The International Society for CNS Clinical Trials, ISCTM, welcomes the opportunity to provide comment on the ***FDA Draft Data Elements for Schizophrenia***. 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 chose to focus on general rather than specific comments, however, the group plans to reconvene to review and provide more detailed response during the January comment period.

ISCTM Working Group on Response to FDA Draft Data Elements for Schizophrenia
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ISCTM General Comments on the Data Elements List:

1. The needs of different trial designs (i.e. short-term, long-term, maintenance, adaptive, monotherapy, adjunctive therapy, pragmatic, explanatory, evaluation of cognition or negative symptoms change, subpopulation groups, etc) are not met by this document. We suggest that branching points be added to the ballot to accommodate inherently different trial designs and efficacy outcomes necessitated by fundamentally different endpoints.
2. The inclusion of a specific scale into a trial should not be mandated.
3. The validation status of the outcomes scales recommended for the inclusion into Data Elements should be documented. This would necessitate some standard categorization of validation that might be done, etc, inter-rater reliability, construct validation, convergent validation, etc.
4. The addition of list scales and assessments acceptable for use as potential data elements is suggested.
5. Data elements should be categorized as recommended/required or optional.

patients with schizophrenia should be added (i.e. metabolic syndrome status, measures of glycemic control, HOMA-IR, etc.)

7. Optional data elements that reflect the general medical preexisting conditions (i.e. diabetes, dyslipidemia, cardiovascular disease, etc.) should be included.
8. Optional data elements for pharmacokinetic assessment should include a recommendation for dose history and timing of sample relative to last dose.
9. Optional data elements that reflect if and how suicidal ideation and behavior will be assessed and captured should be included.
10. The patient recruitment flow chart should capture all sources of patients likely to be used in clinical studies (i.e. database, advertising, web-based recruitment, etc.);
    a. As data and quality of requirements is likely to be different for subjects coming from a variety of sources
11. A glossary of terms used in any final Data Elements document should be developed (i.e., definition of terms like 'episode,' 'hospitalization,' that may be ambiguous) to avoid any possible misinterpretations. All terms should be appropriate to use in a global context.
12. ISCTM suggests that Data Elements should not be constrained by the diagnostic framework of DSM or any other single diagnostic system. This will accommodate the need for other diagnostic approaches, including research criteria that may be necessary in different settings or trials (as in pragmatic trials). This approach also accommodates the evolution in standardized diagnostic criteria such as DSM-V, and others that will occur over time.

<u>ISCTM suggests that the following specific optional data elements could include the following:</u>

Informed consent
Genetic informed consent
Prior/concomitant medication list

Clinical and Laboratory Evaluations:
Medical history
Psychiatric history/mental status
Diagnostic confirmation (i.e. MINI, SCID)
Physical examination
Vital signs
Weight and body mass index (BMI)
Waist circumference measurement
Electrocardiogram
Hematology, chemistry, and urinalysis
Serum thyroid-stimulating hormone (TSH)
Serum prolactin
Glycosylated hemoglobin (HbA1c)
Glucose and lipid panel
Hepatitis screening
Serum insulin and C-reactive protein
Rapid Plasma Reagin (RPR) test
Serum follicle-stimulating hormone (FSH)
Serum human chorionic gonadotropin (β-hCG)
Blood sample for genetic analysis

Blood sample for study drug concentration
Urine drug screen
Urine β-hCG
Adverse event (AE) monitoring
Barnes Akathisia Scale (BAS)
Abnormal Involuntary Movement Scale (AIMS)
Simpson-Angus Scale (SAS)
Positive and Negative Syndrome Scale (PANSS)
Clinical Global Impression – Severity Scale (CGI-S)
Montgomery-Asberg Depression Rating Scale (MADRS)
CDSS
Cognitive testing including:
    Performance Batteries:
    CogState Computerized Cognitive Battery
    CDR Battery
    CNS VitalSigns
    MATRICS Consensus Cognitive Battery (MCCB)
    Brief Assessment of Cognition in Schizophrenia (BACS)
Interview-based Measures of Cognition, including:
    Schizophrenia Cognition Rating Scale (SCoRS)
    Cognitive Assessment Interview (CAI)
Performance-Based Skills Assessment (UPSA)
Negative Symptom Assessment Scale (NSA-16)
Quality of Well-being Scale – Self Administered Version (QWB-SA)
Additional tools to evaluate quality of life and functional PROs
Health Care Resource Utilization Questionnaire
Medication Satisfaction Questionnaire (MSQ)
Columbia Suicide Severity Rating Scale (C-SSRS)

ISCTM suggests that the following inclusion/exclusion criteria (currently utilized in the short-term schizophrenia efficacy trials) be considered as optional data elements. These are illustrative of the expanded data set needed to accommodate the inclusion/exclusion criteria for all types of clinical trials:

Inclusion Criteria

1) Subject agreed to participate by providing written informed consent.
2) Age
3) DSM-IV-TR criteria for a primary diagnosis of schizophrenia (including disorganized (295.10), paranoid (295.30), and undifferentiated (295.90) subtypes as established by:
- clinical interview
- Mini-International Neuropsychiatric Interview
- diagnostic interview
- DSM-IV-TR and duration of illness (i.e. greater than one year)

4) acute exacerbation of psychotic symptoms and marked deterioration of function or duration of stable period (for maintenance studies)
5) PANSS total score ≥ XX at Screening and Baseline
6) CGI-S > XX at Screening and Baseline.
7) Negative test for selected drugs of abuse at Screening and Baseline.

9) Agreement to remain abstinent or use adequate and reliable contraception throughout the study
10) Discontinuation of prior antipsychotic medication for the duration of the study.
11) Stable living arrangement
12) Good physical health
13) Ability to comply with the protocol
14) Acceptable for the protocol concomitant medications

Exclusion Criteria

1) Clinically significant medical illness that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study.
2) Condition that could interfere with absorption, distribution, metabolism, or excretion of medications.
3) History of malignancy
4) History of neuroleptic malignant syndrome.
5) Evidence of severe movement disorder.
6) Imminent risk of suicide or injury to self, others, or property.
7) Clinically significant history of alcohol abuse/alcoholism or drug abuse/dependence within the last XX months.
8) Type 1 diabetes
9) Abnormal laboratory parameter that indicates a clinically significant medical condition
10) Abnormal electrocardiogram
11) Body mass index (BMI) > XX
12) History of hypersensitivity to more than 2 distinct chemical classes of drug or to the study medication
13) Treatment resistant to the class of studied medication (i.e. neuroleptic), for regular trials (might be different for treatment resistant studies)
14) Treatment refractory psychosis
15) Electroconvulsive therapy treatment within the XX months prior to randomization
16) Subject was currently participating or had participated in a study with an investigational compound or device within 90 days prior to signing the informed consent. Subject had participated in three or more studies with an investigational compound or device within 12 months