The International Society for CNS Clinical Trials, ISCTM, welcomes the opportunity to provide comment on the ***HL7 Version 3*** **Domain Analysis Model for Major Depressive 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 *Major Depressive Disorder Data Standards.*

Below please find contributors to the ISCTM Working Group on Response to *Draft Domain Analysis Model for Major Depressive Disorder*
Chair: Andrei Pikalov, MD, PhD, Sunovion
Munaf Ali, PhD, Munaf Ali Consultancy
Theresa Bromley, PhD, e Pharma Solutions
Brian Dirks, MD, Shire
Richard Keefe, PhD, Duke University
Justine Kent, MD, Janssen
Thomas Laughren, MD, Laughren Psychopharm Consulting
Atul Mahableshwarkar, MD, Takeda
Gary Sachs, MD, Bracket
Joyce Tsai, PhD, Sunovion

HL7 Version 3 **Domain Analysis Model for Major Depressive Disorder**

General Comments
We recommend adding a requirement for functional outcome measures in MDD studies. Rationale: Improvement in occupational and/or social function does not strictly correlate with improvement in depressive symptoms. Recommendations: • Include global assessments (CGI-Improvement, CGI-Severity), which would include all aspects of patient function as well as symptoms • Include functional outcome measure, e.g. Sheehan Disability (SDS), World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS) • Include a quality of life assessment, e.g. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Euro Quality of Life 5 Dimensions and 5 Levels (EQ-5D-5L)
We recommend to add depression rating instruments (for adults): Clinician-Rated:

- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hamilton Depression Rating Scale (HAMD)
- Inventory of Depressive Symptomatology, 30-items (IDS-C_{30})

Patient Self-Rated:

- Inventory of Depressive Symptomatology, 30 items (IDS-SR_{30})
- Quick Inventory of Depressive Symptomatology, 16 items (QIDS)
- Beck Depression Inventory-II

Specific Comments

Page	Item	Comment
8	Suitability Assessment	Replace "Positive and Negative Symptoms of Schizophrenia scale PANSS" with "Hamilton Depression Rating Scale, HAMD; Montgomery–Asberg Depression Rating Scale, MADRS"
12	Preliminary Assessment	Replace "Mini-mental Status Exam" with "Mini-International Psychiatric Interview"
20	Drug Monitoring	There needs to be a way to distinguish treatment failure from inadequate response after an antidepressant trial of adequate dose and duration. Rationale: • In clinical practice the decision of whether to switch vs. add an adjunctive treatment may be based upon whether the current treatment failed or whether the patient had a partial, though still inadequate, response • In acute treatment studies, having two previous treatment failures is a common exclusion criterion, but partial responses that remain inadequate may not be exclusionary • For adjunctive treatment studies, having two inadequate responses to previous treatment may be an inclusion criterion, but several treatment failures may be exclusionary Recommendation • To quantify degree of patient response in some way • In the context of prospective treatment during a clinical study utilizing one of the recommended depression rating scales listed under "General Comments" above, quantitative response data are available. The recommended scales allow response to current treatment to be expressed as a % improvement from baseline • A clinician-rated global assessment of improvement (CGI-I) will be useful as an independent measure of clinically meaningful global improvement
21-26	MDD diagnosis	Some specifiers are DSM-IV terms, e.g. "Post-partum" is now "peri-partum" in DSM-5
32	History of Somatic therapy	Consider including Deep Brain and Vagus Nerve Stimulation on this list
32	History of Antidepressant Treatment	Comments to Drug Monitoring are also relevant here: Need to distinguish whether previous antidepressant trials were adequate in dose and duration, and if so, whether they were

		successful, resulted in partial response or treatment failure. Again the recommendation is to quantify response in some way, and in cases where prior patient response information was not captured quantitatively; options include: • A validated patient self-rated questionnaire is the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ) • Assignment of a CGI-I score based on patient interview regarding historical treatment response
34	MDD History	Remove references to schizophrenia episodes; replace with reference to depressive episodes
35	Medical History	Recommend addition of data elements to collect female menstrual/reproductive history, history of hormone-based therapy use, and any temporal relationship with depressive episodes. Rationale: • Info may be useful in subsequent exploratory analyses • Allows determination of menstrual status as a variable affecting treatment response Recommended Questions 1. Menstrual history • Age at first menstrual period • Date of first day of last menstrual period 2. Current childbearing potential: Yes/No • If Yes ○ Does patient have regular menstrual cycles, approximately once per month? ○ Does patient have history of worsening in relation to luteal or premenstrual part of the cycle? • If No (at least 1 year since last menstrual period) ○ If natural menopause: age at last period ○ If surgical: age at surgery, date of surgery, whether ovary-sparing hysterectomy, or bilateral oophorectomy • Presence of perimenopausal symptoms: Y/N ○ Whether current presence of hot flashes, insomnia, mood swings, vaginal dryness ○ Duration since onset of symptoms ○ If hot flashes: intensity, interference with sleep (each rated mild/mod/severe) ○ If interference with sleep: mild, moderate, severe interference 3. Childbearing history • Number of, and age at, pregnancies ○ Completed pregnancies ▪ Whether associated with worsening of mood: yes/no

		▪ If yes, during pregnancy or post-partum ○ Miscarriages ○ Abortions 4. History of current and previous hormone use (including both prescription and over the counter supplements): list each by medication name, preparation type (e.g. pill, patch, topical cream/gel, vaginal ring, vaginal cream, IUD) whether currently used, start/stop dates, duration of use, last dose change, whether associated with mood change • Hormone-based contraceptives ○ Estrogen dose (if applicable) ○ Progesterone dose (if applicable) • Hormone replacement ○ Estrogen dose (if applicable) ○ Progesterone dose (if applicable) • Testosterone, DHEA, or methyltestosterone • Thyroid hormone augmentation
Editorial Comments		
18, 22, 23, 81, 82		Replace “DSM-IV” or “DSM-IV-TR” with “DSM-5” throughout
19	Data Elements Table	…at least one seizure ~~have~~ has occurred…
30	Mental Health Hosp	… of asked directly of patients ~~of~~ or their proxy

Carlotta McKee, Executive Director
P.O. Box 128061 Nashville TN 37212
Telephone: +1-615-383-7688 - Fax: +1-615-296-0454
Email: isctm@isctm.org - Website: http://isctm.org