical research for a wide range of chronic diseases; and
- create a publicly available system which will allow clinical researchers to access a common item repository and CAT.

Each item is a question with an associated set of response options on a survey. The PROMIS Item Banks (Item Banks) represent a collection of items that measure the same construct, such as pain.

The Mid-Course Review was conducted from May 2007 to September 2007 and assessed the progress of the Network over the first two-and-a-half years of funding with a focus on whether the objectives and milestones of the program were being met. The Mid-Course Review helped assess short- and long-term needs of PROMIS in order to bring the project to fruition.

The Roadmap Implementation Coordination Committee (RICC) approved the following general questions to guide the Mid-Course Review:

- Is the project being conducted as planned?
- Have the mid-point goals been achieved?
- Have the goals been modified since the beginning of the project? If so, what is the progress in these modified goals?
- Was the rationale appropriate for process changes since the project's inception?
- Does the project continue to be relevant and significant in relation to re-engineering the clinical research enterprise?

The PROMIS Request for Applications (RFA) objectives guided the implementation of the Network and provided the context for the Mid-Course Review. The Review Panel organized them into four categories to focus the review: organizational, operational, research, and dissemination.

Conclusions

The Review Panel concluded the PROMIS Principal Investigators are successfully collaborating to implement this very important and innovative project and the Network has exceeded expectations with its first two-and-a-half years of accomplishments.

The Review Panel found the PROMIS Principal Investigators have developed an organized, functional, and productive Network that conforms to the RFA objectives. The Network has not modified the program goals since the beginning of the project.

The Network operates as a collection of collaborative committees and working groups and has the intellectual resources to achieve its goals. The PROMIS Principal Investigators are leaders in their respective fields and have demonstrated their collective commitment to the success of the project.

The domain framework, Item Bank selection, and data collection methods, which included focus groups, cognitive interviews, general population and specific patient population sampling, provide a solid foundation on which the PROMIS Principal Investigators can build a system that has the possibility to transform how clinical researchers collect PRO information.

The Network activities are ahead of the timetable described in the RFA, enabling the Network to plan a second wave of clinical validation studies for four chronic disease areas during the fourth and fifth years of the funding period.

PROMIS represents a paradigm shift in how assessments for PRO are created and used in clinical research. In particular, the dynamic functionality of the CAT system is an exciting new feature. The Item Banks and CAT system represent much improvement over the use of assessments which focus on a single disease and are likely to be outdated and/or are culturally irrelevant. Thus, the project is highly relevant and in a position to transform clinical research. It will be critical to have the project's tools and content freely and openly available to clinical researchers.

The Review Panel concludes that the PROMIS goals for the first three years have been met within the first two-and-a-half years and that the project is relevant and timely to reengineering the clinical research enterprise. However, the ultimate success of the project will lie in the validation studies, the implementation of the CAT system, and the adoption of the PROMIS products by the clinical research community.

Recommendations

The Review Panel offers the following recommendations to assure the continued success of the PROMIS endeavor.

Organization of the Network

- ***Sustainability –*** The Network must ensure that a solid, dynamic infrastructure is in place as the PROMIS project continues development and operation.

- ***Contractor Advantage –*** The Steering Committee (SC) should consider whether those contractors currently working on the project should be allowed to compete for subsequent contracts.

Operations

- ***Clinical Relevance –*** The Network should formulate a plan or process for ensuring the items remain up-to-date and clinically relevant.

- ***Sample Diversity*** – The Network should develop a concrete plan for future testing which ensures greater ethnic, minority, and educational representation so the PROMIS products are generalizable.

Research

- ***Item Validity –*** The Network should continue testing the items and Item Banks in different chronic disease areas and ethnic groups to demonstrate their content validity. Moreover, the Network should conduct studies to help end-users interpret what the CAT-generated scores represent.

  Responsiveness to change must be demonstrated for the items and instruments to be considered useful.

Dissemination

- ***Public Information Strategies –*** The Network should consider its multiple constituencies in developing a comprehensive dissemination strategy for PROMIS. This will assist in long-term funding and maintenance of the Item Banks and CAT system.

- ***Presentation of Project Information –*** The Network should have a process for ensuring presentations and publications do not overstate results, and they illuminate both strengths and weaknesses of the project.

Item Banks and Computer Software – The Review Panel urges the Network to put the system software code, including item selection algorithms, into the public domain to facilitate widespread use by clinical researchers, institutions, and commercial organizations.

- ***Short Forms –*** The Network should carefully consider what short forms will be constructed and how these will be used. Short form items should be selected to minimize the potential for differential item functioning (DIF) impact.

- ***Long-Term Support –*** The Network should explore public-private partnerships to manage the long-term costs of the Item Bank and CAT. All potential partners should agree that the PROMIS products should be freely available.

- ***Industry Acceptance –*** To gain the interest and acceptance of the biopharmaceutical industry, the Network must demonstrate that the PROMIS products can be used for an array of chronic disease populations, to capture adverse events, and to distinguish the effects of therapeutic response.

I. SECTION 1: THE PROMIS MID-COURSE REVIEW

The Patient-Reported Outcomes Measurement Information System (PROMIS) is one of the NIH Roadmap initiatives designed to re-engineer the clinical research enterprise.[1] It is developing new ways to measure patient-reported outcomes (PRO) including pain, fatigue, emotional distress, physical functioning, and social role participation, which have a major impact on quality of life across a wide variety of chronic diseases, including cancer, chronic obstructive pulmonary disease (COPD), heart disease, osteoarthritis, psychiatric conditions, rheumatoid arthritis, and spinal cord injury.[2]

I.A. The PROMIS Network

The Network is composed of six Primary Research Sites (PRS) and a Statistical Coordinating Center (SCC) which are each funded for five years. The PROMIS Request for Applications (RFA) specified the structure of the Network, the main objectives, and the yearly milestones for the project. The broad objectives of the Network are to:

- develop and test a large Item Library measuring PRO;
- create a computerized adaptive testing (CAT) system that allows for efficient, psychometrically robust assessment of PRO in clinical research for a wide range of chronic diseases; and
- create a publicly available system which will allow clinical researchers to access a common item repository and CAT.

Please note that a glossary of terms has been provided on Page iv.

I.B. The Mid-Course Review Charge

As directed by the National Institutes of Health (NIH) Office of Portfolio Analysis and Strategic Initiatives (OPASI) and the Roadmap Implementation Coordination Committee (RICC), the Mid-Course Review was conducted by an independent panel of experts (Review Panel) from the fields of survey research, behavioral research, including health-related quality of life, informatics, psychometrics, outcomes research, and clinical research, and included a representative from the Food and Drug Administration (FDA). According to RICC guidelines, a member of the NIH program staff not directly connected to the PROMIS initiative also participated on the Review Panel. KAI Research, Inc. (KAI) facilitated the review.

The Review Panel evaluated the progress of the Network over the first two-and-a-half years of funding. The goals of the Mid-Course Review were to assess whether the:

- objectives and milestones of the program are being met;
- processes and products are technically sound and relevant to the clinical research enterprise; and

- short- and long-term goals that must be achieved in order to bring the PROMIS project to fruition are being pursued.

This review has focused on the Network activities rather than the progress of individual grantees.

The RICC approved general questions to guide the Mid-Course Review process:

- Is the project being conducted as planned?
- Have the mid-point goals been achieved?
- Have the goals been modified since the beginning of the project? If so, what is the progress in these modified goals?
- Was the rationale appropriate for process changes since the project's inception?
- Does the project continue to be relevant and significant in relation to re-engineering the clinical research enterprise?

I.C. The Mid-Course Review Approach

To conduct the Mid-Course Review, information was gathered that related to the RFA objectives guiding the PROMIS initiative's implementation. The objectives comprise four categories:

- *Organizational* – Formation of the Steering Committee (SC) and subcommittees to provide project direction and decision-making, as well as interaction with the Scientific Advisory Board (SAB).
- *Operational* – Identification of domains, items, and assessments, as well as methods for assessing their relevance and utility in a diverse population.
- *Research* – Studies of PRO in specific populations, psychometric properties of a domain, health preferences, methods for collecting PRO, translation of instruments into other languages, etc.
- *Dissemination* – Distribution of the Item Banks and CAT, evaluation of their utility for wide-scale use, strategies for their ongoing development and maintenance, and interaction with potential future users.

The Mid-Course Review focused primarily on the first two categories.

Research questions were proposed, organized to correspond to each of the four categories, and then linked to data elements and information sources.

Because the review was primarily qualitative in nature, data sources included presentations, working papers, publications, responses from the Network, and documents on the PROMIS Web site (www.nihpromis.org) and in the eRoom. The eRoom provides a repository of all documentation related to the PROMIS initiative, such as meeting minutes, a directory of Network participants, a calendar system, and Network protocols.

I.D. Timeline

- *May 9, 2007* – Orientation teleconference, providing the Review Panel with background on the initiative, the Network's progress to-date, and an initial list of research questions.
- *May 22, 2007* – Finalization of the initial research questions and initiation of data collection.
- *June 19, 2007* – A face-to-face meeting between the Review Panel and the Network representatives for additional data collection and elaboration of information and a closed-door discussion for the Review Panel. Recommendations were developed for the final report to OPASI and the RICC.
- *August 9, 2007* – Conference call to review draft final report.
- *July – September 2007* – Final report preparation.

I.E. Limitations

The research design and collected data were primarily qualitative. The review did not include on-site assessments of progress and relied heavily on documents and responses to research questions provided by the Network. The lack of empirical data left the burden of analysis to the expert insights of the Review Panel.

Most communication among the Review Panel members—for developing research questions, reviewing materials, clarifying information, and refining the final report— was conducted electronically. Several teleconferences facilitated consensus building, and the entire Review Panel had one face-to-face meeting.

II. SECTION 2: REVIEW OF THE PROMIS INITIATIVE

The Mid-Course Review focused on the Network's objectives and accomplishments, which are described in this section.

II.A. Objective 1: Organization of the Network

The RFA specified the project would be a cooperative network consisting of four main components:

- Primary Research Sites (PRS),
- Statistical Coordinating Center (SCC),
- Steering Committee (SC) which serves as the main governing board and medium through which NIH interacts with the Network, and
- Scientific Advisory Board (SAB).[2]

The Principal Investigators for the Network are:

- David Cella, Ph.D., Northwestern University
- Dagmar Amtmann, Ph.D., University of Washington
- Darren DeWalt, M.D., University of North Carolina at Chapel Hill
- James Fries, M.D., Stanford University
- Paul Pilkonis, Ph.D., University of Pittsburgh
- Arthur Stone, Ph.D., Stony Brook University
- Kevin Weinfurt, Ph.D., Duke University.

Each PRS is responsible for completing two major tasks:

1. the proposed independent research project outlined in its original application; and
2. the Network research activities, which include developing and shaping the core questionnaires and conducting data collection and analysis.[3]

II.A.1. Statistical Coordinating Center

The SCC, directed by Dr. Cella, has implemented a data management system for the Network to collect and analyze data. The SCC includes collaborators from the University of California at Los Angeles (UCLA), Westat, Inc., the Rehabilitation Institute of Chicago (RIC), and the United BioSource Corporation (UBC).[4]

The SCC is divided into five teams that include protocol development, data management, data analysis, software development, and communication/dissemination.[4]

II.A.2. Steering Committee

The SC, the Network governing and decision-making body, is composed of the Principal Investigators and the NIH Science Officers (Appendix 1). It provides technical assistance, advice, and program stewardship for the grants. The NIH Science Officers serve as liaisons between the Network and other NIH program staff and collaborators.[4]

The SC makes all decisions regarding its organization and research, provides overall scientific direction and establishes and monitors policies and procedures. Three of its members form the Executive Committee (EC), which develops initial recommendations to the SC regarding timelines and task priorities, organizes workgroups, develops meeting agendas, and acts on behalf of the SC on matters that do not require full deliberation.[4]

II.A.3. Scientific Advisory Board

The SAB is a panel of ten independent experts which provides scientific oversight and advice to the Network to ensure that resources developed are relevant and useful to the scientific community. [4]

II.A.4. Committees and Working Groups

The SC has established committees and working groups (Appendix 2) that focus on specific PROMIS objectives.[5] This structure establishes a mechanism for research collaboration and addresses organizational issues. Members of each committee or group collectively address and solve problems; prioritize tasks; collect, analyze and prepare data; and present information at the SC and Network meetings. Chairs of committees and working groups are responsible for maintaining progress between the SC meetings through regularly scheduled conference calls and providing the SC with updates. Additional meetings via teleconference or videoconference are organized by the SC chair or by a majority of its members. Committee members are identified by the SC and include the PROMIS Principal Investigators and their staff members, as well as NIH-approved researchers from outside the Network as needed.

Working groups focus on each of the domain areas as well as the protocols for domain hierarchy, data analysis and qualitative item review. The Advisory Panel on Health Outcomes (APHO) advises the Network on the relevance of its work to clinical research.[5]

II.A.5. Meetings

The Network conducts two-day, in-person meetings two to three times per year to discuss and review the technical aspects of project implementation and analysis and to present data results.[6] The SC, the SAB members, and research support staff attend the meetings.[7] In addition, the SC holds conference calls monthly.[8]

II.A.6. Arbitration

An arbitration process has been established to address disagreements within the Network. An arbitration panel composed of one member selected by the Network, one NIH nominee, and a third member chosen by the first two selected members will review the issue and recommend a course of action to the NIAMS Director. This process does not affect the grantee's right to appeal any adverse action in accordance with PHS regulations 42 CFR Part 50 Subpart D and DHHS regulations 45 CFR Part 16.[3] To date, there has been no need to use the arbitration process.

II.A.7. Completed Network Activities

The Network activities over the first two-and-a-half years have focused on:

- organizing PROMIS into a functional, cooperative Network;
- developing the domain framework;
- creating the Item Banks;
- initiating data collection for Item Bank testing and validation;
- initiating software development
- disseminating project information; and
- initiating plans for project sustainability.[9]

II.B. OBJECTIVE 2: Selection of Domains and Core Items

Three research protocols were developed in order to select domains and identify and review items:

1. *The Archival Data Analysis Protocol* is a statistical analysis plan based on item response theory (IRT). IRT is a body of psychometric theory in which mathematical models are used to analyze data from questionnaires, relating the probability of a certain response to an underlying trait. It guided the analysis of existing data sets to facilitate:

    - construction of the Item Banks;
    - understanding of dimensionality in the five domains;
    - revision of items in the PROMIS Item Library (Item Library);
    - identification of the most useful response sets; and
    - development of new items.

2. *The Domain Hierarchy Protocol* guided the selection of the domains and the development of the domain framework. The World Health Organization (WHO) physical, mental, and social framework was selected as the basis for the PRO domains. Five domains were selected for initial Item Bank construction: pain, fatigue, emotional distress, physical functioning, and social role participation.

3. *The Qualitative Item Review Protocol* guided the process of revising and refining items, developing new items, and testing all items. To develop the Item Library, a database of over 10,000 items was assembled through literature review and expert consultation. Candidate items for the Item Banks were identified and refined from the Item Library. The items were classified and revised through a binning and winnowing selection process and further refined through cognitive interviews and expert review.

Each item is a question on a survey with an associated set of response options. The PROMIS Item Banks (Item Banks) represent a collection of items that measure a construct, such as pain. For example, an item from the Item Bank for pain is: "In the past 7 days, overall how much did pain interfere with your daily activities?" The response options are, "1 = not at all, 2 = a little bit, 3 = somewhat, 4 = quite a bit, and 5 = very much." By answering a series of questions related to pain, the actual pain an individual is experiencing can be quantified and compared with the responses of other individuals.

II.B.1. Domain Framework

The domain framework was developed for applicability to a wide range of diseases.[4] A conference focused on health status in the 1980s identified the following domains as important concepts: symptoms, functional status, role activities, social functioning, emotional status, cognition, sleep and rest, energy and vitality, health perceptions, and general life satisfaction.[10] The domain framework (Figure 1) includes many of these domains.[11]

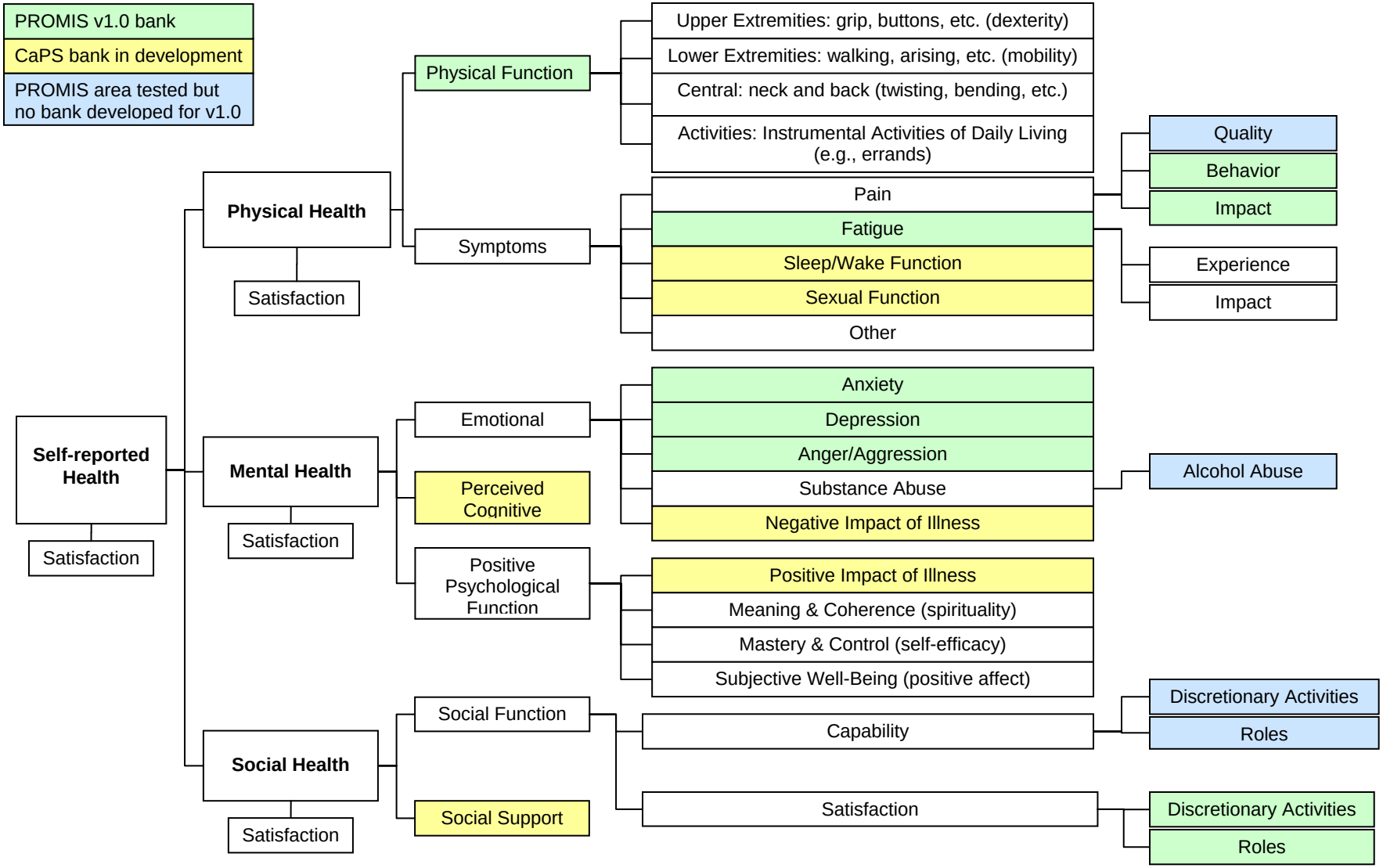
The Network accelerated the process of establishing the domain framework in order to begin Wave 1 testing of the Item Banks within the first two years of the initiative.[4] The Network anticipates that the framework will be reexamined and refined over time[13] and acknowledges that a different group of experts could have developed an entirely different but equally useful framework.[4]

II.B.2. Validating the Domains through Focus Groups

The Network used focus groups to obtain input from selected populations on each of the domains. Generally, two to four focus groups were conducted for each of the five domains.[15] Individuals with and without chronic illness, but with a range of experiences in a given domain, were instructed to consider the relationship between their experience in a specific domain and their health. Results are summarized in executive summaries that capture important themes, as well as additional domains to explore. For example, themes identified in the alcohol focus group[16] include barriers to overcoming excessive use of alcohol, feelings of isolation, polysubstance abuse and alcohol treatment options. Focus groups assisted the Network in verifying domain definitions, identifying common language applied to the domains, and determining potential gaps in domain coverage in the framework.

The Network endeavored to include a diversity of races, ethnicities, and age groups in the focus groups, as well as representation of both genders.[14] However, the focus groups lacked representation of certain races and ethnicities. While 14% of the United States population in 2005 was Hispanic, [25] 7% of physical functioning focus group participants and 2% of emotional distress focus group participants were Hispanic, and there were no Hispanic participants in the pain, fatigue, and social role participation focus groups.[15] Additionally, Asians were absent from the fatigue and pain focus groups, and African Americans were absent from the physical functioning focus groups.

Figure 1: PROMIS Domain Framework
Updated June 30, 2007[11]



II.B.3. Item Library Development

Once domains were defined, the Network identified items for the Item Banks from both well-established and lesser-known existing instruments. The Network conducted literature searches using MEDLINE and Health and Psychosocial Instruments, as well as proprietary databases such as the Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID).[15] Each domain group developed its own search strategy for relevant items, which included manual searches of files to find items that were not identified in the database searches. The resulting Item Library included over 10,000 entries, approximately 7,000 of which were related to the five domains.[4]

An Intellectual Property Subcommittee was established in order to evaluate issues that may arise from the use of existing items and instruments.[17] The Network requested the release of items from authors using a standardized letter. Authors were given four choices for release of their property: 1) full permission; 2) permission to use in the development phase, but not in the final CAT instrument; 3) no permission; and 4) open to negotiated agreement.[18] The Network tracks rights to the items to ensure that they adhere to intellectual property laws.

II.B.4. Archival Data Analysis

Eleven existing data sets were analyzed to assist with development of items and the Item Bank structure.[4] Coupled with item revisions that occurred as part of the Qualitative Item Review Protocol, this process helped establish the Item Library. Items were categorized into the five domains and subjected to Item Response Theory (IRT) analyses.

II.B.5. Qualitative Item Review

The Qualitative Item Review Protocol includes classification of items through a binning and winnowing process and item validation.

II.B.5.a. Binning and Winnowing

Because of the large number of items and instances of redundancy, a selection process of binning and winnowing was employed consistently across the domains.[15] Items were first binned, or grouped systematically, according to their content. Literature review, including previous factor analysis and theory-based studies, informed this process. Items that were inconsistent with the domain definition, redundant, too narrow, disease-specific, or confusing were eliminated.[12]

A secondary review by the SCC ensured that implementation of the binning and winnowing process was consistent across domains. Items were subsequently revised for consistency in style, readability, and consistency of response options and timeframes.[15]

II.B.5.b. Item Validation

Cognitive interviews were conducted on each potential item to assess clarity and relevance to the specified domain.[15] A minimum of five cognitive interviews were conducted on each item, with

an additional three to five interviews performed if an item underwent major revisions. The interviewers utilized a retrospective verbal probing technique, whereby the participant would first complete a paper questionnaire and was then probed by the interviewer for the basis for the response. This process allowed the Network to confirm that the items on the questionnaire were being interpreted as intended.

The Network took steps to ensure that the cognitive interviews included a diverse sample of individuals. However, because of the small number of participants, representative sampling was difficult. No participants in the domains of emotional distress, fatigue and social function were Hispanic or Asian.[15]

Each item was reviewed by a minimum of one white and one non-white interviewee, [15] and two interviewees had to meet at least one of the following criteria: less than 12 years of education; a measured reading level less than the ninth grade; or a diagnosis associated with cognitive impairment. Items were further revised for consistency and assessed for readability.[15] A translation expert provided feedback on the ability to translate the items into other languages, and 500 items have been identified for translation into Spanish. The Network anticipates that the items will be translated into additional languages in the future.

II.B.6. Relevance of Items to Clinical Research

Development of the preliminary domain framework and items included checks to ensure clinical relevance. Domain groups searched for relevant items for inclusion in the Item Library, and winnowing eliminated items which were not relevant to the domain. In cognitive interviews, the interviewees were asked whether each item was an important question to ask.

Statistical analysis of item relevance will be based on Network testing of the items and will include a comparison of the PROMIS items with legacy PRO instruments including the SF-36, HAQ, FACIT-Fatigue, and Brief Pain Inventory. [19]

II.C. OBJECTIVE 3: Development of the Data Management System

The Network has completed specifications for and initiated the development of the PROMIS Assessment Center, software which will house a publicly available CAT system for assessing PRO in clinical research studies for a wide range of chronic diseases. The software is to be suitable for both research and individual patient assessment, and its specifications were developed with input from the PRS investigators and research staff. The SCC merged its existing PRO Assessment, CAT, and Reporting System with the PROMIS software requirements to create a prototype that will lead to a computerized system to administer, collect, and report PRO data, and to serve as a data repository for all PRS collaborators in the Network.[9]

II.C.1. Software Development: The PROMIS Assessment Center

The PROMIS Assessment Center will house the Item Library and will allow clinical researchers to construct an assessment tool or survey from the validated items banks, study protocol, and clinical and PRO data. Survey administration will take place electronically, via the Web using a

computer, a Personal Data Assistant (PDA), or Interactive Voice Recognition System (IVRS). A report of findings will be constructed for researchers and patients.

The goals of the system are to:

- deliver measures,
- streamline subsequent questions based on preceding responses,
- provide accurate CAT scores,
- store and maintain response details,
- monitor score changes over time,
- provide import/export functionalities, and
- support simulations for researchers.[18]

The domain analysis teams are currently working collaboratively to create static short forms that will be available on the PROMIS Web site and in the software system. The short forms are a parsimonious subset of items selected from the Item Banks to yield an accurate estimate at a targeted range of the measured domain. Short forms can be administered in paper or electronic format. They reduce respondent burden and take advantage of the Item Banks without requiring computer administration.

Currently, the Item Library is housed at the SCC and is not yet Web-based. At the end of July 2007, the Network began beta-testing its fourth software release which includes functionality to administer questionnaires and collect data.

II.C.2. Development of Specifications

Business analysis tools and methodologies were used to develop PROMIS software. Use cases, which are short summaries that describe how certain features of the system will function, were developed and the CAT specifications were documented from the information collected. In addition, software features and requirements have been tracked and put in priority order to inform PRS teams of their delivery dates.[20]

Risk analysis was also conducted to plan for potential problems.[20] Common risks identified by PRS team members include:

- User dissatisfaction or lack of acceptance,
- Data loss,
- Lack of data security,
- Lack of system performance or inadequate training, and
- System obsolescence.[20]

II.C.3. Features of Computer Adaptive Testing System

Features of the software system were identified in requirements-gathering workshops and documented in the CAT specifications.[18] Key desired features of the CAT system include the ability to:

- Easily add and update the Item Banks and item parameters,
- Generate reports,
- Support various IRT models and psychometric scoring capabilities,
- Provide short forms,
- Adhere to appropriate security and health information privacy standards,
- Provide a user-friendly interface for navigation and selecting options,
- Support multiple languages, and
- Flag emergency action requirements, such as responses that may indicate suicidal tendencies.[18,20]

II.C.4. User Manuals

The CAT user manuals will be written in two formats:

1. One format will be directed toward information technology experts, and

2. Another will be written for clinical researchers and other users without specific software expertise but who need and want to understand the CAT system.

II.D. OBJECTIVE 4: Data Collection

The PROMIS sampling plan describes how the Item Banks were tested in the general U.S. population as well as in specific clinical populations.[21] The Network developed the plan with the following goals:

- Calibrate items in all of the subdomains,
- Estimate profile scores for particular disease populations,
- Co-calibrate the Item Banks with legacy instruments,
- Confirm the factor structure of the domains and subdomains, and
- Conduct item and Item Bank analysis.[22]

II.D.1. Full-bank Administration

Full-bank administration allows the Network to study dimensionality of the domains, test for differential item functioning (DIF), and simulate CAT.[22] DIF occurs when one group responds

differently to an item than another group despite controlling for differences on the measured construct. Scales containing DIF items may have reduced validity for between-group comparisons, because their scores may be indicative of a variety of attributes other than those the scale is intended to measure.

Assessment of the full Item Banks was conducted with a portion of the general population sample.[21] The 14 Item Banks were paired into seven forms of two related Item Banks to assess unidimensionality using each pair.[21] Each form was administered to a set of 501 individuals.[21] Additionally, one or two legacy instruments, socio-demographic, global health status, and in some cases, co-morbidity items were administered to each participant.[21]

II.D.2. Block Administration

In block administration, each participant was administered a block of items from every Item Bank.[21] Socio-demographic, global health status, and co-morbidity items were also administered. Each block was tested in both a general population and clinical population sample to allow for observation of DIF between the two groups.[21] The clinical populations included individuals with cancer, heart disease, rheumatoid arthritis, osteoarthritis, psychiatric conditions, spinal cord injury, and chronic obstructive pulmonary disease.[22] Block administration allowed determination of IRT-based estimation of item parameters and item linking.[21]

II.D.3. Dimensionality and Differential Item Functioning

Although both classical factor analysis and DIF require that all items are administered to each participant, this was not practical with a universe of 784 items.[21] Instead, the dimensionality of the primary Item Banks was assessed in the general population sample using the seven forms of full-bank administration. The Network expects to evaluate DIF for demographics in all items. However, DIF comparisons with respect to clinical populations are not possible with Wave 1 sampling.

II.D.4. Floor Effects

For each Item Bank, up to six items were identified as likely to exhibit floor effects, or responses that cluster at the lower extreme of the trait, in the general population.[21] These items were targeted to specific clinical populations that are likely to have a higher proportion of individuals provide responses which demonstrate floor effects. The selected items were included in the seven-item block administered to a given clinical population and were also administered to the corresponding general population sample.

The same consideration did not apply to ceiling effects, in which responses cluster at the top of a series of responses, because of the large size of the general population.

II.D.5. Wave 1 Data Collection

The Network utilized Polimetrix, a Web-based polling company, for a majority of the Wave 1 sampling. Participants answered between 146 to 202 items via a Web-based questionnaire.[21]

The length of the tests was limited by the number of items participants could respond to in one sitting.[21] However, it was necessary to have at least 500 responses per item in order for analyses to be useful.[23]

The target sample size for the general population was 7,523 and 4,000 for the clinical population.[21] In order to meet targets for diversity,[11] over sampling occurred so that the final sample size included a general population of 13,250 and a clinical population of 7,883.[24]

The Network aimed for 10-15% of the sample to be Hispanic and another 10-15% to be African American,[21] which approximates the actual 14.4% and 12.8% of the actual U.S. population making up these groups, respectively.[25] However, only 8.8% of the sample was Hispanic and only 8.6% was African American.[24] In addition, the Network did not achieve its target with respect to education level,[11] which was a minimum of 25% with a less than high school education.[21] The SC elected to use the full sample for item calibrations but only a representative sample of the U.S. population for norming purposes.[26]

II.E. OBJECTIVE 5: Data Analysis Initiation

Although data analysis was not a goal for the first two-and-a-half years of the project, the Network did initiate analyses.

II.E.1. Wave 1 Data Analysis

The Wave 1 data analysis will inform key decisions in building the Item Banks and CAT system.[9] The Statistical Analysis Plan includes methods for assessment of patient responses, calibration of Item Banks, and examination of item performance.[27] Factor analysis and other techniques necessary for IRT will be used to assess whether an item encompasses a single domain. If a single dimension is not achieved, modifications will be made.[12] The fit of the IRT model to the data and DIF among key demographics will also be analyzed.[22] All preliminary banks have undergone DIF analysis across socio-demographic variables such as age, gender, and education.[11] Subdomains which will undergo further revision due to violation of unidimensionality or poor fit to IRT model include pain quality, alcohol abuse, and capability or social function.[11]

Linking data sets to a common metric will be accomplished through analysis of T scores (standardized scores), the theta metric (severity of the trait), and CAT simulations.[23] This co-calibration is necessary as different participants will be administered different sets of questions and because new items will continue to be added to Item Banks.[27] Items have been calibrated for physical functioning, pain behavior, pain impact, fatigue, anxiety, depression, anger/aggression, and satisfaction with social function.[11] These tools will soon be available for testing as static short forms and in the CAT system.[11]

On May 7-8, 2007, the SCC hosted a Psychometric Summit to present the findings of the Wave 1 data analyses. The Summit was attended by the SCC analysis team and other PROMIS analysts, domain chairs, and PROMIS Principal Investigators as well as interested NIH Science Officers.

II.E.2. Wave 2 Data Analysis

The SC is focusing Wave 2 activities on validating the five existing Item Banks rather than developing new Item Banks based on feedback and recommendations from the NIH Science Officers and the SAB.[9]

Wave 2 activities will include defining study designs, validation criteria, and study populations and then initiating Network longitudinal clinical research studies of the Item Banks and CAT for patients with:

- Depression and low back pain with a community sample comparison,
- Arthritis,
- Congestive heart failure (CHF), and
- Chronic obstructive pulmonary disease (COPD).[9]

Wave 2 data will be used to validate both the CAT system and static short forms.[11] Responses to the CAT will be compared with responses to static short forms. Sensitivity to change[19] and assessment of DIF by disease[11] will also be examined. In each chronic disease study, participants will complete both PROMIS instruments and disease-specific legacy instruments. For example, the Chronic Respiratory Questionnaire, [23] a common PRO instrument, will be administered to patients with COPD, and responses will be compared to those on the CAT system and short form.

II.F. OBJECTIVE 6: Dissemination of PROMIS Information and Products

To share information and products from the initiative, the Network maintains a publicly accessible PROMIS Web site that contains the Network's plans, accomplishments, and results. The CAT software will be accessible through the PROMIS Web site. The Web site and the CAT system were designed for researchers, clinicians, government agencies, and industry.[28] In addition, the SCC is working with experts at the University of Washington PRS to evaluate the usability and accessibility of the CAT system for individuals with visual, physical, hearing, mobility, and reading impairments, to ensure that the user interface will meet the standards of Section 508 of the Rehabilitation Act.[28] Dissemination of the Item Banks and CAT system will begin in the fourth and fifth years of the project. However, the Network is already considering how to make these useful, relevant, and accepted by their intended users.

To that end, the Network conducted an Inaugural Conference on September 11-13, 2006. More than 200 clinicians, researchers, and policy makers attended the conference and SC meeting to learn more about the PROMIS initiative. The Network shared its accomplishments over the first two years of operation and hosted presentations from researchers conducting similar research around the world. A second PROMIS Conference is scheduled for March 3-5, 2008.

A software usability workshop for a small group of clinical researchers was held in Rockville, Maryland, September 5 and 6, 2007.[9] Following the guiding principles of transparency and inclusion, the Network has been working to keep its research in the public sphere and make it available to a wide audience.

As of June 2007, representatives from the Network have attended conferences and have made 51 presentations on PROMIS.[29] In addition, 19 articles have been published and four additional manuscripts have been submitted for publication.[29] The May 2007 issue of *Medical Care,* the Official Journal of the Medical Care Section, American Public Health Association, published a supplement devoted to PROMIS, including an overview of its development over the first two-and-a-half years, as well as six original research articles describing methods and initial results.[9]

II.F.1. Network Sustainability

To sustain the efforts of the PROMIS project, the Network has initiated communication with the Foundation for the NIH.[9] The Network is also investigating the possibility of establishing a PROMIS Foundation to:

- develop a public-private partnership to sustain the repository;
- develop strategies and form partnership(s) to provide for ongoing development and maintenance of the Item Banks and associated CAT technology; and
- facilitate public access to and support for the Network.

The Network will update the items and domains to ensure their continued relevance and will also monitor clinical and theoretical developments in their respective fields. Beyond the period of the grant, the Network hopes that the non-profit PROMIS Health Organization will oversee updating PROMIS products to ensure continued relevance.[11]

III. SECTION 3: CONCLUSIONS AND RECOMMENDATIONS

The Review Panel concluded the Network has exceeded expectations with its first two-and-a-half years of accomplishments. The PROMIS Principal Investigators, leaders in their fields, are successfully collaborating to implement this very important and innovative project.

The Network operates collectively and collaboratively and has the intellectual resources to achieve its goals. The use of Polimetrix for Wave 1 data collection was identified as a judicious use of resources that allowed the Network to oversample populations and complete data collection ahead of schedule. The Network has been resourceful by incorporating the recommendations of scientific advisors and future users. However, the success of the project will lie in the validation studies, the implementation of the CAT system, and the adoption of the PROMIS products by the clinical research community.

PROMIS represents a paradigm shift in how assessments for PRO are created and used in clinical research. A comprehensive source of validated items and assessments that measure PRO will be of great benefit to the clinical research community. In particular, the dynamic functionality of the CAT system is an exciting new feature. The Item Banks and CAT system represent much improvement over the use of assessments which focus on a single disease, are likely to be outdated, and/or are culturally irrelevant. Thus, the project is highly relevant and in a position to transform clinical research. It will be critical to have the project's tools and content freely and openly available to clinical researchers.

III.A. Conclusions

In response to the general questions that guided the Mid-Course Review, the Network is conducting the project as planned. The goals have not been modified. The mid-point goals have not only been achieved, but have been surpassed. Wave 1 data collection ended ahead of schedule and data analysis is nearing completion. The project is relevant and timely in terms of re-engineering the clinical research enterprise. The Review Panel recommendations in the next section are designed to support the initiative's continued relevance.

III.B. Recommendations

The Review Panel commends the Network on the progress and products to date. Once the project is complete, management of the PROMIS products must be accompanied by continuing research to ensure their dynamic viability.

III.B.1. Organization of the Network

Network organizational activities included the creation of a unifying structure for the individual grantees and the formulation of rules and processes for communication, collaboration, and decision-making. The Review Panel raised the following potential issues and offers recommendations for the Network to consider as the project progresses:

- ***Sustainability*** – If one of the PROMIS grantees leaves the Network, the success of the initiative could be compromised.

  Recommendation: The Network must ensure that a solid, dynamic infrastructure is in place as the PROMIS project continues development and operation.

- ***Contractor Advantage*** – Contractors or subcontractors currently involved with the initiative may appear to have an unfair advantage or conflict of interest in competing for future contracts.

  Recommendation: The SC should consider whether those currently working on the project should be allowed to compete for subsequent contracts.

III.B.2. Operations

Operational activities have included identification of the domains, items, and assessments, as well as methods for assessing their relevance and utility in a diverse population. Potential issues and recommendations for these areas are:

- ***Clinical Relevance*** – For the PROMIS Item Banks and items to retain clinical relevance, they must be dynamic and reflect changes in the environment that may render items obsolete or irrelevant.

  Recommendation: The Network should formulate a plan or process for ensuring the items remain up-to-date and clinically relevant.

- ***Sample Diversity*** – The lack of ethnic, minority, and educational diversity in the focus groups and cognitive interviews may affect widespread use of the Item Banks.

  Recommendations: The Network should develop a concrete plan for future testing which ensures greater ethnic, minority, and educational representation so the PROMIS products are generalizable.

III.B.3. Research

The Review Panel commends the Network on the detailed approach to validation of the Item Banks and offers the following recommendations.

- ***Item Validity –*** The Review Panel recognizes it is often difficult to prove that items are measuring what they are intended to capture and the respondents' understanding of an item is the same as the researcher's. This concept, content validity, must be assessed as the Item Banks are tested in additional chronic disease populations.

  Recommendation: The Network should continue testing the items and Item Banks in different chronic disease areas and ethnic groups to demonstrate their content validity. Moreover, the Network should conduct studies to help end-users interpret what the CAT-generated scores and changes in scores represent.

  Responsiveness to change must be demonstrated for the items and instruments to be considered useful.

III.B.4. Dissemination

Distribution of the Item Banks and CAT system strategies for dissemination, and ongoing development and maintenance are necessary steps to ensure long-term sustainability.

- ***Public Information Strategies –*** Dissemination of information about the project to potential users, and other groups, such as patient advocacy groups, may help to obtain funding and general support for the PROMIS products.

  Recommendation: The Network should consider its multiple constituencies in developing a comprehensive dissemination strategy for PROMIS. This will assist in long-term funding and maintenance of the Item Banks and CAT system.

- ***Presentation of Project Information –*** Dissemination of the Network methods and findings are key to its sustainability. However, it is important that the project is presented in the context of both its capabilities and limitations.

  Recommendation: The Network should have a process for ensuring presentations and publications do not overstate results, and they illuminate both strengths and weaknesses of the project.

Item Banks and Computer Software – The Network's research efforts and the PROMIS products are supported by public funds and public use. Thus, the items and software algorithms should be freely available to all potential users.

Recommendation: The Review Panel urges the Network to put the system software code, including item selection algorithms, into the public domain to facilitate widespread use by clinical researchers, institutions, and commercial organizations.

- ***Short Forms –*** If short forms constructed from the Item Banks contain items with high potential for variability across similar populations, the DIF impact could compromise their validity.

Recommendation: The Network should carefully consider what short forms will be constructed and how these will be used. Short form items should be selected to minimize the potential for DIF impact.

- ***Long-Term Support –*** The Review Panel raised concern over the long-term support of the project, including continued research and maintenance of the CAT system and Item Banks.

Recommendations: The Network should explore public-private partnerships to manage the long-term costs of maintaining the project. All potential partners should agree that the products of PROMIS should be freely available.

- ***Industry Acceptance –*** The Review Panel believes that the Network needs to explore strategies that will induce the clinical research industry, including pharmaceutical companies, to utilize PROMIS.

Recommendation: To gain the interest and acceptance of the biopharmaceutical industry, the Network must demonstrate that the PROMIS products can be used for multiple chronic disease populations, to capture adverse events, and to distinguish the effects of therapeutic response.

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APPENDIX 1: MID-COURSE REVIEW PANEL AND NIH SCIENCE OFFICERS

Mid-Course Review Panel

Lee S. Simon, M.D., Chair - Clinical rheumatologist and Associate Clinical Professor of Medicine at Harvard Medical School. Dr. Simon holds positions at New England Baptist Hospital and Beth Israel Deaconess Medical Center. He has experience working both with the Food and Drug Administration (FDA) and as a consultant to pharmaceutical companies and is a member of the American College of Rheumatology Committee to Re-evaluate Improvement Criteria.

Virginia S. Cain, Ph.D. - Director of Extramural Research at the National Center for Health Statistics at the Centers for Disease Control and Prevention. She is a specialist in survey research and social demography.

Sahar M. Dawisha, M.D. - Medical Officer for the FDA in the Center for Devices and Radiological Health (CDRH). She is a team member and the CDRH representative for the guidance the FDA provides to the clinical research community regarding the use of patient-reported outcome (PRO) measures.

Maria Orlando Edelen, Ph.D. - Assistant Professor in the Department of Psychiatry and Human Behavior at Brown University Medical School. She has research interests that include Item Response Theory (IRT) and quantitative modeling.

Donald C. Manning, M.D., Ph.D. - Anesthesiologist and Vice President of Clinical Research and Development for Celgene Corporation, a pharmaceutical company focused on developing therapeutics for cancer and inflammatory diseases. He maintains an adjunct appointment at the University of Virginia School of Medicine in the Department of Anesthesiology and Pain Management. His research interests include the use of PRO measures for chronic pain in clinical trials.

Clement McDonald, M.D. - Director of the Lister Hill Center at the National Library of Medicine, NIH. He has expertise in medical informatics and electronic medical record systems.

Albert Wu, M.D., M.P.H. - Professor of Health Policy and Management at the Johns Hopkins University Bloomberg School of Public Health. His research focuses on measuring PRO, quality of care and assessment of medical treatment effectiveness, particularly quality-of-life assessment in HIV patients.

NIH Science Officers

William Riley, Ph.D., NIH Chief Science Officer
National Institute of Mental Health

Susana Serrate-Sztein, M.D., NIH Project Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Susan Czajkowski, Ph.D.
National Heart, Lung, and Blood Institute

Lawrence Fine, M.D., Dr.P.H.
National Heart, Lung, and Blood Institute

Laura Lee Johnson, Ph.D.
National Center for Complementary and Alternative Medicine

Louis Quatrano, Ph.D.
National Institute of Child Health and Human Development

Bryce Reeve, Ph.D.
National Cancer Institute

James Witter, M.D., Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases

APPENDIX 2: PROMIS NETWORK COMMITTEES

Participation and Data Monitoring Committee – develops enrollment protocols; ensures representative samples and high response rates; monitors compliance with Institutional Review Boards (IRBs) and the Health Insurance Portability and Accountability Act (HIPAA) regulations; develops audit checks and quality assurance processes; coordinates and collects standardized data from PRS and the SCC; develops performance criteria measures for reviews of individual awardees; and recommends corrective actions for above listed activities.

Intellectual Property Committee – evaluates intellectual property concerns, including copyright, trademark, and other patent issues related to items drawn from existing instruments; manages the involvement of legal counsel; and explores and advises the Network regarding public-private partnerships.

Outreach/End-Users Subcommittee – develops strategies, activities and materials to maximize adoption of PROMIS deliverables; develops educational and instructional materials for products; and organizes presentations and solicits feedback from clinical researchers.

Publications Subcommittee – oversees approval and dissemination of all publications; recommends policy for review and approval of presentations and publications; and evaluates requests for access to data.

Executive Committee –develops initial recommendations to the SC regarding timelines; prioritizes tasks; organizes workgroups; develops meeting agendas; and acts on behalf of the SC on matters that do not require full deliberation.