Standard Approaches to Adverse Event Reporting

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Scope & Goal Of Presentation

Review literature on standard approaches to AE reporting relevant to helping the discussion today

Identify current issues

Outline steps that can be taken to improve the current approach

Benefit of Adverse Event (AE) Collection

In Clinical Trials:

- **Identify events that effect patients (pts)**
- **Notify investigators, pts, regulators & others**
- **Informs conduct of trial & risk management**
- **Reporting of AEs in clinical trials is critical to understanding treatment safety**

Expert Review of Clinical Pharmacology 6(2):185-195, 3/2013

US Spontaneous AE Reporting

- Voluntary reporting
- Most AEs are not detected
  - Often important ADRs missed
- Information is often incomplete & of limited value
  - Differences in definitions, data collection and analysis methods

Institute of Medicine (US) Committee on Data Standards for Patient Safety; Aspden P, Corrigan JM, Wolcott J, et al., editors. Washington (DC): National Academies Press (US); 2004.
Stroke. 2004;35:533-537

General Challenges re: AE data

Incomplete history/info

Concomitant or prior treatments

Comorbidities

Monitoring AEs is complex & labor intensive

- Multiple AEs / pt
- Definitions differ
- Interpretations differ
- Heterogeneity in adjudication

NCI CTCAE is complicated: reproducible, systematic AE capture is difficult

Journal of Clinical Oncology 34, no. 13 (May 2016) 1537-1543.
Am Heart J 2015;169:197-204.

Key factors contributing to AE under-reporting

- Lack of standardized process
- Lack of training & education
- Lack of integrated health information technologies

Drug Saf. 2016; 39(11): 1117–1127.

A Survey of Adverse Event Reporting Practices Among US Healthcare Professionals

- Reasons HCPs cite for not reporting:
  - The patient did not report
  - Difficulty determining cause of event
  - Time
  - Poor integration of reporting system
  - Uncertainty of procedures
  - Fear of punishment, shame & reputation, liability
  - Lack of a perceived benefit

Drug Saf. 2016; 39(11): 1117–1127.
N Engl J Med 2002; 347:1633-1638 November 14, 2002

Accuracy of Adverse Event Ascertainment in Clinical Trials for Pediatric Acute Myeloid Leukemia

Reporting of AEs in clinical trials is crucial to understanding treatment safety

- **Data on AE accuracy are limited**

The current system of AE reporting for cooperative oncology group CTs in pediatric AML underestimates AE rates

The high sensitivity & PPV of Pediatric Health Information System data suggest that using external data sources may improve the accuracy of AE reporting

Journal of Clinical Oncology 2016 34:13, 1537-1543

Improving Reporting

2009-2010: ADRs were detected in 0.5% of patients in a tertiary Midwest pediatric hospital

Historical ADRs were often inaccurately or incompletely documented

An integrative Drug Safety Service (DSS) was implemented to improve the detection & accurate documentation of ADRs

DSS provided extensive hospital staff education on ADR reporting and the role of DSS.

Proactive DSS resulted in a fourfold increase in reporting

Ther Innov Regul Sci. 2013;47(5):566–571.

Research on Adverse Drug Events And Reports (RADAR) project

- ADR reports are of variable quality
- HCPs rarely f/u on queries from FDA or Pharma
  - Near 100% f/u from RADAR investigators
  - Active surveillance provided timelier & more complete information

Arch Intern Med. 2007;167(10):1041-1049
Stroke. 2004;35:533-537

The Missing Voice of Patients in Drug-Safety Reporting

HCPs: systematically downgrade symptom severity

miss & and fail to note AEs

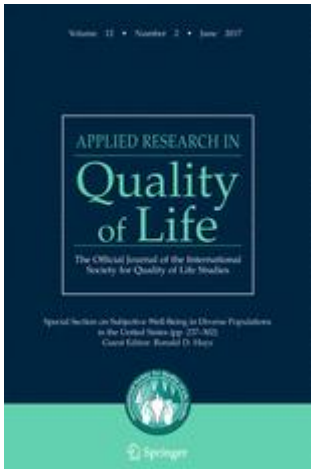
- results in the occurrence of preventable AEs

Collect AE data directly from pts

- Pts report symptoms earlier & more frequently than clinicians

Basch E. N Engl J Med 2010;362:865-869.

Reliability of adverse symptom event reporting by clinicians



The purpose of this study was to assess the reliability of AE reporting of different clinicians for the same pt during the same visit.

- **A retrospective reliability analysis was completed for a sample of 393 cancer pts**

- **Agreement between different clinicians when reporting adverse symptom events is moderate at best**
- **Modification of approaches to adverse symptom reporting, such as patient self-reporting, should be considered**

Qual Life Res. 2012 Sep;21(7):1159-64.

Organizational Change in the Face of Highly Public Errors. The Dana Farber Cancer Institute Experience

Dec 3, 1994, 39-yo *Boston Globe* health reporter Betsy Lehman died: cyclophosphamide OD

- **2nd pt had similar OD**

Failures in SOPs

Changes: New rules, supervision, training, double-check, interdisciplinary teams to report toxicity

Developed & refined error reporting through pharmacy interventions, incident reports, & pt safety rounds

Patient Safety Network May 2005

Organizational Change in the Face of Highly Public Errors. The Dana Farber Cancer Institute Experience

Safety became responsibility of clinical & administrative leaders and trustees

- **Build culture of safety, supporting > transparency & reporting of events**

Developed & refined error reporting through pharmacy interventions, incident reports, & pt safety rounds

Developed order set templates & created an electronic order-entry system for chemotherapy

Patient Safety Network May 2005

Patient Focused Future Considerations

Standardized reporting systems

Ongoing institution-based surveillance - assist HCPs in reporting

Automated surveillance

Chart abstraction to determine AE reports

- Utilize external data sources

Active surveillance vs voluntary reporting

Training & education

Integration of cardiology: cardio-oncology

Include pts in meaningful manner; empowered to monitor & report

- Patient self-reporting

Drug Saf. 2016; 39(11): 1117–1127.
JCO 34, no. 13 (May 2016) 1537-1543
Cureus. 2017 May 18;9(5):e1258
J Clin Oncol. 2008 Nov 10;26(32):5204-12

Thank You

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Backup Information

Adverse reactions to oncologic drugs: spontaneous reporting and signal detection

- **Underreporting is a common problem in PV: it is likely to be higher for oncologic drugs**
- **The perception of risk/benefit of a treatment by physicians is usually conditioned by the clinical severity and prognosis of the disease to be treated**
  - **On this basis, ADRs involving oncologic drugs may be sometimes regarded as a secondary problem, and their spontaneous reporting is usually considered as a low-priority activity in the routine clinical practice.**
  - **Since cancer patients are usually quite ill and the antineoplastic agents used are often quite toxic, the threshold for spontaneous ADR reporting is unfortunately fairly high.**
- **Their reasoning for reporting only very severe and (unusual) suspected ADRs is that their patients experience ADRs very frequently and some practical discretion must be used in reporting.**
- **Furthermore, it is conceivable that the oncologist tends to under-evaluate the importance of recording any adverse event that is not strictly related with the disease progression.**
- **Sometimes, identification of a causal relationship between an event and a treatment is not easy with such complex patients, and the oncologist may tend to ascribe the adverse event to another underlying non-cancer disease, therapy or cancer progression.**

Expert Rev. Clin. Pharmacol. 8(1), 61–75 (2015)

Under Reporting

Potential factors:

- Assessment by clinicians might not represent the experience of pts
- AE might be detected within trials, but is not reported appropriately by investigators or reporting is influenced by sponsors
- Short-term follow-up might not detect long-term & potentially serious toxicities
- Selection of pts with good functional status in clinical trials study results might not apply to pts treated in everyday clinical practice

Lancet Oncol 2016; 17: e209–19

Office of the Inspector General

2012: No improvements in reporting

Hospitals continue to report 1 % of ADEs

Of note, although 60 % of ADEs occurred in hospitals with infrastructure in place for reporting, only 12 % of ADEs were reported by hospitals with such infrastructure

Drug Saf. 2016; 39(11): 1117–1127.

FDA is working with hospitals to modernize data collection about medical devices

Hospital personnel are the front line of surveillance, vigilance, and intervention

Federal law requires hospitals & other user facilities to report

Inspected 17 facilities

Learnings:

- **Some hospitals didn't submit required reports**
- **Inadequate procedures for reporting**
- **HCPs unaware (lack of training)**

Consider modifying current requirements

Posted on October 24, 2016 by FDA Voice

Use and misuse of common terminology criteria for adverse events in cancer clinical trials

Screened 1110 articles, analysis of 166 Ph 3 RCT publications 2011 – 2013

Poor reporting of toxicity in clinical trials:

- AE terms & grades not used correctly
- Inaccurate toxicity reporting
  - Can lead to incorrect tx decision(s)

BMC Cancer. 2016; 16: 392.

Agency for Healthcare Research & Quality

Utilized Common Formats to standardize safety reporting

Allows for aggregation of comparable data at multiple levels (local, regional, national)

Build culture of safety, supporting > transparency & reporting of events

PSOPPC Web site

QuarterWatch™ (Special Report): A critique of FDA's key drug safety reporting system

One year period ending in 3/17/2014 FAERS received 847,039 reports, including 41,884 deaths outside the US & 45,688 deaths in the US

FDA reporting system needs modernization

96% of AE reports were from manufacturers,

Overall quality & value of US drug safety surveillance dependent primarily on manufacturers (collect, code, && follow)

46% of SAE reports submitted by pharma were reasonably complete

Institute for Safe Medication Practice

FDA establishes & enforces reporting requirements

Digital tools & marketing practices that enable extensive contacts between manufacturers, HCPs, & consumers can be extended to provide enhanced postmarket surveillance

Standardized AEs

- An accurate representation of AEs necessitates use of well defined, controlled & broadly accepted terms for thousands of clinical concepts
- Misclassification of AEs can have serious consequences
- Interobserver variation: 2 blinded coders of verbatim terms - 12% coded differently
- Pharma utilizes MedDRA to code the AEs reported by investigators

Contemp Clin Trials. 2008 Sep; 29(5): 635–645

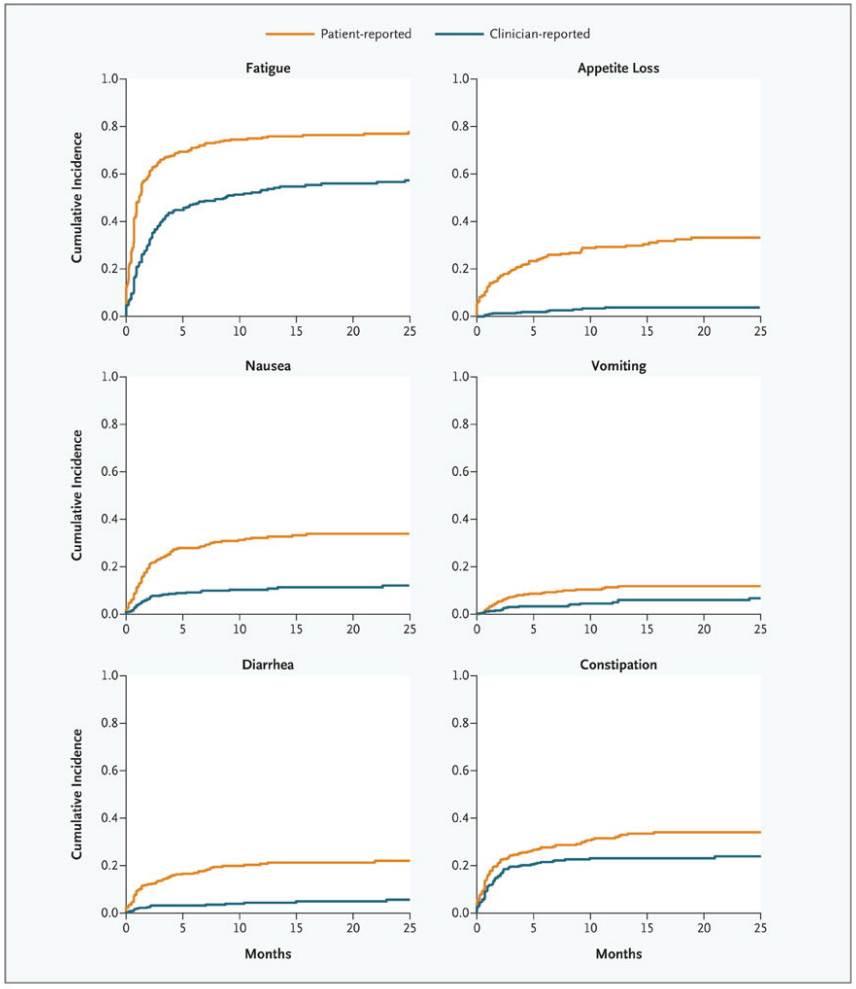
Contemp Clin Trials 2006;27(1):13–22..

AE Reporting in the US

- Voluntary reporting
  - most AE are not detected
- ***There are many ways to detect adverse events—through reporting systems, document review, automated surveillance of clinical data, and monitoring of patient progress. These approaches are ultimately complementary and require a broad range of data elements***

Patient safety : achieving a new standard for care.
Chapter 6, p 200. Inst of Medicine. National Academies Press. 2004

Cumulative Incidence of Adverse Symptom Events over Time as Reported by Patients versus Clinicians at Successive Office Visits.



Basch E. N Engl J Med 2010;362:865-869.

Adverse reactions to oncologic drugs: spontaneous reporting and signal detection

Involvement of well-trained patients in ADR reporting using online tools would be an interesting approach to improve the efficiency of pharmacovigilance of oncologic drugs

In this context, promising preliminary results have been obtained by a group coordinated by Basch at the Memorial Sloan-Kettering Cancer Center in New York

Accelerated the procedures for anticancer drug approval (median time saved compared with regular approval: 3.9 years; range 0.8–12.6 years) [9] since the beginning of 90s [10], and this circumstance may theoretically result in the early release of unsafe or ineffective drugs

Expert Rev. Clin. Pharmacol. 8(1), 61–75 (2015)

Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys.

- Compared with HCPs, patient reports to the YCS contained a higher median number of suspected ADRs per report, and described reactions in more detail. The proportions of reports categorised as 'serious' were similar; the patterns of drugs and reactions reported differed. Patient reports were richer in their descriptions of reactions than those from HCPs, and more often noted the effects of ADRs on patients' lives.
- The addition of patient reports to HCP reports identified 47 new 'serious' reactions not previously included in 'Summaries of Product Characteristics'

Health Technol Assess. 2011 May;15(20):1-234, iii-iv.