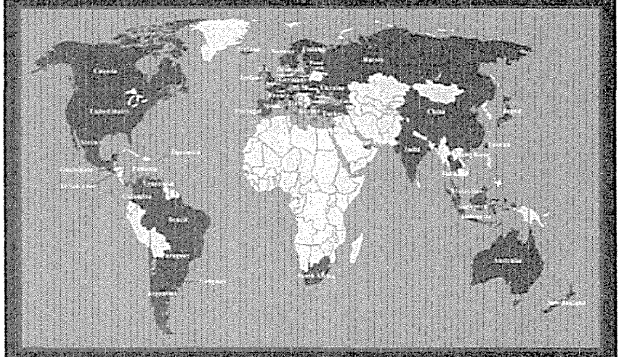
DCRI Facts

- Founded in 1969 with the development of the Duke Databank for Cardiovascular Diseases
- 20+ years of coordinating multi-center trials
- More than 1100 employees, including >220 faculty
- More than 6,500 publications in peer-reviewed journals
- More than 760 phase I – IV clinical trials, registries, outcomes, and health economic research projects in 65 countries
- Collaborated with over 5000 investigators
- Enrolled more than 1.27 million patients

Duke

DCRI – Global Clinical Research Locations



Duke

DCRI trials conducted in 64 countries

Investigator-Initiated Clinical Trial

Duke

Sponsor

A person who takes responsibility for and initiates a clinical investigation . . . may be an individual or company, government agency, academic institution, private organization, or other organization . . .

21 CFR 312.3

Duke

Responsibilities of Sponsor

- Sponsors are responsible for:
  - selecting qualified investigators
  - providing them with the information they need to conduct an investigation properly
  - ensuring proper monitoring of the investigation(s)
  - ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND
  - maintaining an effective IND with respect to the investigations
  - ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug

CFR 312.50 (General responsibilities of sponsors)

Duke

Investigator

An individual who actually conducts a clinical investigation (i.e. under whose immediate direction the drug is administered or dispensed to subject).

21 CFR 312.3

Duke

Responsibilities of Investigator

- An investigator is responsible for:
  - ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations
  - protecting the rights, safety, and welfare of subjects under the investigator's care
  - control of drugs under investigation

CFR 312.60 General responsibilities of investigators

Sponsor-Investigator

- Individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

21 CFR 312

- Sponsor-investigator has all the responsibilities of sponsor and investigators

Potential Risks

- Sponsorship
- Inadequate resources
- Lack of planning
- False claim based on bad data
- Subject safety
- Legal issues from non-compliance

Quality Assurance Models

Clinical Trials Quality*

The drug development process relies on an unbroken chain of evidence through processes and data

* DIA & FDA presentation June 2005, Woodcock, Fendt & Miles

Quality Assurance Approach

"Quality in research is comprised of a wide range of elements. Such elements include a scientifically valid protocol, meaningful informed consent, appropriate attention to patient safety, complete and accurate recording of results, proper performance of tests and evaluations, and appropriate record verification and retention"

In this way we protect the:

- Patient Safety
- Data Integrity - Data-based decisions drive the medical product development industry and are essential to protect the public health.

"Concept Paper: Quality in FDA-Regulated Clinical Research", FDA (4/07)

Quality Assurance

The systematic and independent examination of all trial-related activities and documents.

Duke

Why Quality Assurance?

- Sponsor Violations
  - Clinicians used unapproved product without IND
  - Sponsor shipped product to sites not named in IND
  - Failed to monitor progress of study/did not obtain information from sites
  - Failed to report adverse events to FDA under the IND

Duke

Why Quality Assurance?

- Investigator Violations
  - Enrolled ineligible subjects
  - Enrollment exceeded protocol or IRB limit
  - Did not conduct required evaluations (related to safety assessments)
  - Violated clinical hold
  - Submitted false information to the sponsor
  - Failed to follow protocol requirements
  - Inadequate case histories
  - Discrepancies between source records and CRF
  - Inadequate drug/device accountability records
  - Failure to retain records
  - Failure to notify the IRB of adverse events
  - Lack of supporting raw data for CRF entries
  - Failure to report adverse vents to the sponsor

Duke

Why Quality Assurance?

To bring the conduct of the clinical research to a State of Control from both aspects of Quality and Compliance

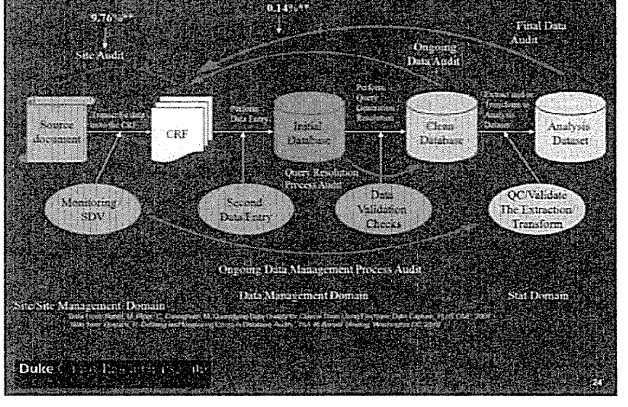
Duke

Data Integrity

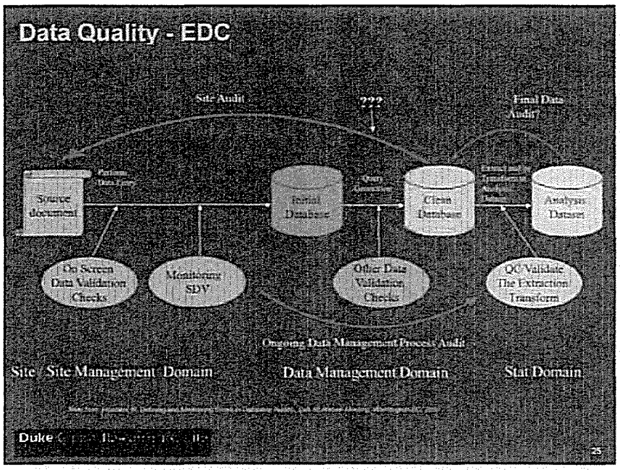
Quality Control and Quality Assurance

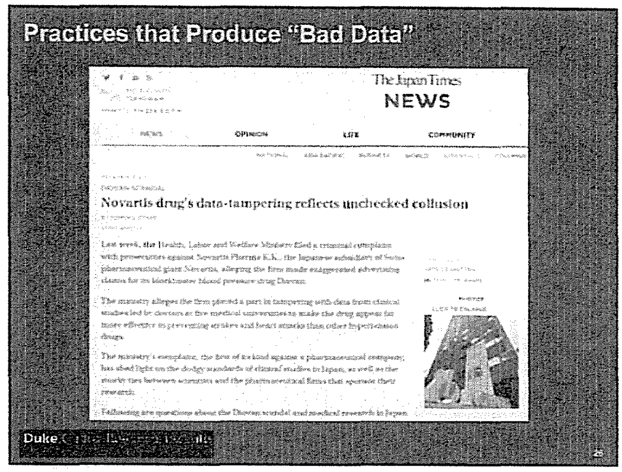
Duke

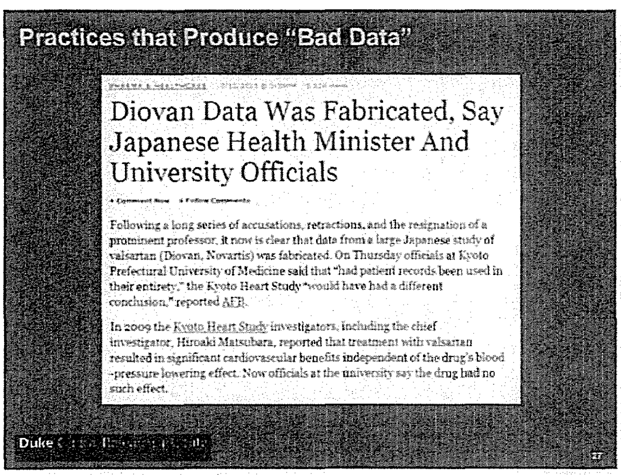
Data Quality – Paper CRF

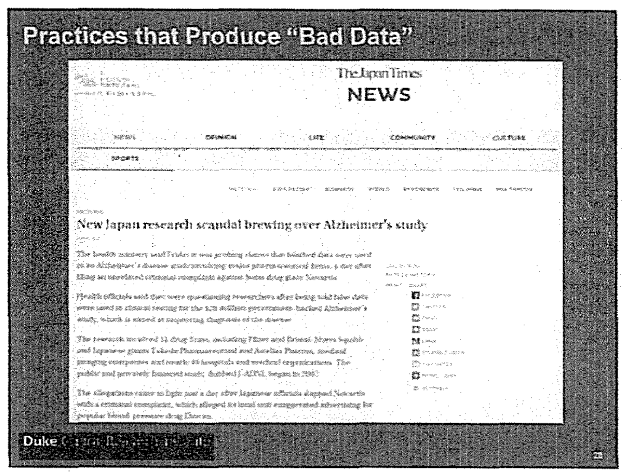


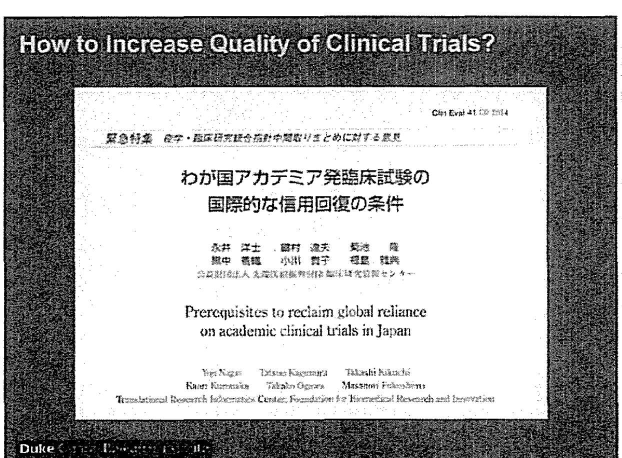
Duke

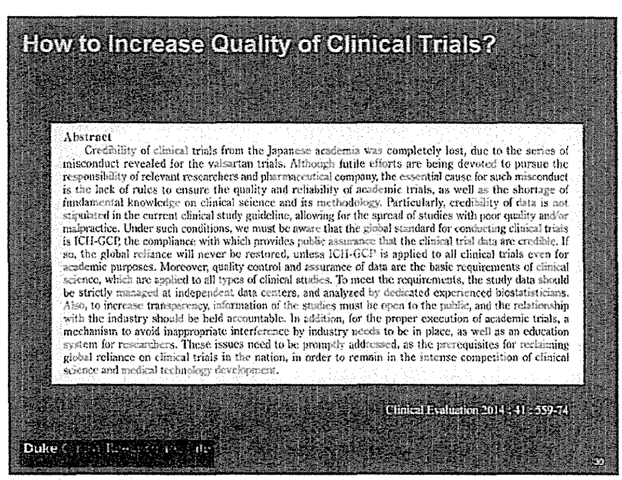








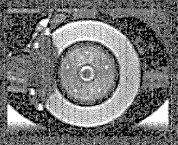




Duke Clinical Research Institute

"No Control" Is Not an Option



Risk-based control model

Why GCP Is Important?

- Because:
  - The rights, safety and well-being of subjects should be protected
  - The clinical trial data should be credible

Principles of GCP

Principles of GCP

- **2.1** Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- **2.2** A trial should be initiated and continued only if the anticipated benefits justify the risks.
- **2.3** The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Principles of GCP

- **2.4** The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- **2.5** Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- **2.6** A trial should be conducted in compliance with the protocol and IRB.
- **2.7** The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.

Principles of GCP

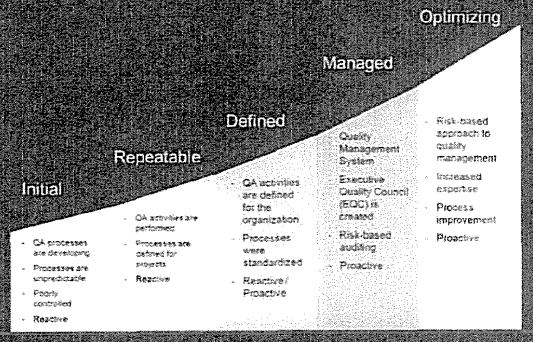
- **2.8** Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- **2.9** Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- **2.10** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Principles of GCP

- **2.11** The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- **2.12** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- **2.13** Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Quality System

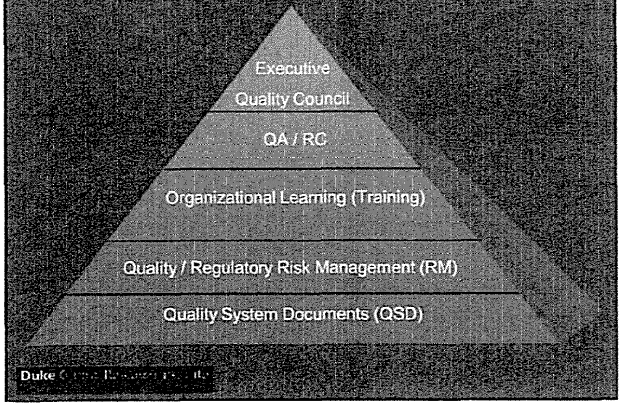
QA Maturity Model



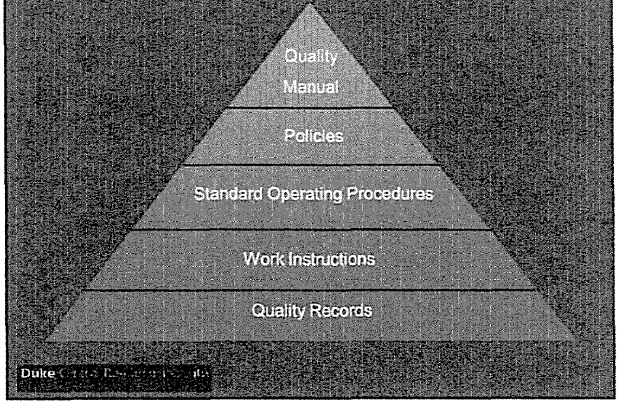
Quality Systems

- A dynamic engine for driving the business
- A method to facilitate oversight and control by management
- A method to drive toward continuous improvement
- Running a clinical trial or clinical program today is tantamount to running a small company
- As such, it should be run as the best company with the best quality system to ensure the highest success of high quality data and regulatory compliance

Quality System



Quality System Documents



Conclusion

- Quality should be built into each step of conducting a clinical study
- Quality Assurance is a necessary function to ensure patient safety, and integrity of data are under control
- In investigator-initiated clinical study, if data integrity is compromised, not only will the safety of patients be jeopardized, but the reputation of the investigator could also be destroyed
- Only quality-driven clinical research can be reliable and sustainable through time

Duke Clinical Research Institute

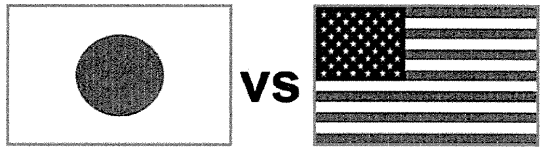
日米の相違

医療機器評価とデータベース研究

Soko Setoguchi, MD DrPH, FISPE
Associate Professor

Duke University School of Medicine
University of Tokyo Graduate School of Medicine

研究者主導臨床研究 日米比較



Japan　　United States

いろいろな臨床研究

- Randomized trials vs. observational studies
- Primary data collection vs. database studies
- Qualitative vs. quantitative studies
- Descriptive vs. etiologic studies
- Small hospital based vs. large population based studies
- Questions related to patients vs. health care policy or economics
- Multiple disciplines involved: clinical medicine, pharmacology, epidemiology, biostatistics, medical informatics, behavioral and social sciences health services and outcome research, health economics

資金

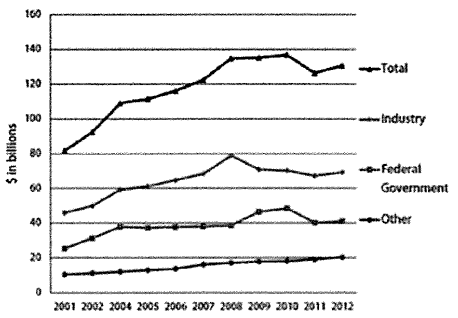
USA

- $130 billion dollars (約1300億ドル) in 2012 per year including basic and clinical research
- Funding sources
  - Industry>government> others

JAPAN

- ?? 円

U.S. Medical and Health Research Investment by Sector



http://www.researchamerica.org/uploads/healthdollar12.pdf

2012 Total: Estimated U.S. Medical and Health Research Expenditures ... 130,383

	2010	'10-'11 Change	2011	'11-'12 Change	2012
National Institutes of Health	34,829	-14.4%	29,831	0.6%	30,012
Department of Defense (medical research, chemical and biological defense)	2,667	-12%	2,346	2.8%	2,412
Department of Homeland Security (biodefense)	2,372	-91.0%	213	9.9%	234
Department of Agriculture (Agricultural Research Service, National Institute of Food and Agriculture, Economic Research Service)	2,168	-19.8%	1,754	11.3%	1,953
National Science Foundation (biological sciences, bioengineering, behavioral sciences, computer and information science and engineering)	1,753	0.4%	1,760	17.9%	2,075
Department of Energy (biological and environmental research, advanced scientific computing research)	1,037	-3.1%	1,005	1.5%	1,020
Environmental Protection Agency (clean air, clean water, health and human ecosystems, pesticides and toxics)	596	-2.3%	582	-2.4%	568
National Institute of Standards and Technology	588	-9.5%	532	4.7%	557
Department of Veterans Affairs (medical and prosthetic research)	581	-0.2%	580	0%	580
Agency for Healthcare Research and Quality	420	-5.2%	398	-1.0%	394
Centers for Disease Control and Prevention (disease control, research and training)	363	25.9%	457	-10.7%	408
Food and Drug Administration	248	2.4%	254	59.8%	406
NASA (Human Research Program)	182	-14.8%	155	1.9%	158
U.S. Agency for International Development	158	0%	158	19.0%	188
Administration for Children and Families (children's research)	43	-4.7%	41	-75.6%	10
Ctrs. for Medicare & Medicaid Services (health services research, demonstration, evaluations)	27	33.3%	36	-47.1%	21
Health Resources and Services Administration	8	42.9%	12	0%	12
Patient Centered Outcomes Research Institute	–	–	1	700%	8
Subtotal	48,222	-16.8%	40,115	2.2%	41,016

Patient-Centered Outcome Research Institute (PCORI)

- With the Patient Protection and Affordable Care Act, the Patient-Centered Outcomes Research Institute (PCORI) was established (March 2010)
- Funding for FYs 2014-2019 averages $650 million(65億ドル) per year.
- PCORI just announced for >$200 million (20億ドル) funding opportunities for Spring 2014 cycle

Other Sources					
Universities (Institutional Funds) (2011)	11,198	6.2%	11,897	4.6%	12,445
State and Local Government (2011)	3,647	5.7%	3,854	-0.9%	3,819
Independent Research Institutes (Institutional funds)	1,259	2.1%	1,285	19.7%	1,538
Philanthropic Foundations (2011)	854	-13.7%	737	79.4%	1,322
Voluntary Health Associations	887	14.9%	1,008	6.5%	1,074
Subtotal	**17,835**	**5.3%**	**18,781**	**7.5%**	**20,198**

データソース

USA

- クレームデータ、レジストリ、コホートデータなどいろいろなデータが存在
- Big Dataは、はやり言葉
  - データリンケージ、ゲノムデータ、電子カルテの普及でデータはどんどん大きくなっている

JAPAN

- NDB
- レジストリ
- コホートデータ

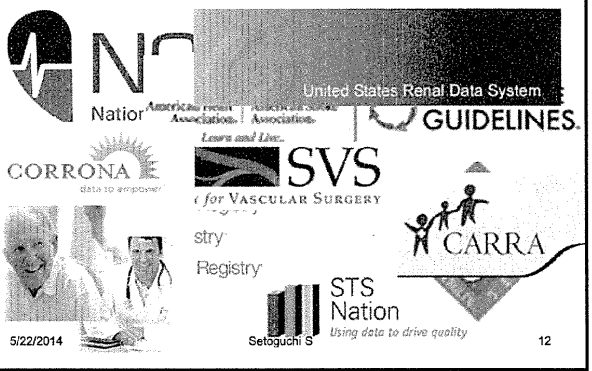
Administrative Databases

- **Claims databases or health care utilization databases'**
- **Examples in North America**
  - Medicaid
  - Medicare + State Pharmacy Assistance Programs or Part D
  - Commercial insurance companies
    - United Health
    - Blue Cross Blue Shield
  - Canadian Provincial claims data
    - Ontario
    - Quebec
    - British Columbia
    - Saskatchewan

電子カルテ(EHR) Database

- Examples
  - Single provider
    - DEDUCE (Duke)
    - RPRD (Brigham and Women's Hospital)
  - Multiple providers
    - Geisinger Clinic Electronic Health Records- 41 Clinics covering ~3 million patients
    - Kaiser Permanente

レジストリ- 例



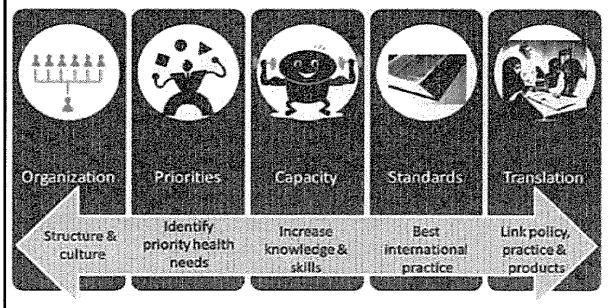
経験、人材
(データベース研究に関して)

USA

- 1970年代からデータベース研究が行われてきている
- 多数の関連分野の大学院があり(例:>44の公衆衛生大学院、75の医療管理学校)があり関連分野の研究者を要請してきている
- 研究をサポートするスタッフを育成、雇用するだけのリソースがある

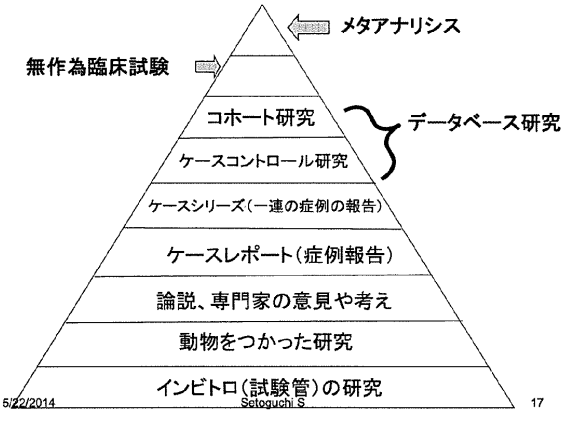
JAPAN

- クレームデータベースの構築と使用は過去10年程度？
- 公衆衛生大学院は10以下？
- リソース不足でサポートスタッフが少ない？



医療機器評価における
データベースの役割

市販前臨床試験と
医療機器の効果と安全性



RCTの長所と短所

無作為臨床試験

長所	短所
無作為化により比較グループが似通っており交絡のリスクがほとんどない	費用や手間がかかる
確立された手法に基づいておこなうことができる	倫理的問題のため行えない場合もある
薬の効果を証明するためのゴールドスタンダードと考えられている	比較的小規模、短期間である 老人や併発疾患の多いもの、子供、妊婦などが除外されやすい 通常の現場での医療とRCTの環境がことなる プラセボ比較はしばしば臨床の疑問には不適切 臨床アウトカム(死亡やイベント)でなくサロゲートアウトカム(例えば血圧、コレステロール値)を比較することも多い

Avorn, NEJM 2009より抜粋、一部変更