CSS recommendations for identification and tracking of abuse-related adverse events during clinical drug development

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Dissecting Signals of Potential Abuse-Related Adverse Events

- Evaluate AE profile (MedDRA) from clinical trials for a signal of abuse potential
- Euphoria-type AEs: including euphoria, euphoric mood, elevated mood, mood altered, feeling drunk, feeling abnormal and hallucinations (visual & auditory)
- Inappropriate affect: inappropriate exhilaration, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation

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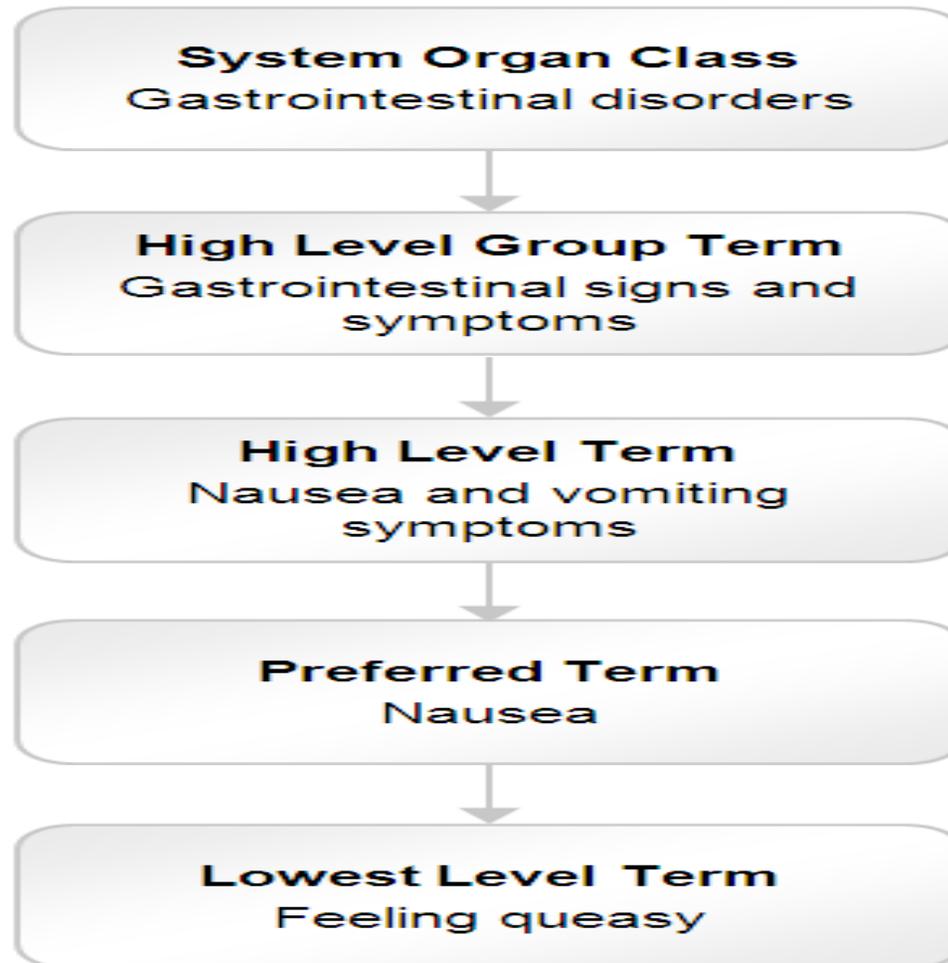
MedDRA Hierarchy

Coding and Manipulation of Adverse Events

- Use standard coding dictionary (MedDRA) to code verbatim AE terms across the entire pooled safety database.

    - Specify version of coding dictionary used.

    - Code all levels of the coding hierarchy (e.g., lower level term, preferred term, high level term, high level group term, system organ class).

- Verbatim terms should be similar/identical to the original term recorded by the clinical investigator. .

- Use statistical software, such as JMP, to confirm the prevalence of AEs once the accuracy of coding is assured.

- Review of narrative summaries is critical, especially for coding.

- Try to make sure AE is not from another drug or from a drug-drug interaction

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Proposed Query to Capture Signals of Potential Abuse-Related Adverse Events

Euphoria-related terms:

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Feeling high

Proposed Query to Capture Signals of Potential Abuse-Related Adverse Events

Dissociative/psychotic terms:

- Psychosis
- Aggression
- Confusion and disorientation

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

- Somnolence
- Hyper/hypo activity
- Mood disorders and disturbances
- Mental impairment disorders
- Drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders

Other:

- Medication tampering

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SMQs

Standardized MedDRA Queries (SMQs) are groupings of terms related to a defined medical condition or area of interest. They are intended to aid in medical event case, signal, and trend identification. Examples for abuse in the most recent MedDRA Version include "SMQ Drug Abuse and Dependence" and "SMQ Drug Withdrawal."

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Narrative Summaries

- Detailed descriptions of abuse–related AEs are critically important.
- Identify AEs that lead to drug discontinuation
- Details are necessary for an adequate understanding and coding of the AE experienced.
- For subjects who've experienced multiple AEs, a single narrative summary that incorporates all AEs is the best way to captures how they occurred.
- Validate coding before manipulation of data.

Drug Class Effects

If a new drug is a member of a known and existing drug class:

- AE's that are typical of members of that class should be prospectively monitored & assessed for the new drug.

- AE incidence rates for the new drug and the older members of the class should be compared.

- These AE's may need to be monitored post-marketing.

Organization of Data

- Tabulations for SAEs, AEs of special interest and all AEs (regardless of severity)

- Identify abuse-related AEs as well as those suggesting dependence upon withdrawal of drug (abrupt discontinuation of drug not always possible)

- Pool all trials and also examine trials individually.

- Relationship between dose or exposure and AE frequency and time of occurrence should be explored

- Support or refute causality or relationship to abuse

- Look for significant difference between drug and placebo incidences and/or a dose-response relationship

Euphoria and Other Adverse Events

Subj No	Treatment	Verbatim	PT	Severity
1	Placebo	Euphoric	Euphoric mood	Mild
2	15 mg	Euphoria	Euphoric mood	Mild
3	15 mg	Feeling dazed	Feeling abnormal	Mild
4	15 mg	feeling of euphoria	Euphoric mood	Mild
		slow thinking	Bradyphrenia	Mild
5	15 mg	euphoria	Euphoric mood	Mild
6	15 mg	euphoric	Euphoric mood	Mild
7	15 mg	feeling floaty	Feeling abnormal	Mild
8	40 mg	Euphoria	Euphoric mood	Mild
9	40 mg	feeling high	Euphoric mood	Mild
10	40 mg	feeling loopy	Feeling abnormal	Mild
11	40 mg	buzzed	Feeling abnormal	Mild
		feeling off	Feeling abnormal	Mild
		smiley	Euphoric mood	Mild
12	40 mg	Euphoria	Euphoric mood	Mild
13	40 mg	Euphoria	Euphoric mood	Mild
14	40 mg	irritable	Irritability	Mild
15	40 mg	disorientation	Disorientation	Mild
		euphoria	Euphoric mood	Mild
16	40 mg	Euphoric	Euphoric mood	Mild
		groggy	Somnolence	Mild
		loopy	Feeling abnormal	Mild

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Abuse-Related AEs: Limitations

- "Abuse-related" terms may overlap with other drug and nondrug-related safety AEs (e.g. depression, cognitive disorders) or are non-specific (e.g. dizziness, paresthesia, and fatigue).
- Some events are difficult to classify; should the verbatim term: psychiatric crisis become a PT of "acute psychosis" (narrative may help).
- Events attributed to other causes may have had some contribution from the drug (such as "alcoholic psychosis").
- Presence of concomitant drugs may affect AEs.
- A long standing AE may not be a treatment emergent AE.
- Multiple AEs in the same subject need to scrutinized for cause and effect; narrative should help.
- Small N's may affect the significance of AEs.
- Some drugs have abuse AEs that are withdrawal AEs from other drugs.
- An AE to us might be interpreted by the subject as pleasurable and be under-reported.

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Conclusions
Topics for Discussion Panel

- What to do if the narrative doesn't help?

- Drop a signal or code your best AE guess?

- Using non-clinical and Human Abuse Potential Studies data to refine search queries.

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