Towards a Classification of Abuse-Related Events in Analgesic Clinical Trials

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Contributors

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- Renee Young, Data Management
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- Beatrice Mendez, Project Management
- (Judith Jones, Degge Group)

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Background

- Abuse-deterrent opioids (ADO) are being developed in response to concerns of addiction/misuse/abuse
- Clinical trials must be able to accurately identify and report behaviors and adverse events that discriminate rates of abuse-related phenomena between products
- There is great variability in the identification, categorization, and coding of misuse and abuse of opioids

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"Abuse-related" problems associated with Rx opioids?

- Fatal overdose
- Nonfatal overdose
- Addiction ("dependence") (to the opioid)
- Addiction (to other things)
- DSM-4 abuse
- Accidental pediatric exposure
- Misuse
- Diversion
- Tampering
- Altering route of administration
- Successful tampering

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More opioid problems…

- Purposeful sedation
- Prescribing error
- Felt intoxicated
- Acted intoxicated
- Early refills
- Increased dose for pain on their own
- Lost medication
- Recreational use
- Doctor shopping
- Rx forgery
- Positive urine tox
- Negative urine tox
- Drank alcohol for pain
- Missed appointments
- Mood disorder

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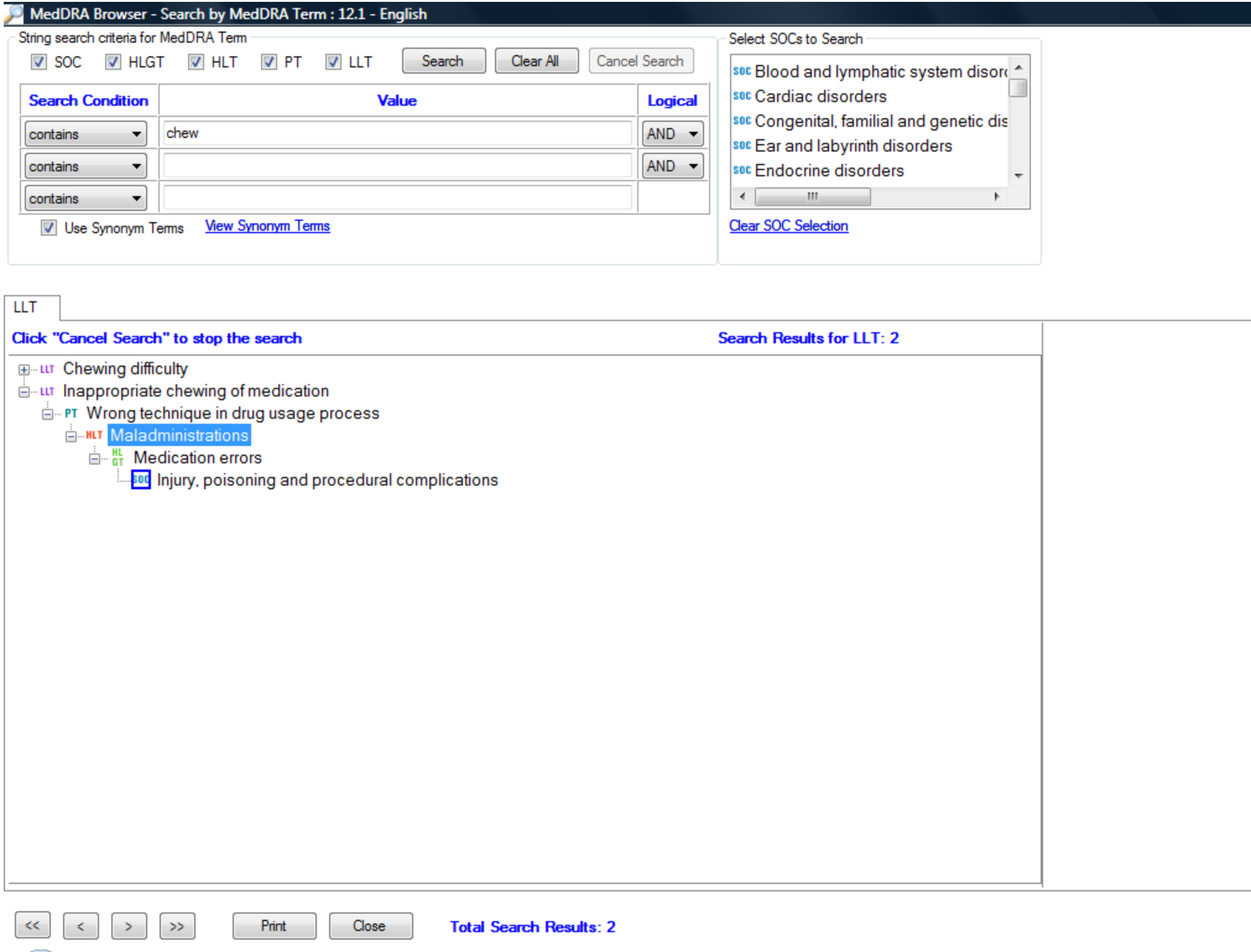
Example: “I Feel High”

Lowest Level Term	Preferred Term	High Level Term	High Level Group Term	System Organ Class
Addict, Drug Abuser, Drug Addict, Injection Drug User, Intravenous Drug User	Drug Abuser	Drug and Chemical Abuse	Lifestyle issues	Social Circumstances
Ex-Drug Abuser	Ex-Drug Abuser	Drug and Chemical Abuse	Lifestyle issues	Social Circumstances
Ex-Intravenous Drug User				
Substance Abuser	Substance Abuser	Drug and Chemical Abuse	Lifestyle issues	Social Circumstances
Euphoria, Euphoric, Euphoric Mood, Exaggerated Well-Being, Feeling High, Felt High, High, High Feeling, Laughter	Euphoric Mood	Emotional and Mood Disturbances NEC	Mood Disorders and Disturbances NEC	Psychiatric Disorders
Elevated Mood, Mood Elevated	Elevated Mood	Emotional and Mood Disturbances NEC	Mood Disorders and Disturbances NEC	Psychiatric Disorders
Distress, Distress Complain Increased, Emotional Distress, Mental Distress	Emotional Distress	Emotional and Mood Disturbances NEC	Mood Disorders and Disturbances NEC	Psychiatric Disorders
Affect Alteration, Affect Altered, Altered Mood, Bad Mood, Mood Alteration NOS, Mood Altered, Mood Change	Mood Altered	Emotional and Mood Disturbances NEC	Mood Disorders and Disturbances NEC	Psychiatric Disorders
Lethargy, Listless	Mood Disorders NEC	Emotional and Mood Disturbances NEC	Mood Disorders and Disturbances NEC	Psychiatric Disorders
Adverse Drug Reaction, Side Effect	Adverse Drug Reaction	Therapeutic and Nontherapeutic Responses	Therapeutic and Nontherapeutic Effects	General Disorders and Administration Site Reactions


MedDRA Browser - Search by MedDRA Term : 12.1 - English
String search criteria for MedDRA Term
SOC
HLGT
HLT
PT
LLT
Search
Clear All
Cancel Search
Search Condition
Value
Logical
contains
chew
AND
contains
AND
contains
Use Synonym Terms
View Synonym Terms
Select SOCs to Search
SOC Blood and lymphatic system disor
SOC Cardiac disorders
SOC Congenital, familial and genetic dis
SOC Ear and labyrinth disorders
SOC Endocrine disorders
Clear SOC Selection
LLT
Click "Cancel Search" to stop the search
Search Results for LLT: 2
LLT Chewing difficulty
LLT Inappropriate chewing of medication
PT Wrong technique in drug usage process
HLT Maladministrations
HLGT Medication errors
SOC Injury, poisoning and procedural complications
<<
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Print
Close
Total Search Results: 2

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Questions

- Is this relevant?
- Was the medication taken to achieve this effect or side effect?
- Reportability? Patient selection
- Is this abuse?
- Is this misuse?

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Example: “Overuse of Medication”

Lowest Level Term	Preferred Term	High Level Term	High Level Group Term	System Order Class
Deliberate Overdose, Drug Overdose Deliberate Self-Inflicted, Intentional Overdose, Non-Accidental Overdose, Overdose Deliberate Self-Inflicted,	Intentional Overdose	Overdoses	Medication Errors	Injury, Poisoning, and Procedural Complications
Overdose Intentional, Acute Overdose, Chronic Overdose, Overdose, Overmedication	Drug Overdose	Overdoses	Medication Errors	Injury, Poisoning, and Procedural Complications
Unintentional Use Beyond Label Duration	Medication Error	Medications Errors NEC	Medication Errors	Injury, Poisoning, and Procedural Complications

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Questions

- Intentional of unintentional?
- Underdose or overdose?
- Addiction or pseudoaddiction?
- Misuse or abuse?
- Consequences?

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Five approaches to comparing abuse-related phenomena

1. Ad hoc sorting of AEs (e.g. Fentora)
2. Standardized sorting of AEs (e.g. SMQ)
3. Expert classification of retrospective data (e.g. C-CASA)
4. Expert classification of retrospective + prospective/prompted data (e.g. Purdue)
5. Prospective evaluation of key outcomes using validated instruments (Haythornthwaite)

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Ad Hoc Sorting of AEs

Review and Assessment of Risks for Abuse and Diversion”

Table 1: Types of Aberrant Drug-use Behaviors (Sponsor identified)	
Abuse/dependence	**Study drug theft**
Overdose	**Lost to follow-up**
Motor vehicle accident	Seeking prescriptions from other sources
Fear of addiction	Lost study drug
Discharged from practice	**Overuse of study drug**
Positive urine drug screen	Acquiring opioids from other medical sources
Unreliability	Unapproved use of a medication used for another symptom
Using nonprescribed medication	

FDA presentation of sponsor assessment, Fentora adcomm, May 2008

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Aberrant drug use behavior

Table 2: Sponsor's Summary of Patients by Risk Category		
Risk Category	Number of Patients¥	Percent
High risk behaviors*	30	3%
Abuse/dependence	8	<1%
Overdose	9#	1%
Positive urine drug screen	13	1%
Other aberrant behaviors	126	13%
None	785	83%

FDA presentation of sponsor assessment, Fentora adcomm, May 2008

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Aberrant drug use behavior

Table 3: Aberrant Behaviors Identified in > 1% of Patients (Identified by Sponsor)		
Behavior	Number of Patients	Percent
Overuse of study drug	44	5%
Study drug thefts	35	4%
Lost to follow-up	33	4%

FDA presentation of sponsor assessment, Fentora adcomm, May 2008

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Serious Adverse Events related to overdose, misuse, or similar

	Non-cancer Population	Cancer Population
Total N	941	358
Accidental overdose	8	0
SAE related to drug dependence/withdrawal/ abuse	2	0
SAE possibly related to oversedation (MVA with severe CNS and orthopedic injury where patient was the driver)	1	0

FDA Analysis, Fentora adcomm, May 2008

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Non-serious adverse events, moderate or severe in intensity, related to CNS depression, psychotropic effects, or respiratory depression, duplicates deleted

	Non-Cancer N=941		Cancer N=358	
Pooled Term	n	%	n	%
Dizzy	22	2.3	1	8.0
Lightheaded	10	1.1	14	3.6
Confusion	14	1.5	2	2.8
Fall	19	2.0	7	2.0
Seizures	0	0	1	0.3
Sedation	61	6.5	14	3.9
Withdrawal	12	1.3	1	0.3
Fracture	17	1.8	2	0.6
Syncope	4	0.4	1	0.3
Likability of opioid	7	0.7	2	0.6
One case each of: Addictive behavior, substance abuse, personality change, six cracked bottom front teeth, paranoia, car accident, impaired balance, physical trauma	8*	0.8	0	0

FDA Analysis, Fentora adcomm, May 2008

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"Our preliminary review of the sponsor's data indicated additional cases of potential abuse than the 30 identified as "high risk" by the sponsor in their report "Review and Assessment of Risks for Abuse and Diversion". Thus, the sponsor's interpretation and conclusions concerning potential health risks of fentanyl buccal tablet when used in non-cancer break-through-pain (BTP) are not consistent with the CSS assessment and underestimate this risk."

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Limitations of ad hoc approach

- Approach non standardized
- Methods not transparent
- Results depend on perspective of who is doing analysis
- Validity of mapping of events to categories unknown
- Requires an accepted classification system
- Relevance of choices of events, diagnoses, or categories of interest is unclear

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Standardized Sorting of AEs

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Introductory Guide for Standardised MedDRA Queries (SMQs) Version 12.0

MSSO-DI-6226-12.0.0

March 2009

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MedDRA

- Medical Dictionary for Regulatory Activities
- Safety-oriented medical terminology with emphasis on ease data entry, retrieval, analysis, display
- Developed by International Conference on Harmonisation (ICH)
- Owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee.

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Standardized MedDRA Query

- Groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest.
- Aid in retrieval of potentially relevant individual case safety reports.
- Terms: signs, symptoms, diagnoses, syndromes, physical findings, labs, etc.
- Joint effort of CIOMS and MSSO since 2003
- Choice of sensitivity-specificity balance

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2.22 *Drug abuse, dependence and withdrawal (SMQ)*

(Production Release September 2007)

2.22.2 Inclusion/Exclusion Criteria

- Included:
  - Drug abuse/dependence:
    - All terms containing "abuse," "intentional misuse," "illicit drug," or "dependence" included as narrow terms
    - Terms observed with abuse but which also occur without abuse (e.g. , "increased tolerance" or "overdose" or "drug level increased" or "drug toxicity") included as broad terms
    - Terms indicating neonatal events
  - Withdrawal
    - All terms containing "drug withdrawal" included as narrow terms
    - Terms only containing "withdrawal" or "rebound" included as broad terms
    - Terms indicating neonatal events

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“Validation” of SMQ

Regulatory agency and/or company "test" it on arbitrarily chosen + and - drugs in their databases and terms are accepted if they are:

1. more frequent in the + control test and/or
2. unquestioningly have face validity as a diagnosis term or the like

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 25, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

Subject: Abuse potential assessment of Zolpimist (Zolpidem tartrate) Oral Spray,

In addition to expedited reporting of the above Events of Interest, the Sponsor proposes to include a discussion in the quarterly periodic report based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" and will review

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Pros and Cons of SMQ

- Standardized
- Flexible
- Accommodates specificity or sensitivity
- Can be used on retrospective data
- Can be combined with other approaches

- Requires an accepted classification system
- Limited validation for case retrieval
- Precision of classification unknown
- GIGO – limited by investigators
- Limited by MedDRA

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3

Expert Classification of Retrospective Data

Expert Classification of Retrospective Data

- You develop a classification system for the clinical phenomena of interest
- Cases are flagged and pulled based on broad search terms
- Trained experts sort cases into groups

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Pros & Cons

- Standardized
- Reliability and validity can be documented
- Can be applied retrospectively
- Experts can consider clinical nuances
- Track record (C-CASA)
- Requires accepted classification system
- GIGO – relies on investigators
- Relies on flagging process

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Dr. Posner to discuss C-CASA

We'll get back to it later.

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4

Expert classification of retrospective + prospective/ prompted data

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Expert classification of retrospective + prompted data

- You develop a classification system
- Investigators are trained or prompted by prespecified flags (e.g. AEs)
- Prompt leads to additional evaluation, completion of CRF, etc.
- Experts adjudicate standard data plus prompted supplemental info

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Pros & Cons

- Standardized
- Reliability and validity can be documented
- Experts can consider clinical nuances
- Track record for approach
- Reduces problem of poor classification due to inadequate data

- Requires accepted classification system
- Relies on prompting process
- Cannot be applied to retrospective data

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Dr. Colucci to discuss a Purdue study using this method.

We'll get back to it later.

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5

Prospective evaluation of key outcomes using validated instruments

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Prospective evaluation of key outcomes using validated instruments

- Decide what your key clinical outcome constructs are
- Find a “fit for purpose” measure of this construct (or develop one)
- Implement it prospectively for all subjects in the study

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Pros & Cons

- Standardized
- Reliability and validity can be documented
- Standard approach in clinical trials
- Reduces problem of poor classification due to inadequate data
- Likely to give most accurate classification of outcomes

- Requires selecting appropriate construct
- Requires validated measure of construct
- Cannot be directly applied to retrospective data

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Dr. Haythornthwaite to discuss potential constructs and available measures

We'll get back to this later.