ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

The International Society for CNS Clinical Trials and Methodology, ISCTM, welcomes the opportunity to provide comment on the ***HL7 Version 3*** **Domain Analysis Model for Generalized Anxiety Disorder**. The ISCTM was chartered in the fall of 2004 as an international society charged with providing a commercial free forum where key stakeholders from academia, industry and regulatory branches can discuss/resolve challenges specific to the design and methodological issues in CNS clinical trials. Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance.

For this response, the group has provided general comments and recommendations regarding the inclusion of scales/questionnaires in *Generalized Anxiety Disorder Data Standards.* Because ISCTM commented on the suicidality related data elements in the previous bipolar data standards document we did not include that material in this review.

Below please find contributors to the ISCTM Working Group on Generalized Anxiety Disorder Data Standards. As shown by affiliations, the group includes individuals from both industry and academia.

Chair: Nicholas DeMartinis, MD, Pfizer
Lawrence Adler, MD, University of Maryland School of Medicine
Chris Brady, PsyD, inVentiv Health
Larry Brownstein, MBA, AiCure
Alvaro Camacho, MD MPH, University of California, San Diego
William Lenderking, PhD, Evidera
Rick Mofsen, BS, Thievon-Wright Consulting
Russell Reeve, PhD, Quintiles
Sudhakar Selvaraj, MBBS., DPhil (PhD), MRCPsych, University of Texas Health Science Center at Houston
Janet Williams, PhD, MedAvante
Joyce Tsai, PhD, Sunovion
Monika Vance, MBA, Santium

Carlotta McKee, Executive Director
P.O. Box 128061 Nashville TN 37212
Telephone: +1-615-383-7688
Email: isctm@isctm.org - Website: http://isctm.org

Dawn Velligan, PhD, UTHSCSA
Antonio Vita, MD, PhD, University of Brescia
Jun Zhao, PhD, AbbVie

HL7 Version 3 **Domain Analysis Model for Generalized Anxiety Disorder**

General Comments
We applaud the HL7 process as an essential step leading to an interoperable medical record serving clinical, research and regulatory needs. Most of the fields are acceptable as currently defined. There was some concern regarding mixed references to DSM-IV and DSM-5 across a number of the data elements that may pose a challenge to aggregating data. While we note the addition of a specific data element specifying the diagnosis coding source (835), we recommend that symptom specific data elements reference DSM-5 rather than DSM-IV since that is the psychiatric diagnostic system moving forward. We recommend harmonizing variable definitions with international standards such as ICD 10 as much as possible. We recommend that the cognition assessments listed in this document be made consistent with those listed for depression studies wherever possible, given the substantial overlap in prevalence and phenomenology between the two disorders.
Class Diagram (p. 6)
Mental health GAD specific elements: We recommend revising reference to DSM-IV diagnostic axes to current DSM-5. We also recommend consideration of separating the Child/adolescent information from the adult information, since the focus of clinical trials will be limited to either the adult or child populations, and the child-related characteristics have substantial differences. Generalized anxiety disorder prior treatment: it should be clarified whether prior combination therapy indicator references medication combinations or a combination of medication with nonpharmacologic treatment. Mental health history summary: includes item for age at first treatment for any psychiatric illness, but does not appear to include specifier for the type of psychiatric illness associated with onset at that age. If this specifier is not addressed by other elements of the class model, this should be added.
Activity Diagram

10. Suitability Assessment for Clinical Study: The PANSS is cited incorrectly, and the acronym misspelled. The instrument is the Positive and Negative Syndrome Scale (Pages 31 and 65).

29. Formal Psychiatric Diagnosis/Diagnoses: The statement that "one diagnosis is given to each patient, no matter how many psychiatric disorders the patient may suffer" to does not appear to accurately reflect the approach to diagnoses is DSM-5; patients may be given as many diagnoses as needed to describe their clinical picture.

Clinical Scenarios

In general, the clinical scenarios were judged to be excellent and challenging, and the majority of relevant issues were well-illustrated.

We suggest revising case subject names to be ordinary/neutral rather than playful; while well-intentioned, the latter is not deemed appropriate given the negative impact of anxiety disorders on patients.

We suggest adding a case presentation for a subject who arrives at a clinical trial center in response to advertising for a GAD study; include scenarios for a subject that does not qualify and needs referral, as well as subjects that successfully complete a study and require referral for further treatment/ follow-up.

A few specific comments have been included in the text of the attached Clinical Scenarios for consideration.

V3_DAM_GAD_R1_I1
_2016SEP_DAM-Clinic

Feedback on List of Scales:

General: It would be useful to separate the list into classed of assessments, such as scales that are used only in special populations (Child-adolescent for example), functional outcomes, cognition assessments, etc.

Anxiety: the GAD7, the Beck Anxiety Inventory (BAI), and the Patient Health Questionnaire (PHQ)/PRIME-MD (particularly useful in primary care settings, assesses depression symptoms as well)

Depression: the Inventory of Depressive Symptoms (IDS), the Quick Inventory of Depressive Symptoms (QIDS), and the Geriatric Depression Scale (to complement inclusion of the Geriatric Anxiety Scale)

General: The Symptom Checklist-90 (SCL-90)

Cognition assessments: It is not clear why the specific set of cognition assessments included in the list of scales were selected.

Carlotta McKee, Executive Director
P.O. Box 128061 Nashville TN 37212
Telephone: +1-615-383-7688
Email: isctm@isctm.org - Website: http://isctm.org

It is recommended that the digit symbol substitution task (DSST, also known as Digit-Symbol-Coding) be added to the scales list in the place of (or, less preferred, in addition to) the existing Symbol Digit Substitution Test version of this task.

We note that these similar tasks are frequently intermixed in discussions; the recommended DSST assessment requires participants to write down a symbol that matches the corresponding digit listed in a key at the top of the assessment. This version of the task has been more commonly used in depression studies, and it fulfills a second key recommendation that the cognition assessments listed in this document be made consistent with those listed for depression studies wherever possible given the substantial overlap in prevalence and phenomenology between the two disorders.

In the service of that objective, additional cognition assessments recommended for the list of scales include the Trail Making Test (A and B), digit span, and the Stroop task.

The MMSE is was judged unlikely to be useful in most GAD studies, since it is sensitive only to relatively severe cognitive impairment, and the addition of an alternative such as the MOCA was suggested. The MMSE could be retained for use in elderly populations.

Specific Comments and Recommendations

DE ID	Item	Comment
501	Difficult to Control Worry Indicator (DSM IV)	DSM IV is considered outdated; since this item is identical in DSM-IV and DSM-5, either the reference to DSM-IV should be removed, or reference to both diagnostic systems should be included
504-506	Trembling, twitching, shakiness [Features Associated with Muscle Tension Indicator]	Consider collapsing features associated with muscle tension into a single data element, as it is included in the list of GAD symptoms in data element 503, and it is unclear whether these three variants demonstrate sufficient clinically meaningful differences to warrant maintaining them as separate data elements
507	Autonomic Feature(s) Hyperarousal Symptoms	Suggest that the definition statement references 'arousal' and not include the word 'tension', which is not judged to be the same construct as hyperarousal from a clinical perspective. It was also noted that there are three specific tension data elements already (504, 505, 506). Consider including additional symptoms of hyperarousal including sweating, flushing,
514	Other Stress Conditions	This item was judged to have limited usefulness because it is nonspecific, and permissible answers are limited to yes, no, or unknown. In order for this item to be useful, it would be preferable to have general categories of physical characteristics

Carlotta McKee, Executive Director
P.O. Box 128061 Nashville TN 37212
Telephone: +1-615-383-7688
Email: isctm@isctm.org - Website: http://isctm.org

		associated with worry or stress to select rather than the current permissible answers.
517	Amount of time Missed Work or School due to Illness	The current permissible value with units of days was judged to be less useful than it could be; specifying a time period would increase the usefulness of this data element, such as days per month, or days in the last six months (which links to duration requirement for GAD diagnosis). It is also recommended that the word 'school' be added to the current definition text, which only includes the word 'work'.
527	Remission Specifier	Providing a definition of partial remission may increase the consistency of data generated with this data element (e.g. partial remission refers to clinically meaningful decrease in anxiety symptoms. Reviewers also commented that the basis for the specified two months duration should be rigorous and well accepted.
837	Duration of illness	This element definition appears to have been revised since the review of the bipolar disorder data standard. The current definition is improved, but it should be recognized that use of the 'first treatment start date for a diagnosis' as a reference for onset of illness for a frequently chronic condition like GAD may underestimate the true duration of illness due to lack of recognition of illness for a substantial period of time prior to first treatment. An alternative should be considered that would also utilize subject description of the onset of symptomatic interference with functioning, in addition to the current text in the definition.
717	Study Remission Indicator	Consider where there is a need for a data element for partial remission, either separate from this data element, or as a permissible entry.'

Carlotta McKee, Executive Director
P.O. Box 128061 Nashville TN 37212
Telephone: +1-615-383-7688
Email: isctm@isctm.org - Website: http://isctm.org