

Evolving Clinical Paradigms-A Focus on REMS and CER

Kimberly Binaso-Stwalley Pharm.D, RPh, CCP,FASCP, CGP, FASHP

**Evolving Clinical Paradigms-
A Focus on REMS and CER**

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Objectives:

- Explain the FDA Amendment Act of 2007 and the inclusion of REMS
- Describe the components of a REMS program and discuss how they might impact senior care
- Describe the American Recovery and Reinvestment Act of 2009 and its focus on CER
- Describe the different types of CER noting the key stakeholders involved and the priority areas for research

REMS

- Definition:
Risk Evaluation and Mitigation Strategy
- Is REMS a new concept?
- Where did REMS come from?
- What elements are specifically required for REMS

FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/2014/08/2014-08-20-ucm181178.pdf>
Accessed: December 21, 2009

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Background

- Medication safety concerns over the last decade
- Over 500 medications now carry a black box warning
- FDA updated or added 31 boxed warnings to medications in 2009 (56 in 2008)
- FDA is under scrutiny for medication safety
- RiskMAPS (Risk Minimization Action Plans)
 - Began in 2002 (Isotretinoin, Thalidomide, Clozapine)
- Drug development in more personalized and specialized (Biologics)

<http://www.ashp.org/import/news/pressrelease.aspx?id=432>, Accessed Dec. 21st, 2009

So what exactly are REMS?

- REMS are requirements that a drug must be dispensed with one or more of the following items:
 - Medication guide and/or package insert
 - Communication plan to health care providers
 - Elements to assure safe use (ETASU)
 - a) Provider and/or pharmacy training
 - b) Lab test requirements
 - c) Patient registries
 - d) Other elements as defined by the FDA

FDA Guidance for Industry Regarding REMS
<https://www.fda.gov/oc/ohrt/2009/GuidanceComplianceRegulatoryInformation/Guidance/UCM184128.pdf>
Accessed: December 21st, 2009

Food and Drug Administration Amendment Act of 2007

- FDAAA
 - reauthorized PDUFA
 - expanded clinical trial registry data bank
 - Allows FDA to collect fees from the pharmaceutical industry for new drug applications
 - Reauthorized best pharmaceuticals for children act, pediatric research equity act, medical device user fee modernization act
 - Statutory authority to require REMS



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REMS and FDAAA

- FDAAA increased FDA responsibilities related to pre and post market drug safety
- FDA can:
 - Require new post-marketing studies/ clinical trials
 - Safety related labeling changes
 - Manufacturers must develop and comply with REMS
- Effective March 2008

**Food and Drug Administration
Amendment Act of 2007**

- FDAAA:
 - A product previously approved with a RiskMAP will be approved with a REMS
 - Products previously approved with a med guide or patient package insert will have a REMS
 - REMS require periodic assessment by the FDA
 - REMS include fines as an enforcement vehicle (\$250,000/violation, \$1million single proceeding, prevention of sale of product)

FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>
Accessed: December 21st, 2009

When can a REMS be required?

- During anytime of a products lifecycle- initial or post approval
- Initial approval:
 - REMS submitted as part of a new drug application
 - FDA determines REMS in necessary to ensure benefits of the drug outweigh the risks


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Timetable for Assessments

- 18 months
- 3 years*
- 7 years



* If risks of drug are adequately being managed, assessed, and identified then no more assessments may be needed

FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/downloads/CDER/CDERG/Compliance/RegulatoryInformation/Guidances/UCM184128.pdf>
Accessed: December 21st, 2009

REMS considerations

- Initial approval:
 - Population size
 - Expected benefit
 - Expected duration of treatment
 - Seriousness of disease or condition
 - Known/ potential adverse events
 - New molecular entity
- Post approval:
 - FDA becomes aware of new safety issues
 - REMS necessary to assure benefits outweigh the risks

FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/downloads/CDER/CDERG/Compliance/RegulatoryInformation/Guidances/UCM184128.pdf>
Accessed: December 21st, 2009

MedGuides

- Simplest form of REMS
- Required if one of the following is determined:
 - drug has serious risks that patients should be made aware of as it could influence use
 - guide could prevent serious adverse events
 - patient adherence to directions for use is critical to the drug's effectiveness
- Inpatient vs. Outpatient?
Regulation: "Applies primarily to human prescription drug products used on an outpatient basis without direct supervision by a health professional"
- Examples: ESA's (Aranesp®, Procrit®, Epogen®)

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Communication Plans

- Education directed at healthcare providers:
 - Letters
 - Medical societies/ professional organization
 - Websites
 - MSL slide deck
- Content:
 - REMS
 - Safety risks
 - Processes for safe use
- Examples: Multaq®, Byetta®



FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/downloads/Drugs/ComplianceRegulatoryInformation/Guidances/UCM184128.pdf>
Accessed: December 21st, 2009

ETASU

- Elements to Assure Safe Use
"Intended to provide safe access to drugs with known serious risks that otherwise would be unavailable"- FDA
- Other REMS requirements not sufficient
- Special training, requirements, certification, and experience for prescribers and pharmacies
- Dispensing of the medication in certain health care settings
- Special monitoring
- Patient Registry
- Examples: Entereg®, Onsolis®



FDA Guidance for Industry Regarding REMS:
<https://www.fda.gov/downloads/Drugs/ComplianceRegulatoryInformation/Guidances/UCM184128.pdf>
Accessed: December 21st, 2009

REMS for Opioid Class?

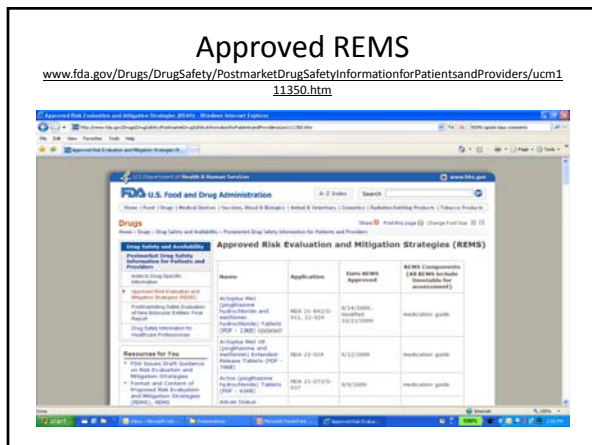
- First REMS for an specific drug class (LA/ ER Opioids)
- Could be applied to both inpatient and outpatient settings
- Over 2,000 comments initially received
- Re-opening of comment period through October 19, 2010
- <http://www.regulations.gov>

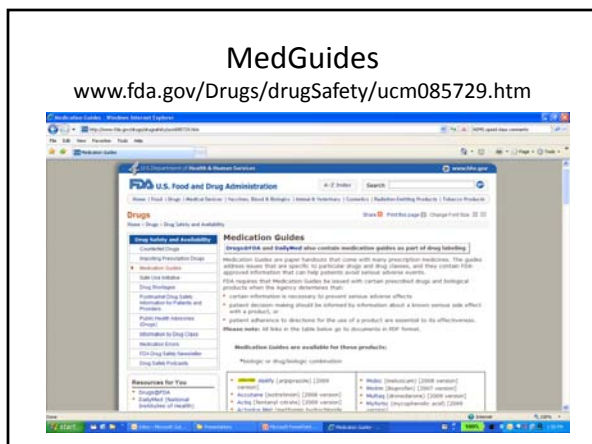


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REMS Concerns

- Lack of a systematic, standardized system
- Patient access
- How effective are medication guides?
- Restricted distribution creates barriers to access for appropriate patients
- Access to a specialized REMS provider
- Pharmacy training
- Administrative burden



American pharmacists association. White Paper on designing a REMS system to optimize the balance of patient Access, medication safety, and impact on the healthy care system. J Am Pharm Association 2009; 49(6): 729-743

Insights for Senior Care



- Continuity of Care/ Transitions of Care
- Medication Guides: inpatient vs. outpatient
- ETASU: Access to medication? Limited distribution?
- Communication among interdisciplinary team, facility, pharmacy, and family
- Will REMS medications be feasible in senior care?

Comparative Effectiveness Research (CER)



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What is CER?

- Institute of Medicine:
“ Comparative Effectiveness Research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or improve the delivery of care. The purpose of CER is to assist *consumers, clinicians, purchasers, and policymakers* to make informed decisions that will improve healthcare at both the individual and population levels”

DuBois R. Demystifying Comparative Effectiveness Research: A case study learning guide. White paper: Cerner Life Sciences: November 2009

Background on CER

- Level of spending on healthcare in US exceeds all other countries
- In 2007, costs rose 6.1% to \$2.2 trillion dollars
- 16.2% of the GDP
- In 2017, healthcare costs are expected to reach \$4.3 trillion dollars
- Professional services (Physician/hospital) still account for a larger % of total expenditure vs. pharmaceuticals (31.3%, 31.1%, 10.1%)

Schumock G, Pickard S. Comparative effectiveness research: Relevance and applications to Pharmacy. Am J Health Syst Pharm Vol. 66; 2009. E2-E10.

Healthcare issues leading to CER:

- Regional variations in medical practice in the US
- Lack of consensus regarding effectiveness of treatment interventions
- Fueled outcomes research movement in 1990's with pharmaceuticals
- Drug development and approval processes do not given enough guidance to decide among drugs or other interventions used for the same purpose.

Schumock G, Pickard S. Comparative effectiveness research: Relevance and applications to Pharmacy. Am J Health Syst Pharm Vol. 66; 2009. E2-E10.

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American Recovery and Reinvestment Act (ARRA)

- Signed by President Obama on February 17, 2009
- Contained \$1.1 billion dollars for CER
- AHRQ obtained \$300 million (10x AHRQ's annual budget for CER)
- NIH obtained \$400 million
- HHS obtained \$400 million
- CER has moved into high visibility
- New legislation may create an agency for oversight

CER at its core:



- Two purposes:
 - 1) Comparison of two or more agents or interventions that are considered true therapeutic alternatives
 - 2) The examination of effects (outcomes) in actual practice
- Not a new concept (ALLHAT, CATIE)

DuBois R. Demystifying Comparative Effectiveness Research: A case study learning guide. White paper: Cerner Life Sciences: November 2009

Understanding Efficacy vs. Effectiveness

- Efficacy: A clinical outcome derived from patients use of a pharmaceutical product in controlled settings. (RC Phase I-III)
- Effectiveness: A clinical outcomes derived from patients use of a pharmaceutical product in "real world" settings. (Post marketing)

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Common Themes to CER

- Comparison of one treatment to one or more other treatments
- Comparison that encompass more than just medications (devices, procedures)
- Assessments include benefits vs. risks
- Include input from key stakeholders
- Cost?

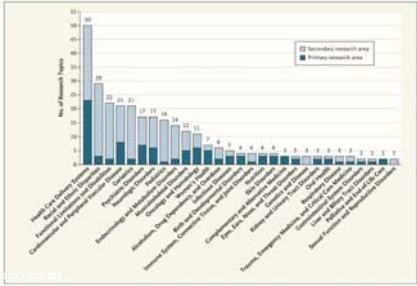
Dubois R. Demystifying Comparative Effectiveness Research: A case study learning guide. White paper: Cerner Life Sciences: November 2009

How do we get started?



- “None of us agree on what CER actually is, but we all agree it will cost about \$5B to do it”
-Jack Rowe, former CEO, Aetna
- “Whenever you observe unanimous support for a new idea in Washington, it means that the concept has not been adequately defined”
- Anonymous policy staff, Washington DC

Distribution of IOM’s Recommended CER Priorities



Inglehart J. Prioritizing CER-IOM Recommendations. NEJM 361:177-178 (2009)

THE NEW ENGLAND JOURNAL OF MEDICINE

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Examples of Top Areas for CER

- A.fib (surgery, catheter ablation, pharmacotherapy)
- Devices for hearing loss in children and adults
- Fall prevention methods (exercise, balance training)
- Upper endoscopy utilization and frequency in GERD patients
- Comprehensive care coordination programs in managing children and adults (medical home)
- Inflammatory diseases (RA, Crohn's, UC, P. Arthritis)
- Eradicating methods for MRSA
- Management strategies for prostate cancer
- Management strategies for patients with dementia + caregivers (community)
- Pharmacological vs. non-pharmacological interventions for AD and other dementias (community+ institutional)

Diamond F. Managed Care, November 2009 Accessed 12/16/2009

Features of CER:



- Three types of CER:
 - a) Randomized controlled trials (RCT)
 - b) Meta- Analysis
 - c) Observational studies
- Key stakeholders may be involved in the process
- Pros and Cons are noted with each study design

DuBois R. Demystifying Comparative Effectiveness Research: A case study learning guide. White paper: Cerner Life Sciences: November 2009

Framework for reviewing CER

- Step 1: Is it applicable to my population?
- Step 2: Consider whether any aspects of the study design might affect the result?
- Step 3: Consider whether the findings might change new research
- Education on how to evaluate this information will be critical for CER to meet its goals

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How will CER Stakeholders use this data?

- Patients/ Consumers: better health management
- Providers: value-based clinical decision making
- Payers/Purchasers: Economic support for healthcare delivery
- Industry: Product differentiation and evaluation
- Policy/ Thought-Leader Organizations: evidence based healthcare quality improvement
- Government: quality of care, evaluate treatments, expand coverage, and support economic choices within limited resources

CER Perspectives-FDA

- FDA acknowledges that certain areas of safety and efficacy must be measured by a relative assessment vs. available therapies
- In some cases, placebo control clinical trials is unethical
- Much harder to get second, third, and fourth drugs in a class approved
- Superiority analysis



CER Perspectives- Payer

“Right now, P&T committees all over the country make decisions based upon three components required for FDA approval- safety, efficacy, and tolerability. Where we need to go is to look at effectiveness, not efficacy.”


“ Committee members look beyond the usual safety and efficacy data to include such things as total cost of care, quality of life, and outcomes”.

- Brian Sweet, Chief Clinical Officer, Wellpoint

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AHRQ CER Website
<http://effectivehealthcare.ahrq.gov/index.cfm>



The screenshot shows the AHRQ CER Website homepage. The main heading is "Effective Health Care Program" with the subtitle "Helping You Make Better Treatment Choices". Below this, there is a section titled "What is Comparative Effectiveness Research" which explains that this research is designed to inform health care decisions by comparing or placing on the effectiveness, benefits, and harms of different treatment options. It also lists key points such as: "Researchers look at all of the available evidence about the benefits and harms of each to choose for different groups of people from existing clinical trials, clinical practice, and other research. These are called research reviews, because they are systematic reviews of existing evidence." and "Researchers conduct studies that generate new evidence of effectiveness or comparative effectiveness of drugs, treatment, practices, or health care services." The page also includes a sidebar with navigation links and a search bar.


NPC CER Learning Guide



The screenshot shows a presentation slide titled "DEMISTIFYING COMPARATIVE EFFECTIVENESS RESEARCH". The slide features a large blue circle graphic and the text "REPORT BY JENNIFER HAY AND OTHER CONTRIBUTORS". The slide is displayed in a software window titled "Alpha Slide".

Discussions around CER

- How far does \$1.1 billion dollars get you?
- Impact to specific patient populations such as geriatrics/ senior care?
- Personalized medicine?
- What about cost effectiveness?
- Do prescribers want this information at point of care?
- Who is qualified to interpret these results?
- Perfect storm or the perfect opportunity?



The icon shows a stick figure with a question mark above its head, symbolizing a question or a point for discussion.

Dubois K. Demystifying Comparative Effectiveness Research: A case study learning guide. White paper: Cerner Life Sciences; November 2009

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Summary

- As part of post marketing safety concerns, REMS requirements are continuing to emerge
- Collaboration among health care professionals regarding REMS requirements are essential to minimize the burden while improving patient safety.
- CER is designed to look at outcomes associated with the real world effectiveness of a product or intervention
- The purpose of CER is to assist *consumers, clinicians, purchasers, and policymakers* to make informed decisions that will improve healthcare at both the individual and population levels
