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# Improving Drug Safety: A Systems Approach

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- **Introduction**
- **Current System**
- **Limitations of Current System**
- **Proposal for the Future**

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# Improving Drug Safety: A Systems Approach

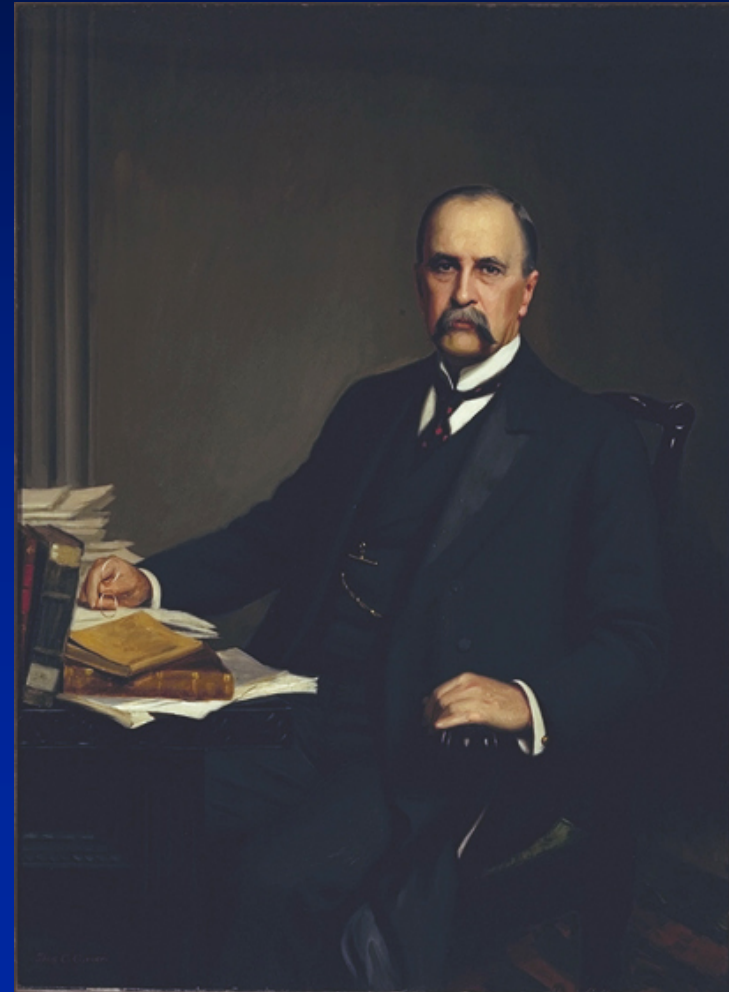
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- **“A desire to take medications is, perhaps, the greatest feature which distinguishes man from other animals.”**

Sir William Osler, 1891



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# Improving Drug Safety: A Systems Approach

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**“If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind , and all the worse for the fishes.”**

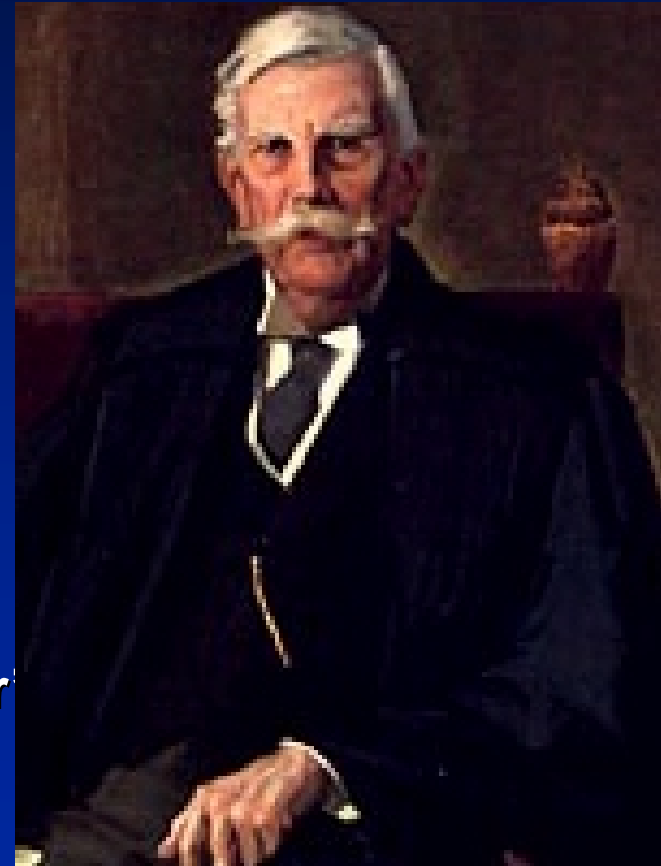
**Oliver Wendell Holmes**

**Medical Essays, “Comments and Counter**

**Currents in Medical Science**



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# Patient Safety and Medical Errors

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- **Iatrogenic injuries: up to 180,000 US deaths each year, and disability or prolongation of hospital stay in another 1.3 million**
- **Medical errors: 44,000-98,000 annual deaths, more than MVA, breast cancer, or HIV**
- **Medical errors: annual costs of \$17-29 billion**



# Risks Associated With the Use of Drugs

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- Adverse drug events are the most common iatrogenic causes of patient injuries



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# Phases of Drug Development



**PC: Preclinical studies**

**1: Dose escalation in normals**

**2: Dose ranging, first time in patients**

**3: Pivotal trials for registration**

**4: Post-marketing, not always required**



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# Data Sources for Pharmacoepidemiology Studies

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- Spontaneous case reports of adverse reactions
- Aggregate population-based data sources
- Computerized collections of data from organized medical care programs
- Data collected for pharmacoepi on an ongoing basis
- Existing data collected as part of other ad hoc studies
- Data collected de novo



# Spontaneous Case Reports of Adverse Reactions

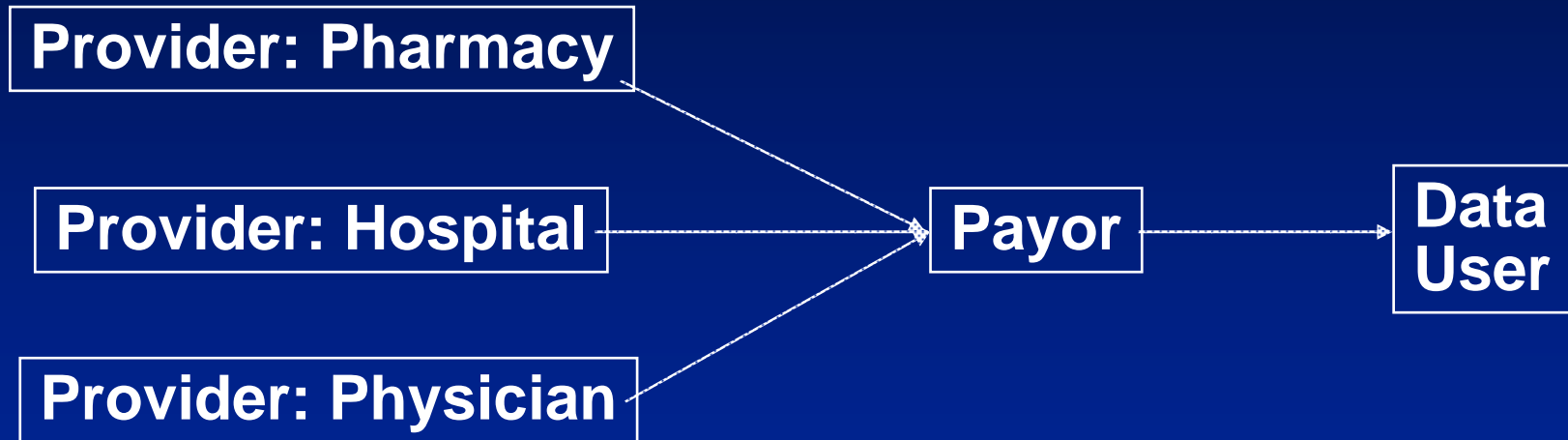
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- Relied on for hypothesis generation
- A 1950s era system, which has been computerized
- AERS for drugs, or VAERS for vaccines
- The plural of “anecdote” is not “data”



# Computerized Collections of Billing Data: Sources of Data

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# Key Problem of “Historical” Pharmacoepidemiology

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- Adverse drug events are the most common iatrogenic causes of patient injuries
- Most are the result of an exaggerated but otherwise usual pharmacological effect of the drug
- Yet, historically these have been ignored by pharmacoepidemiology, as they do not represent a focus of commercial and regulatory interest





***"Less than one in ten thousand—something like one in fourteen thousand—gets these side effects. Hardly anybody gets these side effects. They're extremely rare. You should be very proud."***

1 Do you remember which symptoms you began with, and which are side effects?



J. Harris



R

...OF COURSE, WITH ANY  
PRESCRIPTION DRUG,  
THERE ARE SIDE EFFECTS...



PHARMACY

SALE



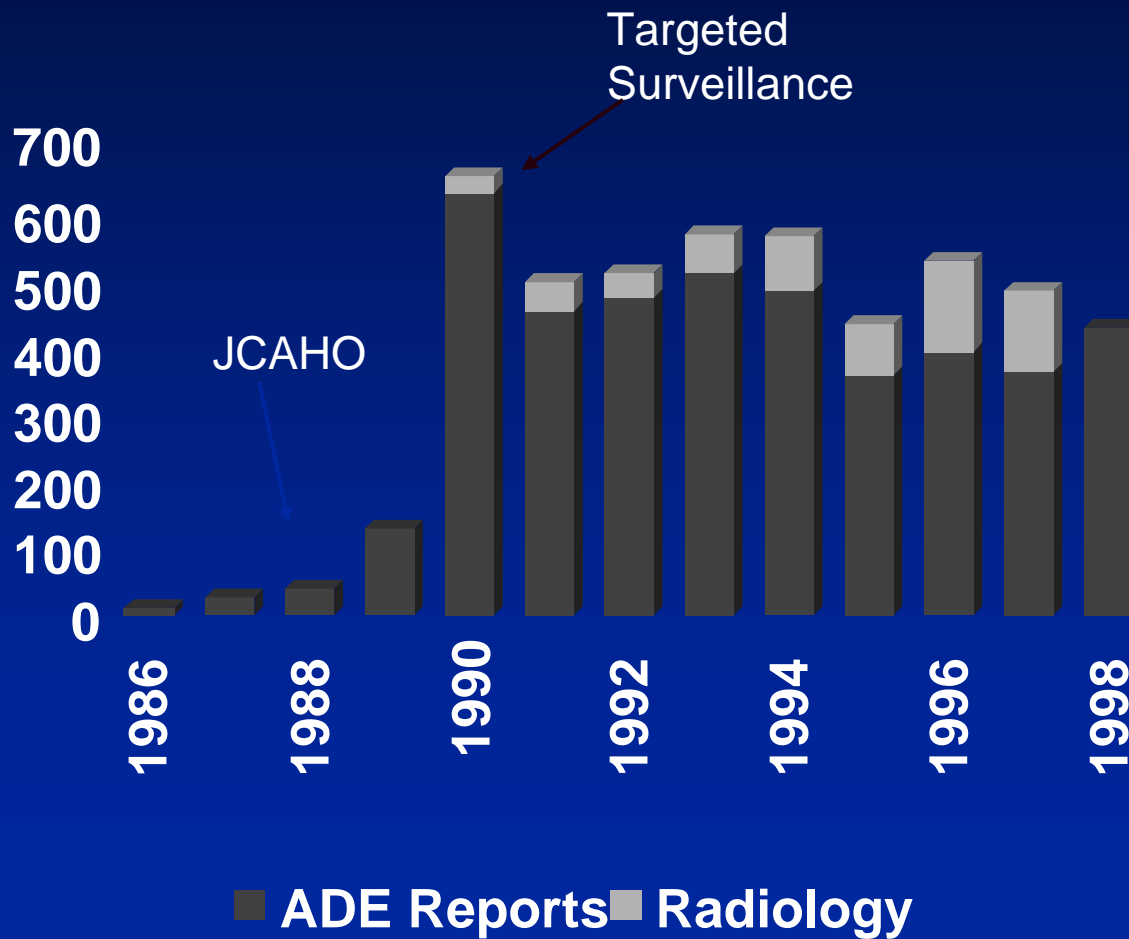
DRUG  
CO.S

# Drug Use and Effects Program

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- Adverse drug reaction reporting
- Drug usage evaluation
- Pharmacy cost containment

# ADE Annual Report



# Increasing Use of IT Interventions

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- Immediate EPIC alerts with withdrawal of trimethobenzamide, pergolide, tegaserod, rofecoxib, and valdecoxib
- EPIC-delivered warnings regarding celecoxib, metoclopramide, rosuvastatin



# IT Interventions/Evaluations Underway

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- **Metoclopramide RCT**
- **Warning fatigue**
- **Warfarin + NSAID RCT**
- **Insomnia/hypnotic RCT**
- **Warfarin + TMS RCT**



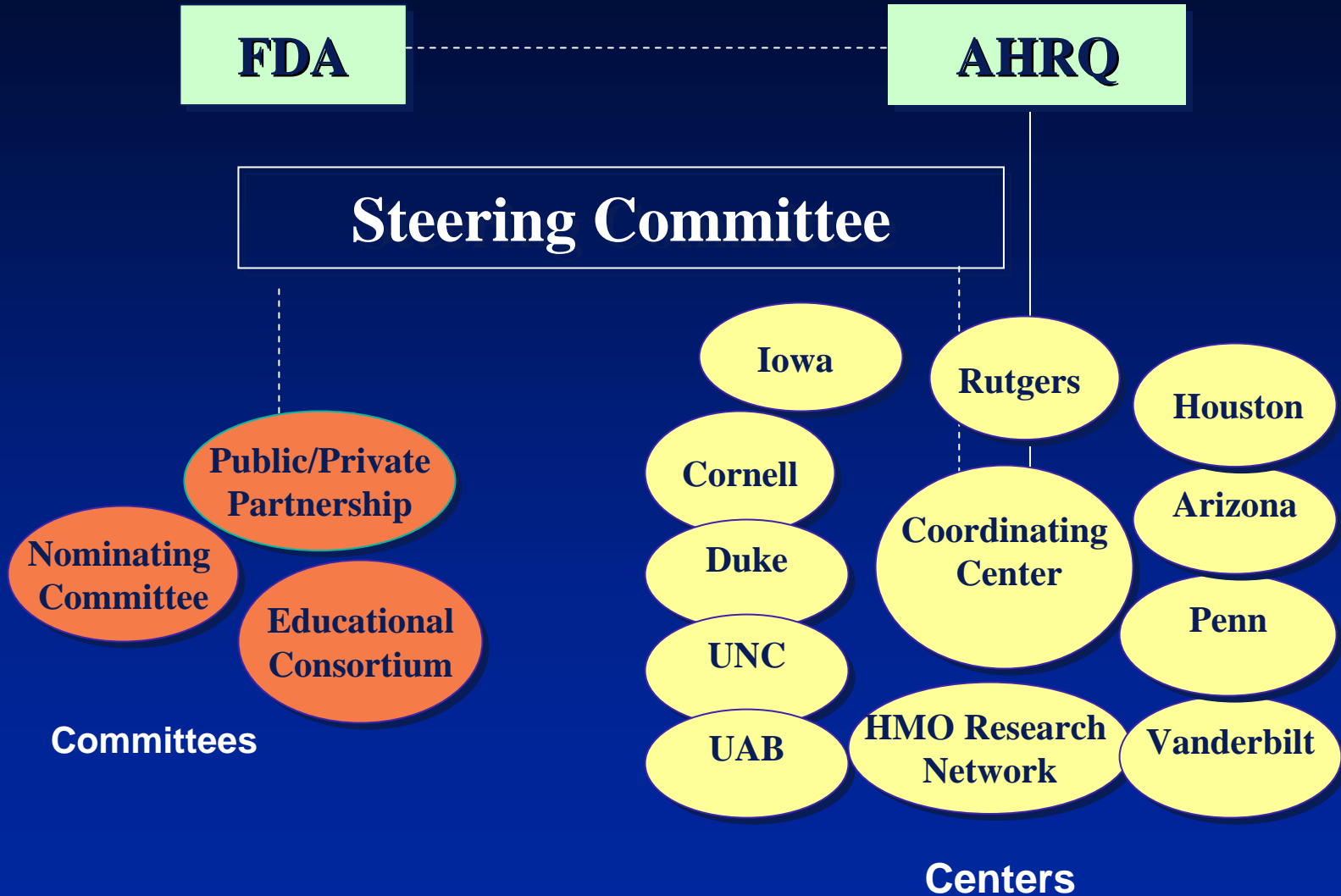
# Possible Future Interventions

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- ACEIs and lipid lowering in diabetics
- Anticoagulation in AF
- Anti-rejection therapy in transplant patients
- Beta-blocker and aspirin use post-MI
- Drug selection in hypertensives
- Drug use in CHF
- Osteoporosis prophylaxis

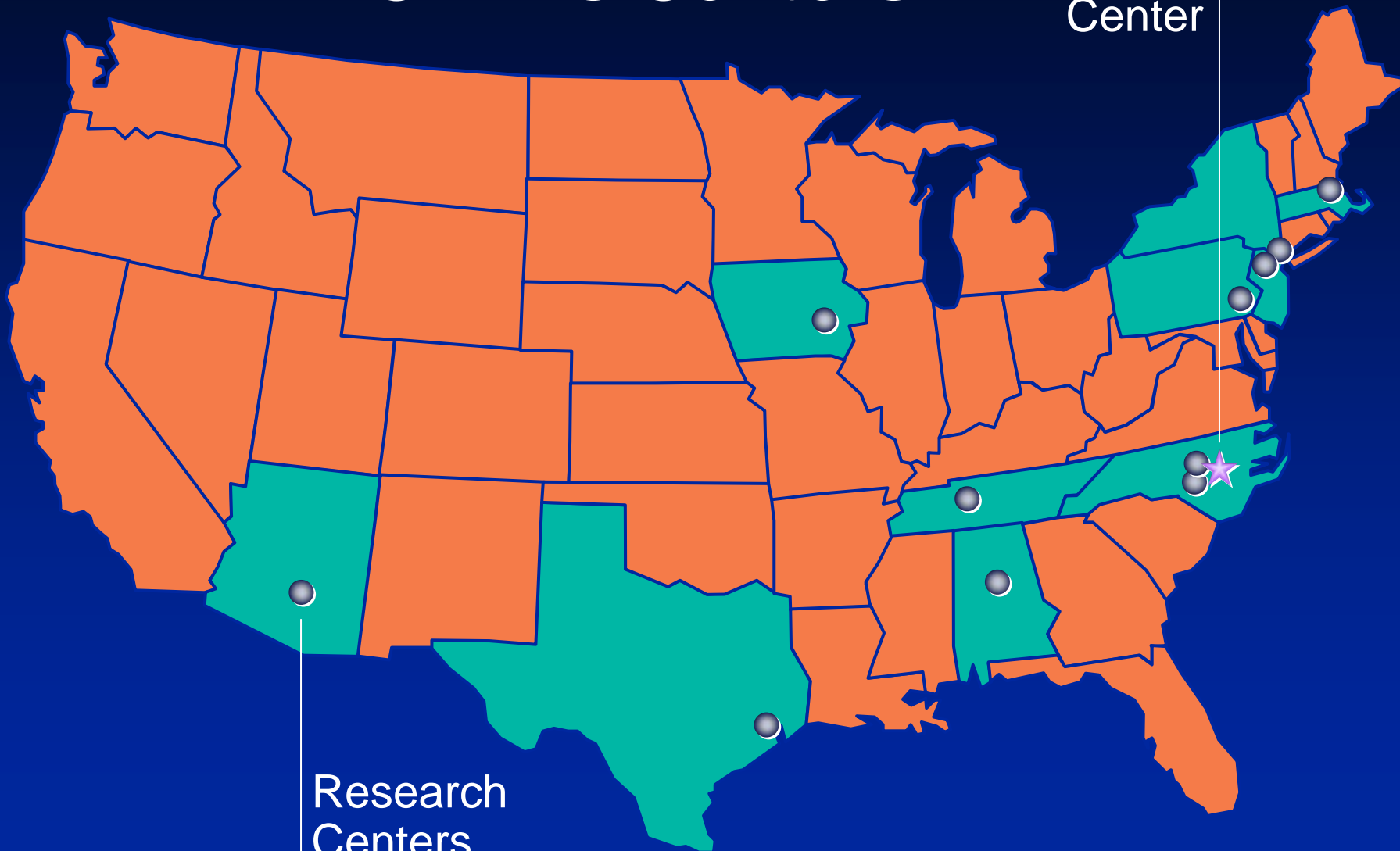


# CERTs Structure



# CERTs Centers

Coordinating  
Center



Research  
Centers



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# Limitations of Pre-marketing Trials-1

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- **Carefully selected subjects may not reflect real-life patients in whom drug will be used**
- **Study subjects may receive better care than real-life patients**
- **Short duration of treatment**
- **No info on comparative effectiveness**



# Limitations of Pre-marketing Trials-2

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- **↑ development costs lead to ↑ need for immediate huge sales (“blockbuster drugs”), and aggressive marketing practices**
- **Yet, development programs with 3000 patients cannot reliably detect adverse events with an incidence of  $< 1$  per 1000, even if severe**



# Resulting Opportunities

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- 51% of drugs have label changes due to major safety issues discovered after marketing
- 20% of drugs get new “black box” warnings after marketing
- 4% of drugs are ultimately withdrawn for safety reasons



# Other Issues in Current System

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- **No incentive for sponsor to complete promised post-marketing safety studies**
- **DTC ads lead to over-use of the drug by patients for whom use of the drug is not compelling**



# Net Effect

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- Public misunderstands “safety”: post-marketing discovery of a drug ADR means someone “messed up”
- Increasing concern about the safety of our drugs
- Over-reaction leads to increased pre-marketing requirements with delayed access and drugs dropped from development



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HAMBURGER	\$2.35	<b>RISKS</b>	<b>BENEFITS</b>
CHEESEBURGER	\$2.95	INCREASED	PROFITABILITY
TUNA SALAD	\$2.75	DECREASED	DEBT
EGG SALAD	\$2.65	LOSS OF	CONTROL
OMELETTE	\$3.10	CONTROL	LOSS OF CONTROL
BEEF STEW	\$3.45	CONTROL	LOSS OF CONTROL
FISH FILLET	\$3.10	CONTROL	LOSS OF CONTROL
LIT		CONTROL	LOSS OF CONTROL





# Risk Management

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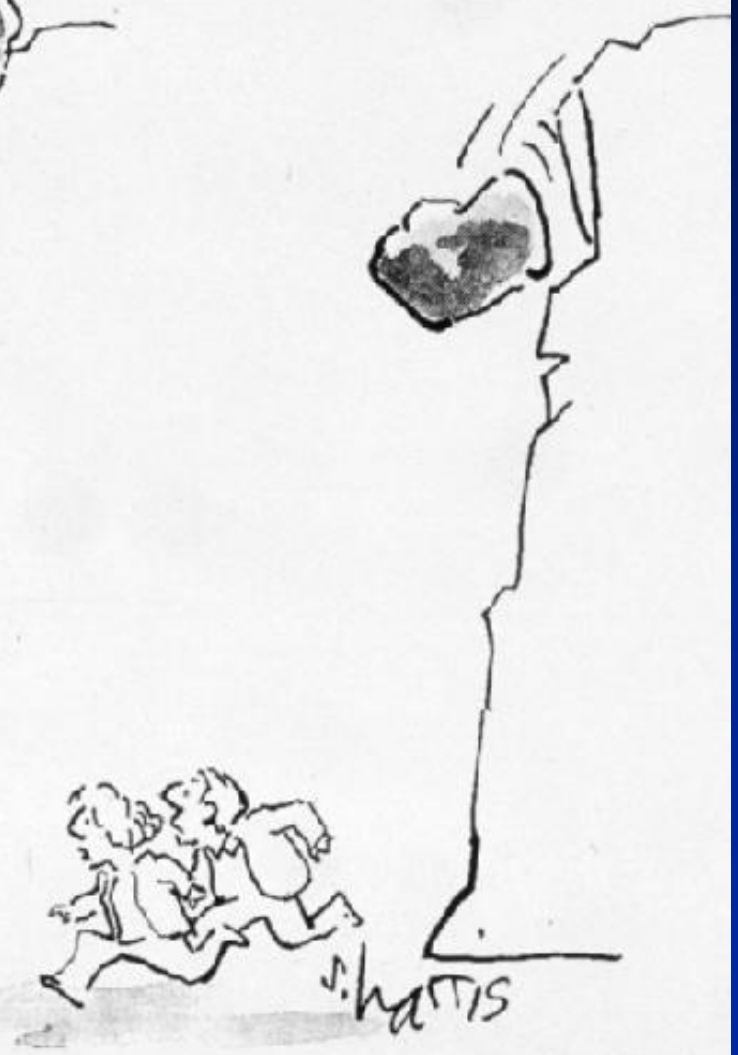
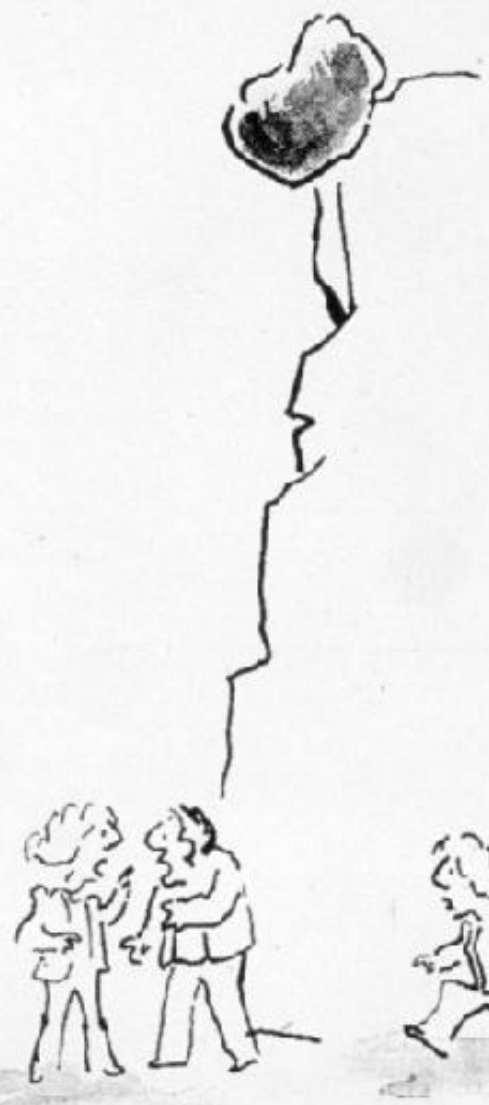
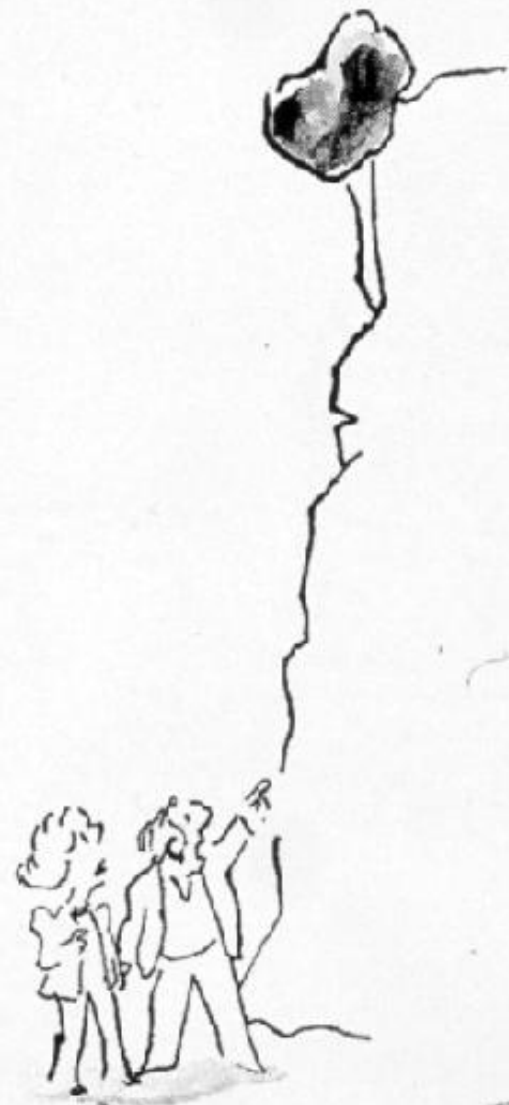
- **“Systematic information-sharing or actions undertaken to improve the balance of a drug product’s benefit(s) relative to its risk(s)”**
- **Broad categories**
  - Informational interventions
  - Active or administrative programs



RISK PERCEPTION

RISK ASSESSMENT

RISK MANAGEMENT



# Risk Management Tools: Informational

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- **Product labeling**
- **Patient informational materials**
  - Medication guides
  - Patient package inserts
- **Targeted health care provider education**



# Risk Management Tools: Active Intervention

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- **Constrain patient use**
- **Constrain health care prescribing or dispensing**
- **Restrict manner of product distribution**
- **Withdraw marketing status**
  - IND access
  - Complete market withdrawal

# Many Drugs With Risk Management Plans

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abacavir

isotretinoin

alosetron

mifepristone

bosentan

pemoline

clozapine

sodium oxybate

dofetilide

thalidomide

felbamate

tolcapon

fentanyl



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QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

# Evolution of Therapeutics

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**Empiric Choice of Therapy**



**Statistical Predictive Models of Patients Likely to Benefit or Suffer Harm**



**Personalized Medicine**

# Evolution of Therapeutics

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**Empiric Choice of Therapy**



**Statistical Predictive Models of Patients Likely to Benefit or Suffer Harm**



**RiskMAPS**



**Personalized Medicine**



# Risk Minimization Action Plans (RiskMAPs)

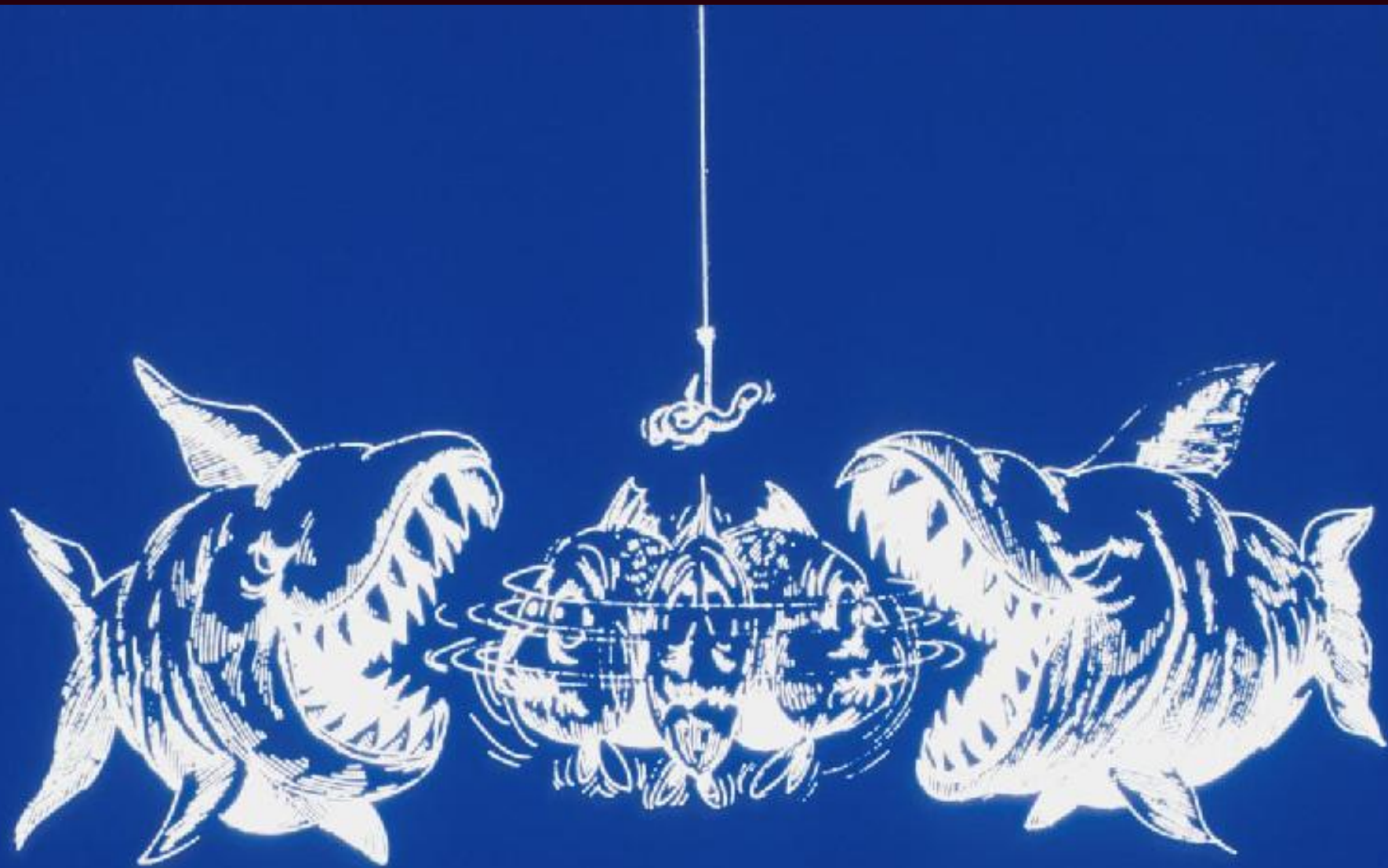
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- RiskMAPs are key potential contributors to the public's health
- The goal of RiskMAPs is to improve the risk/benefit balance of drugs
- Like any intervention, RiskMAPs should be evaluated for their safety and effectiveness
- The use of RiskMAPs is consistent with the trends underway in the nation's health system, to improve patient safety



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RiskMAPs are a logical next step toward the eventual goal of personalized medicine



**“Decisions usually involve risk.”**

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