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Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations

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1. Introduction

In the last decade, non-therapeutic use of prescription medications has increased markedly. In 2010, 2 million Americans initiated nonmedical prescription analgesic use in the past 12 months, and 5.1 million used prescription analgesics nonmedically in the past month [34]. Nonmedical use of opioid analgesics resulted in an estimated 425,000 emergency department visits in 2010, an increase of 156% from 2004 [32], and substance treatment for an estimated 754,000 individuals in 2010 [34]. The morbidity and mortality associated with non-therapeutic use of opioids are also rising. In 2010, overdoses in which prescription opioid analgesics were involved resulted in more than 16,500 deaths [10]; a four-fold increase since 1999 [11].

Analgesic clinical trial investigators and sponsors, as well as the regulators evaluating study findings, require precise estimates of inappropriate drug use events occurring in these trials. Currently, a critical weakness is that distinct patterns of inappropriate use are typically grouped under ill-defined terms such as “misuse” or “abuse.” To be most useful for evaluating each drug’s abuse potential, accurate and consistently defined terminology is needed. Although the terminology for drug misuse, abuse, and related events (MAREs) has been evolving since the 1950s [30], to date, consensus definitions are lacking. For example, MARE terminology has been used heterogeneously for various purposes, including: (1) the diagnosis of clinical diseases such as substance use disorders [eg, 2,44]; (2) medicolegal and regulatory applications [eg, 37,40]; (3) epidemiologic surveys [eg, 8,9,36]; (4) patient care [eg, 1,18]; and (5) research.

The lack of consensus in MARE terminology also results from using terms both to describe *single events* that may signal a drug’s abuse potential (eg, ‘abuse’ of a drug for a psychotropic effect [9,13,19,23,36,39,40]), as well as to diagnose an individual’s *ongoing pattern* of problematic drug use (eg, ‘substance abuse’ in DSM-IV-TR [2]). In addition, in spite of widely used classifications for diagnosing ongoing problematic drug use (ie, DSM-IV-TR [2]; ICD-10 [44]), these classifications are ill-suited to certain problems associated with prescription medication use [16,30], leading clinicians, organizations, and researchers to create idiosyncratic new terms such as misuse, nonmedical use, and aberrant medication-

taking behaviors [29,45], exacerbating inconsistencies in MARE terminology. When MARE terms are used idiosyncratically, inconsistently, or haphazardly, it is difficult for researchers, clinicians, and regulators to make accurate, evidence-based recommendations that could help reduce inappropriate analgesic use.

In contrast, efforts to standardize suicidal adverse event terminology [27,28] have produced a tool to capture suicidal events occurring in clinical trials. Initial testing has shown this tool to be reliable, sensitive, and specific [7,27]. In light of this success, our intention was to develop standardized classifications and definitions of MAREs. We begin with a systematic review of existing consensus definitions for 14 MARE terms appearing in the medical literature. Building upon these efforts, we propose a consensus-based set of classifications and definitions of MARE terms as a first step in developing a tool to adequately identify and classify analgesic drug (i.e., any medication with analgesic properties) use *events* deviating from prescribed use as they occur in clinical trials and post-approval adverse event surveillance and monitoring.

2. Method

2.1. Literature search

We searched the US National Library of Medicine PubMed database [<http://www.ncbi.nlm.nih.gov/sites/entrez>] for terminology, classifications, and definitions of 14 terms related to substance abuse (aberrant behaviors; abuse; addiction; craving; dependence; diversion; euphoria; harmful/hazardous use; intoxication; misuse; nonmedical/non-therapeutic use; physical dependence; psychological dependence; and tampering; see Electronic Table 1) developed and proposed by professional groups as well as national, regional, and international organizations and agencies. These terms were selected because they represent common substance abuse-related concepts discussed in the medical literature. Synonymous terms that are used infrequently were not included in the search (see Electronic Table 1).

The main search algorithm was: “([*term searched*]) AND (drug OR substance OR medication) AND (definition OR classification OR terminology).” Search results were limited to articles in English published from 2000 to the present in order to capture contemporary articles and reviews. Our search excluded pediatric populations. Electronic Table 1 presents the final search algorithms used for each of the 14 terms.

2.2. Selection criteria

Articles were considered relevant if they (1) reviewed terminology or (2) contained consensus definitions from expert groups or major medical and health organizations for *any* of the terms of interest. Selection of articles was performed in three steps. In the first step, citations retrieved from the literature searches were screened by reading the title, and any that failed to fulfill our search criteria were excluded. In the second step, the abstracts of non-excluded citations from step one were retrieved to further refine the selection. In the third step, the full articles for those citations not excluded in step two were retrieved and reviewed.

For each selected article (ie, those that reviewed abuse-related terminology or presented consensus definitions), 20 or more related citations were screened using the PubMed “Related Citations” tool, without exclusions based on publication date, to ensure inclusion of all relevant articles and classification systems. In addition, the reference list from each selected article was searched, again without publication date exclusions, for publications containing relevant definitions or classification systems. We also manually searched the present authors’ personal libraries for relevant articles. When unpublished definitions from major institutions, organizations, and agencies (eg, National Center on Addiction and Substance Abuse at Columbia University; Federation of State Medical Boards of the United States) were described in a review article [5,6,12,15,20,26,30,45], the web sites of these institutions were searched for publicly available definitions of relevant abuse-related terminology.

3. Results

3.1. Search results

The PRISMA (Preferred Reporting Items for Reviews and Meta-Analyses) figures for each abuse-related term are illustrated in Electronic Figure 1. Each search yielded between 8 and 2794 articles (Electronic Table 1). Definitions were extracted from original papers that presented consensus definitions and from the websites of organizations referenced in published reviews. Tables 1–5 present the terms, the definitions provided, and the sources of the definitions.

3.2. Background considerations

Two major organizations, the World Health Organization and the American Psychiatric Association, have developed criteria to classify and describe psychiatric disorders, including substance use disorders (ICD-10 [44]; DSM-IV-TR [2]). The criteria for substance use disorders are not intended to categorize individual events that may occur in patients taking prescription medications, but are instead designed to be used diagnostically (Electronic Table 2). Some of these diagnostic criteria, therefore, are difficult to apply appropriately to patients with chronically painful medical conditions on pharmacotherapies [1]. For example, using the ICD-10 and DSM-IV-TR criteria, a patient with chronic pain who develops “tolerance,” “escalates dosage of an analgesic medication,” and “spends disproportionate amounts of time seeking the medication” may be diagnosed with a psychiatric disorder (ie, as having dependence syndrome [ICD-10] or substance dependence [DSM-IV-TR]; NB, symptoms such as tolerance and withdrawal within the context of medical treatments such as prescription analgesics will no longer contribute to a psychiatric diagnosis in DSM-5). However, it is possible that such a patient may be experiencing inadequate pain management and is therefore exhibiting a reasonable response to poorly controlled or worsening pain symptoms [1,4,19,42]. Another challenge with these diagnostic systems is that the terms “dependence syndrome” and “substance dependence,” which include several distinct addiction symptoms, may be easily confused with the term “physical dependence.” Physical dependence, a physiological process that may occur while taking any substance affecting the central nervous system, is only relevant to a patient’s experience when that substance is

abruptly withdrawn from the patient or the patient is administered an antagonist; it does not necessarily signal the presence of a substance use disorder [23,24,30].

The next section presents definitions and classification systems that were not developed for psychiatric diagnoses and do not reiterate the ICD-10 and DSM-IV-TR definitions and that, therefore, provide a basis for developing consensus definitions and classifications for MAREs occurring in clinical trials and post-approval adverse event surveillance and monitoring. All definitions are presented in Tables 1–5; terms with four or more definitions or classification systems are described below.

3.3. Summary of terminology definitions

3.3.3. Misuse—Definitions of “misuse” emphasize that the use of the substance does not follow medical indications or prescribed dosing [8,22,29,39,43] (Table 1), which bears similarity to certain abuse definitions [14,23,43] (Table 2). In some, although not all definitions, misuse is specifically restricted to prescription or over-the-counter medications [19,22,31,39]. Two definitions propose that misuse occurs only when a drug is taken with a therapeutic intent (ie, the use does not involve seeking psychotropic or euphoric effects) in a manner other than as prescribed [19,39].

3.3.1. Abuse—Among the various definitions of “abuse,” the major characteristic that frequently appears was that the substance be used for nontherapeutic purposes to obtain psychotropic (eg, euphoric, sedative, or anxiolytic) effects [9,13,19,23,36,39,40] (Table 2). Some definitions also require that use contradicts medical advice, that the medication is not taken as prescribed [14,23,43], or that there is harm to the user or to others associated with the use [29]. One definition indicates that abuse can also be used to refer to illegal use of a substance [19].

3.3.2. Addiction—“Addiction” is primarily defined as compulsive substance use that occurs despite personal harm or negative consequences [1,23,29,41,43] (Table 3). Many definitions also state that addiction is a chronic disease [1,3,23,29] that may involve impaired control [1,3,43] and craving [1,3]. Two definitions also identify addiction as involving neurobiologic dysfunction [1,3].

3.3.4. Dependence—Physical and psychological dependence are defined separately by the classification systems reviewed. All definitions of “physical dependence” suggest that it is associated with withdrawal symptoms or a withdrawal syndrome [1,23,29,41,43] (Table 4) and most indicate that it is a physiologic response to a drug that manifests due to rapid reduction in exposure or exposure to an antagonist [1,23,29,41]. Some physical dependence definitions also include the development of tolerance to the effects of the substance [23,29,43].

There are fewer consensus definitions of “psychological dependence” and many of those that exist have elements in common with addiction and abuse. For example, two definitions focus on impaired control or compulsion [41,43] and two definitions discuss drug use to alter mood or attain a positive effect [29,41]. Definitions of psychological dependence also suggest that psychological dependence involves craving [5,29], as well as other

psychological symptoms when a medication is withdrawn [5]. Psychological dependence is further characterized as a “non-physiological attachment” to a medication that is associated with relieving negative effects and symptoms [12,29].

3.3.5. Other terms—Each of the remaining terms (ie, “aberrant behavior,” “craving,” “diversion,” “euphoria,” “harmful or hazardous use,” “intoxication,” “nonmedical or nontherapeutic use,” and “tampering”) is defined by only one to three classification systems (see Table 5 for these definitions).

3.3.6. Summary of existing definitions—The various definitions of the terms “misuse,” “addiction,” “abuse,” “physical dependence,” “psychological dependence,” “intoxication,” and “nonmedical” or “non-therapeutic use” have elements within each term that are consistently used across the classification and definition systems (Table 6). Most of these terms, however, also incorporate unique elements. Such inconsistencies are likely to produce unreliable data on MAREs that occur in clinical trials. In addition, none of these definition systems was created specifically to be used in clinical trials, and therefore may contain idiosyncratic elements (eg, the American Medical Association definition of misuse includes drug use that varies from socially accepted use [29]) or describe ongoing patterns of behavior rather than a single event (eg, addiction is characterized as a chronic condition by many definitions [1,3,23,29]). For the terms “aberrant behavior,” “euphoria,” “harmful” or “hazardous use,” and “tampering,” our search returned only a single definition per term, nor were these definitions cited by other consensus processes, which may indicate limited agreement about the use of these terms and their definitions. Consensus MARE terms and definitions that are designed for clinical trials, particularly of analgesics, are needed in order to adequately and reliably assess treatment risks [21].

4. Proposed classification and definitions for abuse-related events

4.1. Methods

A multidisciplinary group of academic, industry, clinical, public health, and regulatory experts in pain and addiction – the Abuse Liability Evaluation for Research, Treatment, and Training (ALERTT) Working Group – was convened by the Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION; <http://www.acttion.org>) public-private partnership. The ALERTT Working Group met to develop consensus recommendations regarding a classification system and definitions of MAREs with the long-term goal of using these classifications and definitions to *prospectively*, accurately, and reliably capture a drug’s likelihood of engendering non-therapeutic use or not as prescribed therapeutic use during a clinical trial. Background presentations focused on the success of similar efforts in classifying both suicide-related events in antidepressant clinical trials and MAREs in poison control center surveillance, as well as preliminary proposals for MARE classifications and definitions. Extensive discussion of these proposals occurred during the meeting, arriving at a group consensus regarding preliminary classifications and definitions. Subsequent to the meeting, a preliminary draft was circulated among the authors for consideration and suggestions for

revisions. Finally, revisions of the classifications and definitions occurred by means of email correspondence until consensus was achieved among all of the authors.

4.2. Classifications and definitions for MAREs

Six mutually exclusive MARE categories were identified and defined: (1) Misuse Event Indicator; (2) Abuse Event Indicator; (3) Suicide-Related Event; (4) Therapeutic Error; (5) None of the Above; and (6) Unknown (Figure 1). In addition, five supplemental designations that can provide additional information about the MARE categories were also defined: (1) Withdrawal; (2) Tampering; (3) Diversion; (4) Addiction-Related Indicator; and (5) Overdose. These supplemental designations are intended to identify any additional signs or symptoms that may indicate problematic treatment effects. Use of a severity scale to capture the clinical consequences of each MARE (eg, none, mild, moderate, severe, death) was also considered. Discussions of the proposed MARE classifications and definitions focused on (1) the intent underlying the event, (2) the individual causing the event, (3) the outcome of the event, and (4) the utility of specifying a term to be a mutually exclusive event category or a supplemental designation to qualify events. The proposed consensus definitions of each of these classifications follow. The terms ‘drug product’ and ‘drug substance’ are used in these classifications as defined by the US FDA Code of Federal Regulations Title 21 [38].

4.2.1. Misuse Event Indicator—Any intentional therapeutic use of a drug product in an inappropriate way. Misuse specifically excludes those events that meet the definition of an Abuse Event Indicator.

NB: (1) Therapeutic use refers to use to reduce an aversive symptom or state; (2) inappropriate use should be considered in context (eg, clinical trial protocol, clinical care), and may include failure to follow directions for the use of a drug product (eg, use of a drug in a manner other than prescribed, directed by a healthcare provider, or presented in information provided to the patient).

4.2.2. Abuse Event Indicator—Any intentional, non-therapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect.

4.2.3. Suicide-Related Event—A self-injurious or potentially self-injurious behavior associated with at least some intent to die or that resulted in death. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury (adapted from [28]).

4.2.4. Therapeutic Error—A mistake in a therapeutic regimen.

NB: Examples of therapeutic error include administration of a drug product in the wrong dose, by an incorrect route, or to the wrong person; administration of a drug product resulting in a drug interaction due to drugs or foods that are known to interact; administration of the wrong drug product; or inadvertently consuming a greater than

prescribed dose of a drug product (eg, a double dose) due to memory lapse. Therapeutic errors may be made by the patient, physician, pharmacist, clinical study staff, etc.

4.2.5. None of the Above—Sufficient information exists to determine that none of the previous categories apply.

4.2.6. Unknown—Insufficient information exists to determine which category applies.

4.2.7. Withdrawal—Symptoms or signs due to the decline in blood concentration of a drug product (eg, after dose reduction, at the end of a dosing interval, after discontinuing treatment) or due to the administration of an antagonist.

4.2.8. Tampering—The inappropriate manipulation of a drug product.

4.2.9. Diversion—Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession. Diversion can occur with all categories except Therapeutic Error.

NB: Examples of diversion include giving or selling a drug product for any purpose, even therapeutic, to any individual.

4.2.10. Addiction-Related Indicator—Behavioral, cognitive, and physiological phenomena that may develop after exposure to a substance (typically on a repeated basis), which may include a strong desire to take the drug, difficulties in controlling drug use, persistent drug use despite harmful consequences, intractable and distracting thoughts about the drug, or placing a higher priority on drug use than on other activities and obligations.

4.2.11. Overdose—Any act that results in drug exposure exceeding that which is generally recommended or medically accepted.

NB: Non-fatal overdose that is likely to result in a serious toxic reaction, but not death, must be distinguished from fatal overdose that results in death. This category is not meant to apply to all cases of abuse in which, by definition, drug exposure exceeds that which is recommended.

4.3. Examples—1a: A participant taking a non-steroidal anti-inflammatory drug (NSAID) for osteoarthritis (OA) pain in an open label post-approval surveillance and monitoring study experiences no reduction in OA pain. However, she states that she continues to take the drug for its reduction of hemicrania continua and dry eyes. If the adjudicator determines that the participant's intent was therapeutic in nature, this event would be classified as a 'misuse event indicator' given that it occurred without approval from a clinician. There would not be any supplemental designations assigned to this event.

1b: If the participant continued taking the NSAID for the prevention of dementia at the recommendation of her clinician, this would not be classified as a MARE because the use is advised by the clinician.

2a: A participant with breakthrough cancer pain in a randomized clinical trial of a novel opioid formulation takes an excessive dose of study drug to combat insomnia. If the adjudicator judged that the intent of the event was to treat insomnia, the event would be classified as a ‘misuse event indicator’ with the supplemental designation of ‘overdose.’

2b: If the participant stated that an excessive dose of study drug was used to combat insomnia, but based on additional evidence the adjudicator judged that the participant’s intent was to achieve euphoric effects, the event would be classified as an ‘abuse event indicator’ with the supplemental designation of ‘overdose.’

2c: If the participant stated that he gave a single dose of study drug to his spouse for the spouse’s insomnia, and the adjudicator judged that statement to accurately reflect the participant’s intent, this would be classified as a ‘misuse event indicator’ with the supplemental designation of ‘diversion.’

3a: A participant with chronic low back pain in a randomized clinical trial of a novel opioid formulation craves the study drug and often finds that she “can’t wait” until her next dose. There is no evidence that she has ever taken the drug other than as directed. This event would be classified as ‘none of the above’ with the supplemental designation of ‘addiction related indicator.’

3b: If the participant craved the study drug and began to take additional doses because it made her “feel good,” but not to further reduce her pain, this would be classified as ‘abuse event indicator’ with the supplemental designation of ‘addiction related indicator.’

4: A participant with OA in an open label trial of an opioid analgesic misunderstood how to take his medication. Rather than swallowing the pill, he stated that he crushed it and mixed it into his food. If the adjudicator judged that the event was accidental, it would be classified as ‘therapeutic error’ with the supplemental designation of ‘tampering.’

5: A participant with painful diabetic peripheral neuropathy in a clinical trial of an anticonvulsant indicates that she ran out of her study drug 1 week early and a day later started feeling jittery and nauseated. These feelings lasted for a few days, but then remitted on their own. If the adjudicator cannot determine the intent underlying the medication shortage, this would be classified as ‘unknown’ with the supplemental designation of ‘withdrawal.’

As these examples illustrate, our system depends on inferring the participant’s intent before classifying an event. In some cases, the intent will be relatively straightforward (eg, examples 1a, 3a, 3b). However, in many other instances (eg, examples 2b, 5), a participant’s intent may not be known or may be masked to obscure problematic drug use or diversion. When a participant’s statements about intent are unclear or misleading, event classification relies on a judgment of all contextual factors surrounding the event.

4.4. Implementation of MARE classifications and definitions

The proposed MARE classifications and definitions are intended as an initial step in effectively and accurately assessing problematic analgesic drug use during clinical trials or

post-approval surveillance and monitoring. Currently, adverse events indicating a treatment's abuse liability may be ignored or misclassified, leading to imprecise rates of MAREs. Use of the proposed standardized MARE classifications and definitions is expected to contribute to greater reliability and validity of the rates of analgesic drug MAREs.

Although it may be possible to use these classifications and definitions outside of clinical trials and post-approval surveillance and monitoring [see 28 for an example from suicide classifications], retrospective case report form reviews or observational studies may infrequently contain all necessary information to determine how an adverse event should be classified (eg, the intent of drug accountability discrepancies may not be reported). The next step in this effort, which is currently underway, is to develop a tool to prospectively assess adverse events that may indicate treatment abuse liability using the proposed MARE classifications and definitions.

5. Discussion

In our systematic review of 14 abuse-related terms, we identified classifications and definitions that are relevant for the categorization of MAREs in clinical trials and during post-approval adverse event surveillance and monitoring. Particularly noteworthy is that because the ICD-10 and DSM-IV-TR definitions of dependence syndrome and substance dependence, as well as harmful use and substance abuse, were developed for substance disorder psychiatric diagnoses, they appear to be less applicable to the broader and non-diagnostic problem of prescription medication non-adherence occurring in clinical trials (NB, as previously indicated, the forthcoming DSM-5 attempts to improve upon this). Furthermore, the term dependence is inconsistently used, in some cases referring to patterns associated with addiction (ICD-10, DSM-IV-TR) and in other cases referring to normal adaptations resulting from prolonged exposure to a substance [23,24,30]. In addition, certain behaviors exhibited by people with chronic pain fulfill diagnostic criteria for the ICD-10 dependence syndrome or DSM-IV-TR substance dependence even though these behaviors may possibly result from seeking pain relief and not from substance addiction [1,4,19,42].

Several organizations have attempted to remedy the limitations of the ICD-10 and DSM-IV-TR definitions by developing definitions for additional MARE terms. Despite, and likely also because of, the multiple efforts to define and classify MARE terms, no consensus definitions exist to capture and assess MAREs in analgesic clinical trials [21]. Consistent elements can be seen across existing definitions of misuse, abuse, addiction, physical dependence, psychological dependence, intoxication, and nonmedical or nontherapeutic use. However, there are also discrepancies in how these terms have been defined, with individual proposals containing unique criteria. In addition, certain criteria were shared among different terms. For example, specific components of misuse definitions are quite similar to components of abuse and nonmedical or nontherapeutic use definitions, and definitions of psychological dependence were closely related to addiction and abuse definitions. This lack of consensus regarding definitions of MARE terminology, as well as shared characteristics between distinct terms, has greatly hindered efforts to evaluate medication misuse, abuse, addiction, aberrant behaviors, and other associated problems that occur in clinical trials.

There is a compelling need to standardize the classification and definition of MAREs that can occur in clinical trials of treatments with abuse potential in order to accurately distinguish treatments that have an abuse liability from treatments without such liability. Our proposed system of mutually exclusive and exhaustive consensus definitions can provide the basis for more effective assessment of events indicative of abuse potential in clinical trials and in post-marketing adverse event surveillance and monitoring. Currently, we are creating a tool to determine which adverse events should be adjudicated into these proposed MARE classifications, what information is necessary to collect when these events occur (eg, the intent of an act), and how to implement such a system. Ultimately, our intention is that these classifications and definitions, as well as our adjudication tool, will work in tandem with current abuse potential assessment (eg, knowledge of a treatment's mechanism of action; abuse and dependence potential trials) to facilitate the development of medications that are less likely to be abused.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Select 1		Indicate Severity, Dosage Form, and Administration Method using lists below			SUPPLEMENTAL DESIGNATIONS: one or more may be selected				
		Severity	Dosage Form	Administration Method	Tampering	Withdrawal	Addiction-related Indicator	Diversion	Overdose
EVENT CATEGORIES	Misuse-event Indicator								
	Abuse-event Indicator								
	Suicide-related Event								
	Therapeutic Error								
	None of the Above								
	Unknown								

Figure 1.

Recommended MARE classification system

For each event, one event category would be chosen, the severity of the event could be recorded, the dosage form and method of administration would be identified, and any supplemental designations providing further information about the event would be selected. Dosage forms:

OS: Solid dosage form designed to be swallowed intact; TM: Solid dosage form designed for administration through oral mucosa (e.g., buccal, sublingual); TD: Solid dosage form designed for transdermal administration (e.g., patch); SS: Semisolid dosage form designed for transdermal administration (e.g., gel, ointment, lotion, cream); OL: Liquid dosage form designed for administration by swallowing (e.g., solutions, suspensions, emulsions); NL: Liquid dosage form designed for administration intranasally (e.g., metered sprays); NA: Aerosol dosage form designed for administration intranasally; PI: Inhalants or sprays designed for pulmonary administration; UNK: Dosage form unknown

Administration method:

Oral; Sublingual; Nasal insufflation (i.e., “snorted”); Vaporized and inhaled; Injected; Unknown

Definitions of MARE categories:

Misuse-event Indicator: Any intentional therapeutic use of a drug product in an inappropriate way. Misuse specifically excludes those events that meet the definition of an Abuse-event Indicator.

Abuse-event Indicator: Any intentional, non-therapeutic use of a drug product or substance, even once, for the purpose of achieving a desirable psychological or physiological effect.

Suicide-related Event: A self-injurious or potentially self-injurious behavior associated with at least some intent to die or that resulted in death. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury (adapted from Posner et al, 2007).

Therapeutic Error: A mistake in a therapeutic regimen.

None of the Above: Sufficient information exists to determine that none of the previous categories apply.

Unknown: Insufficient information exists to determine which category applies.

Definitions of supplemental designations:

Tampering: The inappropriate manipulation of a drug product.

Withdrawal: Symptoms or signs due to the decline in blood concentration of a drug substance (eg, after dose reduction, at the end of a dosing interval, after discontinuing treatment) or due to the administration of an antagonist.

Addiction-related indicator: Behavioral, cognitive, and physiological phenomena that may develop after exposure to a substance (typically on a repeated basis), which may include a strong desire to take the drug, difficulties in controlling drug use, persistent drug use despite harmful consequences, intractable and distracting thoughts about the drug, or placing a higher priority on drug use than other activities and obligations.

Diversion: Any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession. Diversion can occur with all categories except Therapeutic Error.

Overdose: Any act that results in drug exposure exceeding that which is generally recommended or medically accepted.

Table 1**Misuse definitions**

Source	Definition
National Poison Data System [8]	Intentional improper or incorrect use.
Tufts Health Care Institute expert panel [19]	Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
National Center on Addiction and Substance Abuse at Columbia University [22]	Using [controlled prescription drugs and over-the-counter medications] for purposes not prescribed or intended such as to get high, feel stimulated or sedated; taking more of the substance than prescribed or recommended; or taking the substance too often or for a longer period of time than was prescribed or recommended.
American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	Any use of a drug that varies from a socially or medically accepted use.
Consensus from Henry Ford Health System expert panel [31]	Prescription opioid misuse: opioid-obtaining behaviors that raise clinician concern about their appropriate use.
US Food and Drug Administration [39]	The use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner. This definition includes patients using a drug for a different condition than that for which the drug is prescribed, patients taking more drug than prescribed or at different dosing intervals, and individuals using a drug not prescribed for them although for therapeutic purposes.
World Health Organization [43]	Use of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications.

Table 2**Abuse definitions**

Source	Definition
National Poison Data System [9]	Intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any reason is included.
Researched Abuse, Diversion and Addiction-Related Surveillance [13]	Use to get high; use in combination with other drugs to get high; use as a substitute for other drugs of abuse.
Federation of State Medical Boards [14]	The use of any substance(s) for non-therapeutic purposes or use of medication for purposes other than those for which it is prescribed.
Institute of Medicine [18]	Same as ICD-10 and DSM-IV.
Tufts Health Care Institute expert panel [19]	Any use of an illegal drug; the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, eg, getting high.
National Institute on Drug Abuse [23]	The use of a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited.
American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	The use of a psychoactive substance in a manner detrimental to the individual or society but not meeting criteria for substance or drug dependence.
Substance Abuse and Mental Health Services Administration [36]	Nonmedical use of a substance for psychic effect, dependence, or suicide attempt or gesture.
US Food and Drug Administration [39,40]	The nonmedical use of a drug, repeatedly or even sporadically, for the positive psychoactive effects it produces.
World Health Organization [43]	Persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice.

Table 3**Addiction definitions**

Source	Definition
American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine [1]	A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
American Society of Addiction Medicine [3]	A primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response.
Federation of State Medical Boards [14]	Same as AAPM, APS, ASAM, 2001.
Institute of Medicine [18]	Same as ICD-10 and DSM-IV.
Tufts Health Care Institute expert panel [19]	Same as AAPM, APS, ASAM, 2001.
National Center on Addiction and Substance Abuse at Columbia University [22]	Same as ICD-10 and DSM-IV-TR.
National Institute on Drug Abuse [23]	A chronic, relapsing disease characterized by compulsive drug seeking and use despite serious adverse consequences, and by long-lasting changes in the brain.
American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	A chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological, or social harm to the user and continued use despite that harm.
US Food and Drug Administration [39]	Same as AAPM, APS, ASAM, 2001.
University of Wisconsin Pain & Policy Studies Group [41]	Refers to maladaptive pattern of behaviors and compulsive use of drugs despite harm.
World Health Organization [43]	Repeated use of a psychoactive substance or substances, to the extent that the user (referred to as an addict) is periodically or chronically intoxicated, shows a compulsion to take the preferred substance (or substances), has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means.

Table 4**Physical and psychological dependence definitions**

Source	Definition – physical dependence
American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine [1]	A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
Cheatle & Savage review [12]	Same as AAPM, APS, ASAM, 2001.
Federation of State Medical Boards [14]	Same as AAPM, APS, ASAM, 2001.
Tufts Health Care Institute expert panel [19]	Same as AAPM, APS, ASAM, 2001.
National Institute of Drug Abuse [23]	An adaptive physiological state that occurs with regular drug use and results in a withdrawal syndrome when drug use is stopped; often occurs with tolerance. Physical dependence can happen with chronic – even appropriate – use of many medications, and by itself does not constitute addiction.
American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	A physiological state of adaptation to a drug or alcohol, usually characterized by the development of tolerance to drug effects and the emergence of a withdrawal syndrome during prolonged abstinence.
University of Wisconsin Pain & Policy Studies Group [41]	The physical adaptation of the body to the presence of an opioid; it is characterized by signs of withdrawal when use of an opioid is stopped abruptly, or when an opioid antagonist is administered to an individual who was been on chronic opioid therapy.
World Health Organization [43]	Tolerance and withdrawal symptoms.
Source	Definition – psychological dependence
Ballantyne & LaForge review [5]	The psychological component of withdrawal, which comprises both unpleasant emotional effects (withdrawal anhedonia and dysphoria) and motivational effects (craving during withdrawal), the latter being partly mediated by physical withdrawal.
Cheatle & Savage review [12]	A non-physiological attachment to the availability of the prescribed medication that may be a natural response to effective relief of distressing symptoms.
American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	The emotional state of craving a drug either for its positive effect or to avoid negative effects associated with its absence.
University of Wisconsin Pain & Policy Studies Group [41]	A behavioral pattern characterized by a compulsion to obtain a drug for mood altering effects.
World Health Organization [43]	The experience of impaired control over drug use.

Table 5

Definitions of other MARE terminology

Term	Source	Definition
Aberrant behavior	Tufts Health Care Institute expert panel [19]	A constellation of behaviors that have grown to be recognized by clinicians as potentially indicative of prescription opioid abuse.
Craving	National Institute of Drug Abuse [25]	A subjective state in humans that is associated with drug dependence.
	World Health Organization [43]	Very strong desire for a psychoactive substance or for the intoxicating effects of that substance.
Diversion	RADARS [17]	The unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace.
	Tufts Health Care Institute expert panel [19]	The intentional removal of a medication from legitimate distribution and dispensing channels.
Euphoria	World Health Organization [43]	A sense of well-being.
Harmful or hazardous use	World Health Organization [43]	Harmful use: A pattern of psychoactive substance use that is causing damage to health. The damage may be physical (eg, hepatitis following injection of drugs) or mental (eg, depressive episodes secondary to heavy alcohol intake). Hazardous use: A pattern of substance use that increases the risk of harmful consequences for the user. Some would limit the consequences to physical and mental health (as in harmful use); some would also include social consequences. (In contrast to harmful use, hazardous use refers to patterns of use that are of public health significance despite the absence of any current disorder in the individual user.)
Intoxication	American Medical Association – Council on Scientific Affairs, Panel on Alcoholism and Drug Abuse [29]	Changes in physiological functioning, psychological functioning, mood states, or cognitive processes, or all of these, as a consequence of excessive consumption of a drug; usually disruptive.
	World Health Organization [43]	Same as ICD-10.
Nonmedical or nontherapeutic use	National Survey on Drug Use and Health [33]	Use of [prescription-type pain relievers] without a prescription or use that occurred simply for the experience or feeling the drug caused.
	Drug Abuse Warning Network [35]	Patients who took a higher than prescribed or recommended dose of their own medication, patients who took a pharmaceutical prescribed for another person, malicious poisoning of the patient by another individual, and documented substance abuse involving pharmaceuticals.
	World Health Organization [43]	Use of a prescription drug, whether obtained by prescription or otherwise, other than in the manner or for the time period prescribed, or by a person for whom the drug was not prescribed.
Tampering	Tufts Health Care Institute expert panel [19]	Manipulating a pharmaceutical dosage form to change its drug delivery performance in a way not specified by the manufacturer.

Table 6

Common and unique elements in definitions of prescription medication MARE terminology

Term	Common element (included in 2 definitions)	Unique elements (included in 1 definition)
Misuse	Use that contradicts medical advice or that is not as prescribed [*] Restricted to prescription or over-the-counter medications Restricted to use for a medical purpose	
Abuse	Use for nontherapeutic, recreational purposes Use to obtain psychotropic or euphoric effects [§] Use that contradicts medical advice or that is not as prescribed [*]	Harm to the user or others [#] Illegal use of a substance Use for dependence or suicide attempt
Addiction	Compulsive use [†] Use despite harm or negative consequences [#] Chronic disease Impaired control [†] Craving [†] Neurobiologic dysfunction	
Physical dependence	Associated with withdrawal symptoms or a withdrawal syndrome Adaptive physiologic process Occurs when drug is rapidly withdrawn Tolerance to substance effects	
Psychological dependence	Compulsive use and impaired control [†] Craving [†] Characterized by drug use to obtain psychotropic or euphoric effects [§] Avoidance of negative effects and symptoms associated with drug absence	Unpleasant emotional and motivational effects Non-physiological attachment to availability of a drug
Diversion	Removal of a medication from legal distribution	
Intoxication	Disrupts psychophysiological functions	Associated with excessive use
Nonmedical or nontherapeutic use	Use of prescription drug without a prescription	Prescription drug use to obtain psychotropic or euphoric effects [§] Prescription drug use that is not as prescribed [*]

[§]Element occurs in definitions of abuse, psychological dependence, and nonmedical or nontherapeutic use

* Element occurs in definitions of misuse, abuse, and nonmedical or nontherapeutic use

Element occurs in definitions of abuse and addiction

† Element occurs in definitions of addiction and psychological dependence

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