

Focus Article

Measures That Identify Prescription Medication Misuse, Abuse, and Related Events in Clinical Trials: ACTION Critique and Recommended Considerations

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Abstract: Accurate assessment of inappropriate medication use events (ie, misuse, abuse, and related events) occurring in clinical trials is an important component in evaluating a medication's abuse potential. A meeting was convened to review all instruments measuring such events in clinical trials according to previously published standardized terminology and definitions. Only 2 approaches have been reported that are specifically designed to identify and classify misuse, abuse, and related events occurring in clinical trials, rather than to measure an individual's risk of using a medication inappropriately: the Self-Reported Misuse, Abuse, and Diversion (SR-MAD) instrument and the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS). The conceptual basis, strengths, and limitations of these methods are discussed. To our knowledge, MADDERS is the only system available to comprehensively evaluate inappropriate medication use events prospectively to determine the underlying intent. MADDERS can also be applied retrospectively to completed trial data. SR-MAD can be used prospectively; additional development may be required to standardize its implementation and fully appraise the intent of inappropriate use events. Additional research is needed to further demonstrate the validity and utility of MADDERS as well as SR-MAD.

Perspective: *Identifying a medication's abuse potential requires assessing inappropriate medication use events in clinical trials on the basis of a standardized event classification system. The strengths and limitations of the 2 published methods designed to evaluate inappropriate medication use events are reviewed, with recommended considerations for further development and current implementation.*

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Key words: Medication abuse, medication misuse, abuse potential.

Weighing an analgesic medication's benefits against its risks of abuse to inform scheduling, labeling, and treatment guidelines^{20,32} requires identifying abuse potential (ie, use for nonmedical psychoactive effects³²) during drug development. This necessitates careful, thorough, and standardized assessment and classification of inappropriate medication use events (ie, misuse, abuse, and related events [MAREs]²⁷; see Table 1 for definitions; see also U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion³¹) occurring in clinical trials. At the current time, there are no standardized, commonly accepted methods to capture and categorize events related to misuse or abuse in clinical trials. A potential model for such an instrument, the Columbia-Suicide Severity Rating Scale, was developed to categorize suicidal ideation and behavior events occurring in antidepressant clinical trials.^{18,19} The Columbia-Suicide Severity Rating Scale classifies events comprehensively, efficiently, and accurately retrospectively as well as prospectively while limiting the over-identification of suicidal ideation and behavior. The prospective version has been recommended for assessing suicidal ideation and behavior in trials submitted to the U.S. Food and Drug Administration.³³ A similar instrument is needed to evaluate abuse potential in analgesic clinical trials.

Recent Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (<http://www.immpact.org>) recommendations¹⁶ and a review of instruments measuring aspects of inappropriate medication use²⁸ emphasize the importance of: 1) evaluating a medica-

tion's abuse potential in a manner that is distinct from assessing the risk that a participant might use medications inappropriately, and 2) determining the putative intent underlying potential inappropriate use events to distinguish abuse events from other events. To that end, identifying inappropriate medication use events in clinical trials is critical for understanding abuse potential. When such events occur, it is also necessary to capture additional characteristics (ie, tampering, withdrawal, addiction, diversion, and overdose²⁷; Table 1) because these supplemental details may imply problematic treatment effects that can inform the assessment of abuse potential. Further, prospectively assessing inappropriate use events within the context of an ongoing clinical trial, with training for study staff to determine the putative intent of these events, is essential for accurate classification.¹⁶ In general, although currently available instruments measuring inappropriate medication use have clinical utility to evaluate patient adherence to opioid therapy in clinical practice, a recent review indicated that they do not distinguish between types of events, consider intent, or evaluate a specific medication's abuse potential per se (see Table 2 for a summary).²⁸

In light of the challenges in measuring inappropriate use events to identify medications with abuse potential, the Abuse Liability Evaluation for Research, Treatment, and Training (ALERTT) working group of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTION; <http://www.action.org>) public-private partnership met to examine the 2 approaches of which we are aware that have specifically been developed to assess these

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