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 Bipolar 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 *Bipolar Disorder Data Standards.*

Below please find contributors to the ISCTM Working Group on Bipolar Disorder Data Standards.
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***HL7 Version 3* Domain Analysis Model for Bipolar 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. We are concerned about variable definitions which represent a composite criteria (such as the DSM criteria for mania) when the permissible values are only Yes or No. Since permutations and combinations of many symptoms satisfy such variables, aggregation of disparate data under the same definition will undermine the utility of the data set. In addition since the DSM criteria continue to evolve, composite variables that reference the DSM diagnostic criteria seem parochial and are certain to be become outdated. We recommend harmonizing variable definitions with international standards such as ICD 10 as much is possible. This might be accomplished by defining raw variables (such as the items in a rating scale for agitation, irritability or insomnia) which can in turn be specified in the definition of derived variables (DSM 5 criteria for major depression with mixed features). We are not clear about your purpose in listing specific rating scales. If the intent is to provide a standard set of acceptable measures, we would prefer to see the list expanded to include all measures in studies of bipolar disorder submitted to clinical trials.gov. If, however, the intent is to provide a list of commonly used scales so that researchers can draw on the fields defined in those scales, we recommend the inclusion of scales covering additional domains considered important to bipolar disorder (Neurocognitive, sleep measures, social functioning, protective factors, etc.)

Specific Comments and Recommendations		
DE ID	Item	Comment
4	DSM-IV Diagnosis Axis	DSM IV is considered outdated. Relevant information captured in other data elements with more specificity

5	Diagnosis	Make ICD codes permissible
226	Diagnosis coding source	List non-DSM sources
2	Primary diagnosis indicator	Add method of ascertainment or consider dropping
7	Diagnosis Date	Renaming variable as "Assessment date" would add clarity
230	Duration of illness	Often unreliable. Consider using date of first formal Dx and leverage ongoing calculations of time spans; depending on purpose. The text “This data element may be derived from the first treatment start date for a diagnosis and the current date.” Is problematic because in many cases the diagnosis may be based on recollections of events many years before the first actual BP episode or treatment not prescribed by physicians or not started by the patient. Diagnosis made on this basis is far less reliable than contemporaneous assessments and should not be aggregated with assessments of higher reliability.
81	Diagnosis clinical relevance indicator	This is a very vague and often unreliable concept. At a minimum, criteria should be provided defining what constitutes clinical relevance.

227	With Anxious Distress Indicator	Definition need not be tied to DSM 5. It would be preferable to code the symptoms that are present with sufficient severity to count toward the diagnosis.
300	Bipolar with mixed features indicator	Definition need not be tied to DSM 5. It would be preferable to code the symptoms that are present with sufficient severity to count toward the diagnosis. This might done by creating a coding convention for all mood episodes: a three place decimal xxx.000- xxx.999 where the first decimal place is the number of symptoms meeting criteria for depression, the second decimal place is the number of symptoms meeting criteria for hypomania/mania, and the last is the number of symptoms common to both mania and depression.
312	Relative timing of manic episode	We appreciate this idea, but worry about the reliability and practicality of pattern identification. Many manic /

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		hypomanic episodes may go un-diagnosed prior to initial diagnosis.
316	Frequency of bipolar disorder episodes in past 12 months	Counting episodes is inherently unreliable. We suggest clarifying whether full and/or truncated episodes can count and what duration of recovery is required for two occurrences of the same polarity to be counted as separate episodes. For instance, how many episodes should be counted for a sequence in which the patient experiences two weeks of depression followed by 2.5 weeks of euthymia, and two weeks of depression?
317	Mood or behavior incidents between bipolar disorder episodes	The purpose of this variable is unclear to us. Is the intent to characterize mood and behavior during periods of euthymia? Without clear definitions and reference to specific time frames, it would be better to drop this variable.
318	Development of Psychotic Symptoms Following Previous Non Psychotic Episode Indicator	To clarify whether this refers to a subsequent mood episode with psychosis or the occurrence of psychotic symptoms in the absence of a mood episode. If the latter, we suggest capturing the duration of the euthymic interval before and after the psychotic symptoms.
204	Catatonic feature specifier	We prefer an indication of the particular symptoms of catatonia that are present rather than yes/no to the specifier. Redefine as a derived variable
205	Melancholic feature specifier	We prefer an indication of the particular symptoms of melancholia that are present rather than yes/no to the specifier. Redefine as a derived variable
214	Atypical feature specifier	We prefer an indication of the particular atypical symptoms that are present rather than yes/no to the specifier. Redefine as a derived variable
221	With postpartum onset specifier	We prefer an indication of the particular symptoms that are present rather than yes/no to the specifier. Redefine as a derived variable
227	With peripartum onset indicator	We prefer an indication of the particular symptoms that are present rather than yes/no to the specifier. Redefine as a derived variable

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322	Hallucinations indicator	Requires a timeframe (this minute, this hour, this day this week, this episode??)
323	History of hallucinations indicator	Indication of the ascertainment method would be helpful
324	Delusions indicator	Requires a timeframe (this minute, this hour, this day this week, this episode??)
325	History of delusions indicator	Indication of the ascertainment method would be helpful
222	Seasonal pattern of recent episodes	We prefer an indication of the particular elements of the pattern that are present rather than yes/no to the specifier. Redefine as a derived variable
83	Age of onset	We preferred this to be a derived variable. The ascertainment method should be indicated.
14	Past 24 months number episodes	Counting episodes is inherently unreliable. We suggest clarifying whether full and/or truncated episodes can count and what duration of recovery is required for two occurrences of the same polarity to be counted as separate episodes.
109	Previous episodes indicator	For bipolar patients, it would be best to separately indicate prior episodes of each polarity
113	History of suicide attempts indicator	Definition should read: “Indicates that the patient has made at least one suicide attempt at any time in the past.”
355	Suicide intent classification	Assessment required for this classification is particularly difficult with psychotic patients.
50	Lifetime number of law enforcement arrests	Ask separately for events related to depression and events related to hypomania/mania
332	School truancy during mental health episode indication	Ask separately for events related to depression and events related to hypomania/mania
333	School failure during mental health episode indication	Ask separately for events related to depression and events related to hypomania/mania

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334	Occupational failure during mental health episode indication	Ask separately for events related to depression and events related to hypomania/mania
335	Divorce/relationship failure associated with the mental health episode	Ask separately for events related to depression and events related to hypomania/mania
336	Antisocial behavior associated with a mental health episode indicator	Ask separately for events related to depression and events related to hypomania/mania
337	worsening or ongoing symptoms due to premenstrual. Indicator	Ask separately for events related to depression and events related to hypomania/mania
338	relatives and friends troubled by hypomanic episode indicator	"Concerned" and "troubled" have different connotations. This variable needs better definition especially since the presence of these concerns is an indicator of impairment, which is the distinguishing characteristic of mania.
339	Prior mood stabilizer drug therapy indicator	The term mood stabilizer is commonly used but problematic. Better to ask about specific medications and treat mood stabilizer therapy as a derived variable.
240	number of prospective drug trial failures	Please expand the permissible values beyond 0, 1, and 2. Consider permissible as zero, one, two, three, four, five or more.
34	First episode indicator	The reliability of designating the current episode as the first lifetime episode is particularly difficult in the case of hypomania/mania. We believe for bipolar disorder it would be best to create a derived variable based on asking separately about prior occurrences of depression and abnormal mood elevation.
345	Response/stability indicator	We understand standard definitions for response, but are not aware of any accepted standard definitions for "stability".
131	Treatment changed for worsening psychiatric symptoms indicator	This would be better asked separately for somatic vs. psychosocial treatments.
67	Daily living situation	Add incarceration to permissible values

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352	Bipolar full remission indicator	Need to identify source. Lack of indication could just mean no record available rather than a data point supported by a formal assessment
Add	Current Clinical Status	This variable was used in STEP-BD to assign a current week status based 8 mutually exclusive clinical statuses to the current week assessment: Permissible values: (Pure full Syndromic States) Depressed, Manic, Hypomanic, (Euthymic states) Recovered (8 Consecutive weeks with euthymia), Recovering (Euthymic < 8 weeks), (Subsyndromal States) Continued Symptomatic (partial remission, without meeting criteria for "recovered".), Roughening (≥2 new symptoms after meeting criteria for recovered). We recommend expanding permissible values to include mixed features: (Full Syndromic States with Mixed Features) Depression with Mixed Features, Manic with Mixed Features, Hypomanic with Mixed Features
Add	Duration of Bipolar Recovery	Indicating the duration a period full remission from both depression and Hypomania/mania
Add	Worsening or Ongoing of Symptoms Due to illicit drug use, substance or alcohol abuse	Worsening or Ongoing of Symptoms Due to illicit drug use, substance or alcohol abuse Permissible values
Add	Presence of suicidal ideation:	Suicidal Ideation: A desire or wish or need or preference to be dead or a thought about being dead in relation to another experience of suicidality or a thought to hurt, harm, or injure oneself with the intent or awareness that one could die as a result or any

		strategizing for or accounting of or thought(s) of future action(s) for suicide attempt (including thoughts to make a plan). The ideation may concern but is not limited to, the method, the means, the location, the date, and/or any unfinished tasks. Permissible values: Medical history, structured interview. Coded as: 1. Yes, current/recent (< 24 months); 2. Yes, past (>24 months); 3. No; 4. Undetermined/unknown
Add	Occurrence of suicidal behavior	Suicide behavior: Any (set of) behavior(s), either incomplete or completed, that are either 1) not viewed by the patient to be potentially lethal and stop short of taking action on a suicide attempt, but assist the patient in preparing to take action on a suicide attempt, or 2) perceived by the patient to be potentially lethal, connected with any level of intent to die, that does not result in a fatality, or 3) a fatality clearly and confidently (evidence is beyond any reasonable doubt) caused by self-injurious or purposely reckless or negligent behavior that is connected with any level of intent to die as a result of said self-injurious or purposely reckless behavior. Permissible values: Medical history, structured interview. Coded as: 1. Yes, current/recent (< 24 months); 2. Yes, past (>24 months); 3. No; 4. Undetermined/unknown
Add	Occurrence of suicide attempt	Suicide attempt: Any (set of) behavior(s), either incomplete or completed, perceived by the patient to be potentially lethal, connected with any level of intent to die that does not result in a fatality. The behavior may not result in any actual harm to the patient. The (set of) behavior(s) may be or may be not complete due to an interruption by events outside of the patient's body or existence, or may be incomplete due to the patient aborting the already started, perceived lethal behavior(s)

		before it (they) are fully executed. The intent to die can be inferred by a reasonable group of experts, but should not be assumed without compelling evidence. Permissible values: Medical history, structured interview. Coded as: 1. Yes, current/recent (< 24 months); 2. Yes, past (>24 months); 3. No; 4. Undetermined/unknown

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