

Tracking the Unknown: Challenges with Evaluating Aberrant Behaviors in Clinical Trials

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*Scientific consulting and writing
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Disclosure

- *Altreos Research Partners Inc. provides consulting services to the pharmaceutical industry on abuse liability and clinical pharmacology*



DIVERSION



- Post-market, “diversion” is when drugs are transferred from a licit to an illicit channel of distribution or use
- In clinical trial context “diversion” may occur if:
 - Subject sells or shares the drug with another individual
 - If another individual takes/administers the drug without the subject’s consent
- Subjects in clinical trials may also engage in other ‘aberrant’ drug-taking behaviors, such:
 - Taking too much drug
 - Taking drugs by inappropriate routes
 - Taking drugs longer than medically necessary
 - Taking drug for reasons other than primary indication

Diversion and aberrant behaviors may signal that the study drug has inherent abuse potential and ‘value’ as a drug of abuse

High risk and low risk study populations?

High risk

Individuals with substance use disorders (e.g., those on OMT)

Medium risk?

- Chronic non-cancer pain
- Anxiety disorders? (sedatives)

Low risk?

- Phase 1 populations (usually supervised)
- Probably the vast majority of other psychiatric/neurologic patient groups, e.g., depressive disorders, schizophrenia, epilepsy, etc.

FDA 2010 Guidance

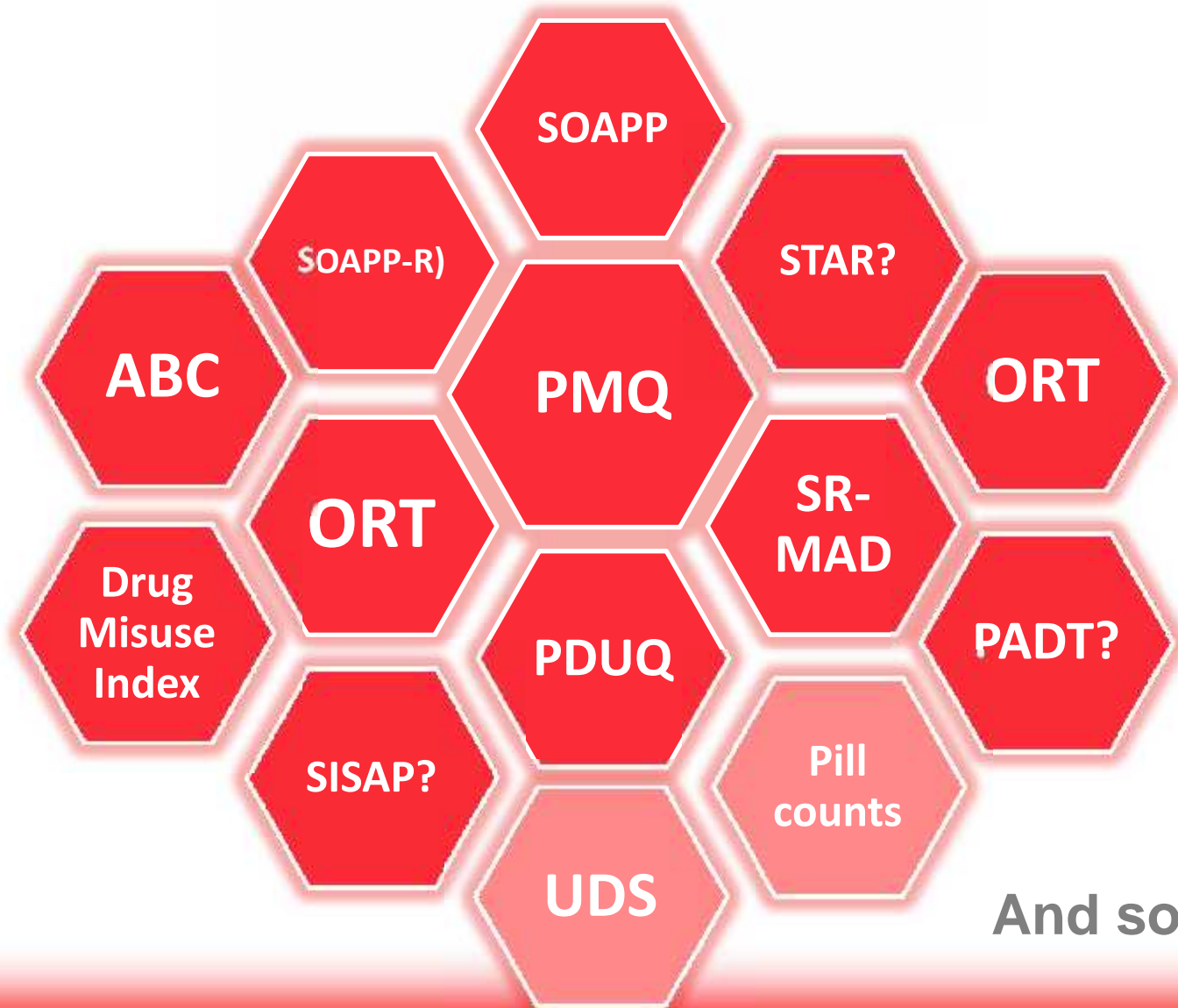
- *Phase 3 trials provide ... data relevant to abuse, dependence potential, **drug diversion, and accountability, as related to study subjects (completers and dropouts)***
- *Sponsors should make every effort to do the following:*
 - *Set criteria, collect data, and tabulate the abuse, misuse, **noncompliance, and diversion cases** across the studies and study sites with special attention to **aberrant drug behaviors that may be indicative of drug abuse, misuse and/or diversion.***
 - *Provide complete information, including case report forms and final outcomes, on all instances of addiction, abuse, misuse, overdose, **drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study.***
 - *Provide information on the risks of addiction, abuse, misuse, overdose, and drug diversion in the study populations. Pertinent data can include measurements of **drug accountability, tolerance, physical dependence, or withdrawal symptoms, and the presence of signs or symptoms of drug abuse, misuse, overdose, or drug diversion.***

Prospective and Retrospective Assessments During Clinical Development

- Prospective assessments may include:
 - Simply implementing a predefined plan for monitoring cases of diversion or aberrant drug behaviors, or
 - May include specific ‘checklists’ or tracking systems
- Retrospective assessments include examining already collected data sources, such as:
 - Subject discontinuations
 - Drug accountability/administration records
 - Protocol deviations
 - Compliance

**Major issue with both is that
SUBJECTS DON'T USUALLY TELL YOU WHEN THEY ARE
DIVERTING OR MISUSING DRUG**

Aberrant Behaviors Checklist and Other Indicators



And so on...

Issues with the Checklists

- Most are designed to identify patients at risk and inform management of the patient, not to monitor/assess ‘misuse’ of specific study drugs
 - Many of the items address the patient’s individual risk factors – mostly noise and likely to have low sensitivity for evaluating specific drugs
- Other indicators?
 - “We identified no reliable data on the accuracy of *urine drug screening, pill counts, or prescription drug monitoring programs* to identify aberrant drug-related behaviors, or on effects of using such interventions on patient outcomes” – Chou et al. 2009
- Clinical importance of findings in the absence of head-to-head comparators?
 - Possibly use historical data with prescription opioids as a benchmark for ‘high abuse liability’ (*where data are publically available*)
- Most developed for pain indications and/or opioids
 - Application to other drugs (NMEs)/patient groups is unclear
 - High investigator/subject burden for what is likely a low signal

Site and Investigator Training

- Prospectively alerting sites and investigators to be aware of diversion and aberrant behaviors
- Standardize training on how to record and follow-up on such events
- Training needs to take into account that subjects are unlikely to admit to diversion or misusing the drug
 - **Subject likely won't say "I am abusing the drug", "Oh right, I sold that"**
 - Subject may say "I have cravings for the drug" or "I feel addicted" to the drug
 - Subject may repeatedly ask for more drug despite stable medical condition and adequate efficacy
 - Subject repeatedly "loses" or reports thefts of study drug
 - Subject reports using the study drug to help them "relax"

Retrospective Assessments



Diversion as an AE

- MedDRA
 - “Drug diversion”
 - Part of Drug Abuse and Dependence SMQ
 - “For the purposes of term selection and analysis of MedDRA coded data, drug diversion means that a drug is diverted from legal and medically necessary uses toward uses that are illegal and typically not medically authorised or necessary”
- However
 - Low level term of “recreational drug abuse”
 - Often not specific to study drug
 - “Took street diazepam” = diversion
 - *EMA perspective on Medication Errors and MedDRA coding and reporting*
- Reporting diversion as an AE is extremely rare

MedDRA ‘Medication Errors’

- Drug administered at inappropriate site
- Inappropriate schedule of drug administration
- Incorrect route of drug administration
- Overdose (‘Overdose’ is considered to be a medication error in MedDRA hierarchy)
- Intentional drug misuse
- Chemical submission (assault and memory loss)
- Such terms are relatively rarely reported and may not indicate intention to abuse/misuse

Other Retrospective Evidence of “Diversions” or Aberrant Behaviors

Lost medication

Did not return study drug

Stolen drug

Patient lost to follow up

Non-compliance

Overuse

Overdose

Repeated loss of study drug

Protocol deviation, compliance, drug accountability, patient discontinuation listings

Drug Accountability

- Thefts of study drug:
 - By subjects, their families/friends, ‘break-ins’
 - From study center(s) or in transit
 - For controlled substances, criminal matter that must be reported to DEA
- Drug accountability/administration records
 - Drug losses
 - Discrepancies
 - Such occurrences are relatively common but typically involve isolated events or small quantities and not “abuse potential”
 - Are there subjects who repeatedly “lose” medications?
 - Patient population under study? (e.g., older, and/or cognitively impaired populations make more medication errors)
 - Comparison of rate of loss/stolen medications to placebo or comparators



Compliance and Protocol Deviations

- Overuse or Inappropriate Use
 - Compliance: often summarized for efficacy trials anyway
 - “Overuse” often defined as compliance > 120%
 - But may not always/often reflect ‘abuse’ or tolerance, but rather errors, investigator ‘titration’ etc.
 - Lack of efficacy, but subject continues to take drug?
 - May be difficult to assess for individual subjects (matching individual subject’s efficacy data against their drug administration record?)
- Protocol deviations
 - Deviations related to study drug administration (e.g., improper dose administered)

Reasons for Discontinuation

- Reasons for discontinuation can be examined for aberrant behaviors related to the study drug:
 - Noncompliance with study drug
 - Protocol violations
 - Lost to follow-up
 - But...critical follow-up data:
 - Nature of the noncompliance/violation? **Details often not available**
 - Did they return the study drug? **Often not known**

With all these retrospective data, there is usually insufficient detail to determine if the event was related to abuse

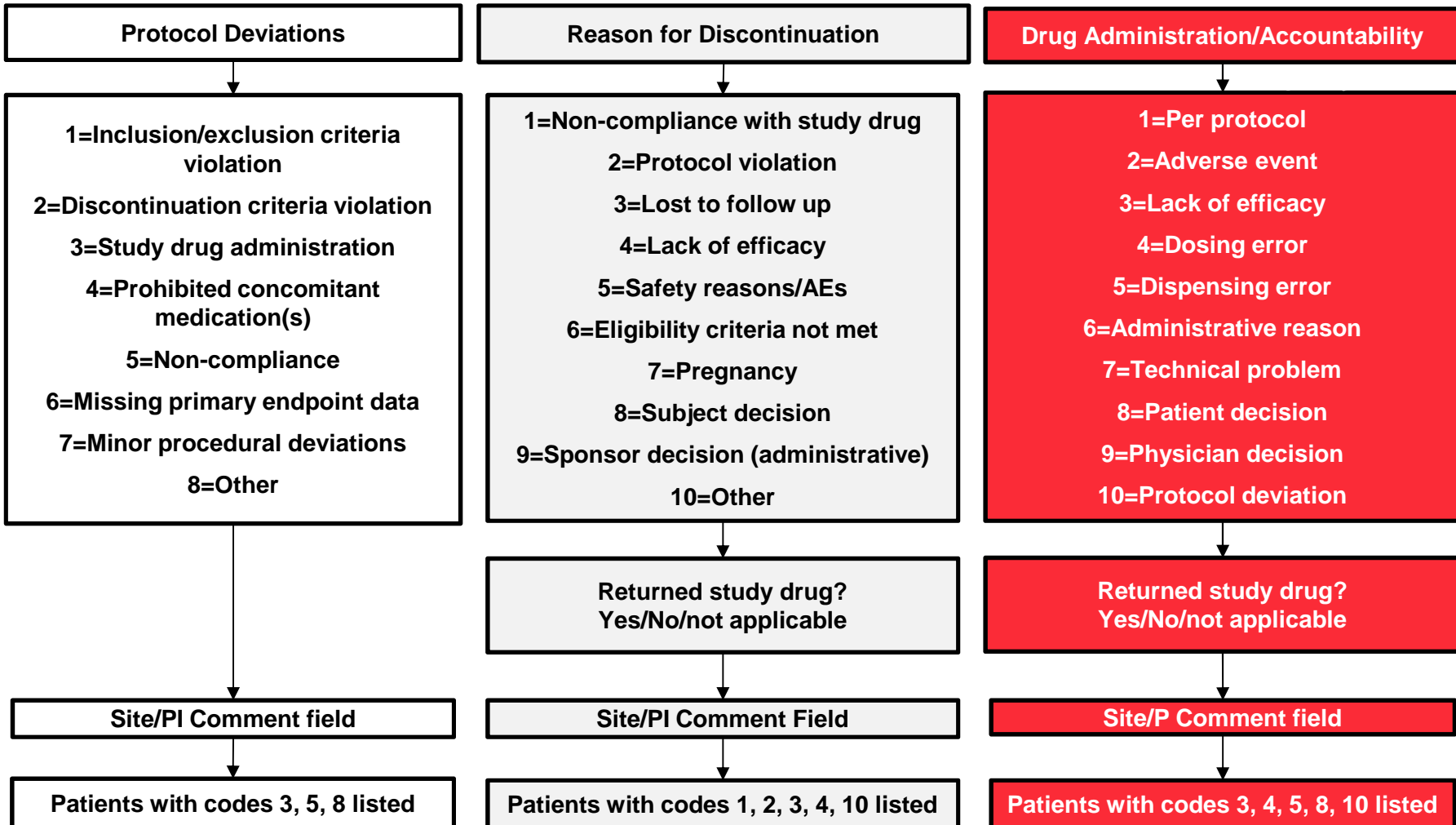
Retrospective Assessments

Please **database** administration records, protocol deviations, reasons for discontinuation, compliance, etc.



Consistent categories for such events and ‘coding’ across the clinical program can simplify retrieval and analysis at NDA submission stage

Adapted from Mansbach & Schoedel, Pharm Med in Press



Example Listing X.X.X.X

Study No.	Subject No.	Source of data (code)	Returned study drug?	Compliance	Comments
ABC	1234-001	Protocol deviation 5	Yes	87%	...
ABC	4567-002	Discontinuation 3	No	135%	

Challenges in tracking diversion and aberrant behaviors

- Predictive validity and low signal detection
 - Large amount of data to examine (retrospective) but the vast majority of discrepancies, deviations etc. are unlikely to be related to abuse
 - Patients don't admit to diversion and aberrant drug behaviors
 - The open market?
 - Most NMEs won't have any street value – very limited 'market'
 - Opioids and some other classes may have known value
 - **My unscientific survey:**
 - Recreational user websites occasionally mention opioid clinical trials as being of interest (to 'get hands' on a drug of abuse)
- Interpretation and clinical relevance
 - What constitutes a 'signal', particularly when examining retrospective data sources – such data are not in the literature and sponsor has no basis of comparison

Conclusions

- Two most important thing you can do to track diversion and aberrant behaviors in clinical trials:
 - 1) **Alert/train sites and investigators** to these events/behaviors and train on recording/tracking
 - 2) **Systematize/code and database** standard clinical trial data, *with comment fields*
- Other items such as checklists, UDS, etc. probably not useful for most indications/drugs, other than perhaps opioids/pain patients
 - May improve over time, however, signal detection is still likely to be very low for the majority of indications and NMEs

Thank you

