




MADDERS™

MISUSE AND ABUSE DIVERSION DRUG REPORTING
SYSTEM

**Presentation to Cross-Company Abuse Liability Consortium
April 16, 2015**

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History

- Recognition of haphazard assessment of abuse in clinical trials
- FDA commissions Columbia to develop C-SSRS
- Problem of abuse assessment reviewed at IMMFACT XII meeting (10/09) with recommendations for developing systematic approach
- GW Pharma partners with Analgesic Solutions to develop method to identify and classify abuse-related events in clinical trials
- ACTION collaborates with AS to create system to standardize assessment of abuse-related events based on GW system
- ALERTT-1 meeting defines events of interest and standardizes terminology
- ALERTT-2 meeting: consensus on use of MADDERS system
- MADDERS is operational and currently being used in multiple clinical trials

Precedent: C-SSRS (Columbia Suicide Severity Rating Scale) designed to . . .

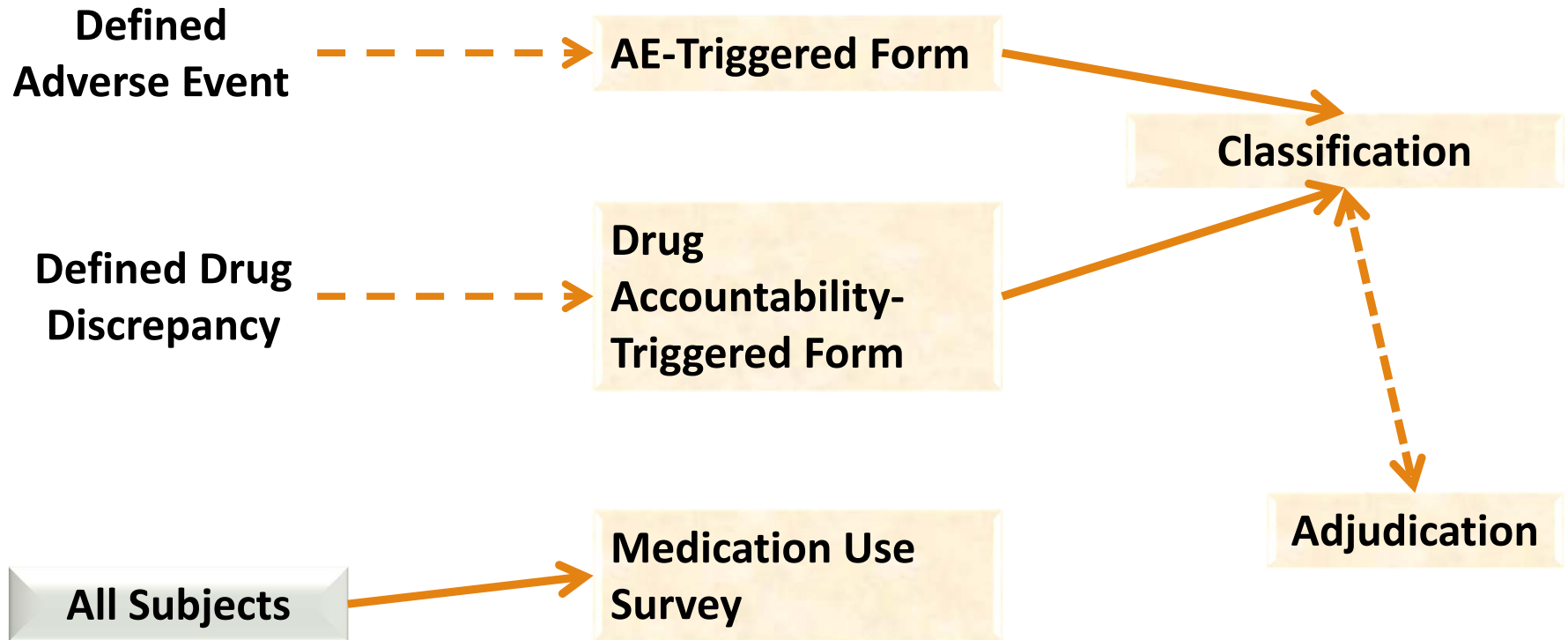
Standardize definitions of suicidal ideation and behavior and nonsuicidal self-injurious behavior and corresponding probes

Quantify the full spectrum of suicidal ideation and suicidal behavior and gauge their severity over specified periods

Distinguish suicidal behavior and nonsuicidal self-injurious behavior

Employ user-friendly format allowing integration of information from multiple sources (e.g., direct patient interview, family, medical records).

MADDERS™-P



MADDERS Classification

		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	Select 1								
	Misuse-event Indicator								
	Abuse-event Indicator								
	Suicide-related Event								
	Therapeutic Error								
	None of the Above								
Unknown									

Supplemental Adverse Event Form

AEI (copy the verbatim description of the AE from the AE form):	
1.	<p><i>(Amount of study medication used) Discuss with the patient the amount of study medication taken prior to the onset of the AEI.</i></p> <p>a. The last dose of study medication taken before the onset of the AEI was</p> <ul style="list-style-type: none"><input type="checkbox"/> Protocol-specified dose – go to Question 2<input type="checkbox"/> Less than protocol-specified dose – go to Question 2<input type="checkbox"/> More than protocol-specified dose – complete Question 2b on intent- <p><i>(Intent of greater use) IF the patient took <u>more</u> study medication than specified by the protocol discuss the patient's intent of taking additional study medication.</i></p> <p>b. The patient's intent of taking more than the protocol-specified amount of study medication prior to the AEI was:</p> <ul style="list-style-type: none"><input type="checkbox"/> To get more of the effect being studied by the protocol<input type="checkbox"/> To achieve a therapeutic goal other than that being studied by the protocol<input type="checkbox"/> To enjoy a non-therapeutic or recreational effect of study medication; e.g. "get high"<input type="checkbox"/> To attempt to end his/her life<input type="checkbox"/> Unintentional (accident or misunderstanding of instructions)<input type="checkbox"/> Other – explain: _____
2.	<p><i>(Route of administration) Discuss with the patient the route of administration that study medication was taken <u>just prior to onset of the AEI.</u></i></p> <p>a. Did the patient take study medication <u>only</u> by the route of administration as specified by the protocol?</p> <p><input type="checkbox"/> YES – go to Question 3 <input type="checkbox"/> NO – complete Questions 2b and 2c</p> <p>b. <i>(Alternate route of administration) The patient took study medication by the following alternate route of administration:</i></p> <ul style="list-style-type: none"><input type="checkbox"/> Oral (swallowing/chewing) <input type="checkbox"/> Nasal/Inhalation<input type="checkbox"/> Injection <input type="checkbox"/> Rectal<input type="checkbox"/> Other: _____

Supplemental Drug Accountability Form

Drug Accounting Discrepancies	
1.	<p>a. <i>(Tampering)</i> Is there any evidence that the patient attempted to tamper with the study medication (e.g. break into vials, open tubes or otherwise manipulate medications)? <input type="checkbox"/> YES – complete Questions 1b and 1c <input type="checkbox"/> NO – go to Question 2</p>
	<p>b. <i>(Tampering evidence)</i> Please describe tampering evidence: _____ _____</p>
	<p>c. <i>(Explanation of tampering)</i> Discuss with the patient the tampering evidence and try to determine the intent for tampering. <u>Check all that apply.</u></p> <ul style="list-style-type: none"><input type="checkbox"/> Accidental (e.g. dropping a vial)<input type="checkbox"/> In order to use more study medications than specified by the protocol for one or more of the following reasons (<u>check all that apply</u>):<ul style="list-style-type: none"><input type="checkbox"/> To enhance the effect being studied by the protocol<input type="checkbox"/> To achieve the following therapeutic goal other than that being studied by the protocol. _____<input type="checkbox"/> To enjoy a non-therapeutic or recreational effect of study medication; e.g. “get high”<input type="checkbox"/> To attempt to end his/her life<input type="checkbox"/> In order to use it by the following route of administration that is not specified by the protocol<ul style="list-style-type: none"><input type="checkbox"/> Oral (swallowing/chewing) <input type="checkbox"/> Nasal/Inhalation<input type="checkbox"/> Injection <input type="checkbox"/> Rectal<input type="checkbox"/> Other: _____<input type="checkbox"/> Other –explain: _____

Medication Use Survey

(Diversion) Please ask the patient about sharing of their study medication to determine if someone else used their study medication; i.e. patient gave it to someone else or someone else took it from them.

1. How often did someone other than the patient take or use their study medication?
 Never Once or twice Occasionally Frequently

(Tampering) Please discuss with the patient how some patients might tamper with their drugs or alter the study medication form (e.g. crushing a tablet). Note that discussions of intent of tampering and routes of administration used after tampering are covered by Drug Dosage and Routes of Administration sections below.

2. Did the patient try to break into the packaging of the study medication to use it in a manner other than as prescribed by the study protocol (e.g. break into a spray bottle, open a tube of gel, break open blister packaging, or use more than one dose at a time)?
 No Yes – describe method used

(Drug Dosage) Please discuss with the patient the amount of study medications and dose frequency that they used during the study to determine if they used more than the amount specified in the protocol. Additional study medication refers to an amount or frequency that was greater than that specified in the protocol.

3. How often did the patient run out of study medication between scheduled clinic visits?"
 Never Once or twice Occasionally Frequently
4. Did the patient ever take additional study medication by accident (i.e. unintentional dosing at wrong time or taking too many tablets)?
 Never Once or twice Occasionally Frequently
5. Did the patient ever take additional study medication with the intent of getting better therapeutic benefit of symptom/disease being studied (e.g. greater pain control in a pain study)?
 Never Once or twice Occasionally Frequently

System components

- User's Manual (for sites)
- Technical Manual (for sponsor)
- Training Program
- Triggering AE list and drug accountability discrepancy criteria
- 4 forms:
 - Supplemental Drug Accountability Form
 - Supplemental Adverse Event Form
 - Medication Use Form
 - Classification Form
- Adjudication Committee
- Study Report

Current Use of MADDERS™

- 1 study completed, 3 ongoing, 2 being launched, more coming
- Adult and Pediatric versions
- More than 300 research personnel in more than 60 sites successfully completed the MADDERS training and are currently using system
- Adjudication committee in operation
- To date, the process has worked well and the procedures have been easily incorporated into clinical trials.

Strengths and Limitations

STRENGTHS

- Standardizes identification and classification of events
- Formally developed and tested
- Sufficient information captured at time of visit to classify events
- Minimizes risk of later disputes about abuse-related event rate
- Supports evidence generation for labeling, scheduling, treatment guidelines

LIMITATIONS

- Requires investigator judgment to determine when an AE is a triggering AE
- Further research needed to assess “known groups” validity
- Further research needed to quantify sensitivity/specificity



Summary

- The MADDERS system has been developed, tested, and refined with patient, investigator, and ACTION input and is available for new studies
- MADDERS provides a standard method for identification and classification of potentially abuse-related events
- The system appears to function well operationally
- One study has been completed, 3 are ongoing, and 2 are currently launching
- Further research is needed to explore aspects of validity