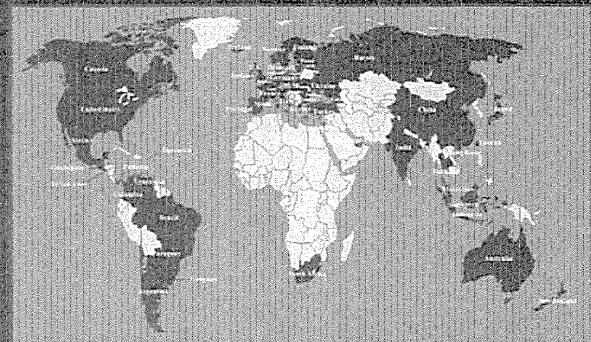


DCRI Facts

- 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 Clinical Research Institute

DCRI – Global Clinical Research Locations



Duke Clinical Research Institute | DCRI trials conducted in 64 countries

Investigator-Initiated Clinical Trial

Duke Clinical Research Institute

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

10

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 Clinical Research Institute

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

11



Duke Clinical Research Institute

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

Duke Clinical Research Institute

14

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

Duke Clinical Research Institute

15

Potential Risks

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

Duke Clinical Research Institute

16

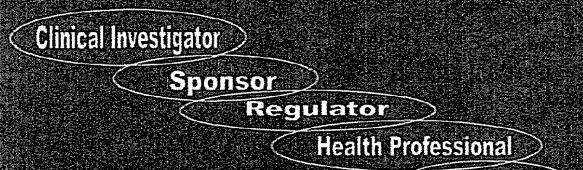
Quality Assurance Models

Duke Clinical Research Institute

17

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

Duke Clinical Research Institute

18

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)

Duke Clinical Research Institute

19

Quality Assurance

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

Duke Clinical Research Institute

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

Hochberg, P. Regulatory Challenges for Investigator-Sponsored Research: An FDA Perspective. FDA CBER, October 21, 2012

Duke Clinical Research Institute

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 events to the sponsor

Hochberg, P. Regulatory Challenges for Investigator-Sponsored Research: An FDA Perspective. FDA CBER, October 21, 2012

Duke Clinical Research Institute

Why Quality Assurance?

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

Hochberg, P. Regulatory Challenges for Investigator-Sponsored Research: An FDA Perspective. FDA CBER, October 21, 2012

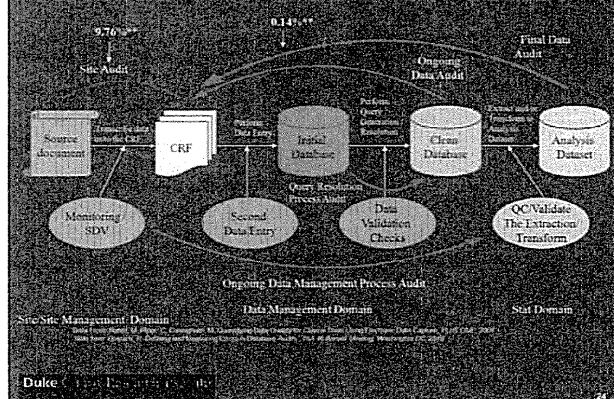
Duke Clinical Research Institute

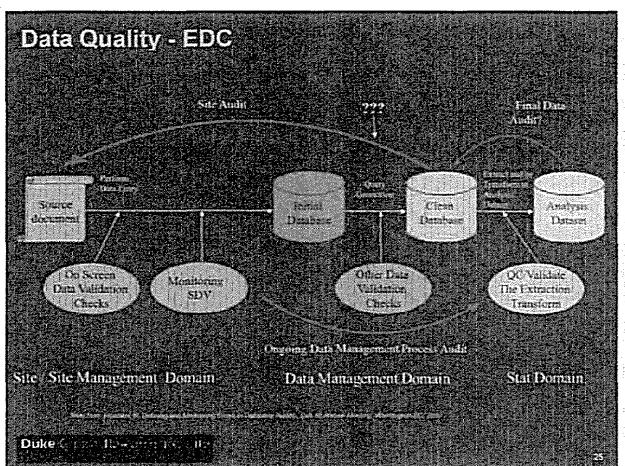
Data Integrity

Quality Control and Quality Assurance

Duke Clinical Research Institute

Data Quality – Paper CRF





Practices that Produce “Bad Data”

Novartis drug's data-tampering reflects unchecked collusion

Last week, the Hatch, Labor and Welfare Ministry filed a criminal complaint with prosecutors against Novartis Pharma K.K., the Japanese subsidiary of Swiss pharmaceutical giant Novartis, alleging the firm made exaggerated advertising claims for its blood-pressure-lowering drug Diovan.

The ministry alleges the firm planned a plan to tamper with data from clinical studies and decisions at three medical universities to make the drug appear far more effective in preventing strokes and heart attacks than other hypertension drugs.

The ministry's complaint, the first of its kind against a pharmaceutical company, has shed light on the shoddy standards of clinical studies in Japan, as well as the links between universities and the pharmaceutical firms that sponsor their research.

Earlier this month, Chinese authorities announced they had seized 100,000 boxes of Diovan in Beijing.

Practices that Produce “Bad Data”

Diovan Data Was Fabricated, Say Japanese Health Minister And University Officials

Following a long series of accusations, retractions, and the resignation of a prominent professor, it now is clear that data from a large Japanese study of valsartan (Diovan, Novartis) was fabricated. On Thursday officials at Kyoto Prefectural University of Medicine said that "had patient records been used in their entirety," the Kyoto Heart Study "would have had a different conclusion," reported AFP.

In 2009 the Kyoto Heart Study investigators, including the chief investigator, Hiroaki Matsubara, reported that treatment with valsartan resulted in significant cardiovascular benefits independent of the drug's blood-pressure lowering effect. Now officials at the university say the drug had no such effect.

Practices that Produce “Bad Data”

New Japan research scandal brewing over Alzheimer's study

The health ministry said Friday it was probing claims that falsified data were used in an Alzheimer's disease study involving tens of thousands of seniors. It also said an unspecified criminal complaint against Swiss drug giant Novartis is under way.

Health officials said there were questionable researchers after being told false data were used in claims to receive the 2.5 billion yen grant from the Alzheimer's Society, which is asking for re-opening of the survey.

The research involved 13 drug firms, including Pfizer and Bristol-Myers Squibb, and Japanese groups. The Alzheimer's Society of Japan, funded by the government, is carrying out the study, which involved 45 hospitals and research organizations. The public and private financed study, dubbed J-ADZL, began in 2006.

The allegations came on Friday just a day after Japanese officials alleged Novartis with a research misconduct, which alleged it had sent exaggerated advertising for popular blood-pressure drug Diovan.

How to Increase Quality of Clinical Trials?

Clin Eval 41:33-34 2014

緊急特集 基本・医療研究統合活動中間取りまとめに対する意見

わが国アカデミア発臨床試験の国際的な信用回復の条件

森井 伸士・藤村 流矢・長池 駿
島中 義穂・小川 靖子・程晶 駿典
公募財團法人 先端医療研究開発財團 医学研究開発センター

Prerequisites to reclaim global reliance on academic clinical trials in Japan

Yosi Nagai, Tatsuo Kigurenra, Takashi Nagashima,
Kaoru Kurokawa, Takanori Ogawa, Masatoshi Fukuhara
Translational Research Information Center, Foundation for Biomedical Research and Innovation

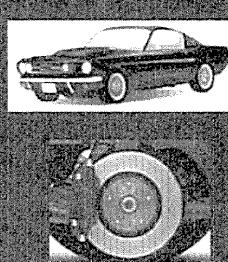
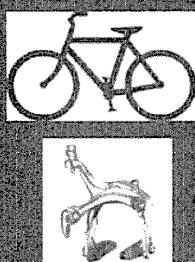
How to Increase Quality of Clinical Trials?

Abstract

Credibility of clinical trials from the Japanese academia was completely lost, due to the series of misconduct revealed for the valsartan trials. Although futile efforts are being devoted to pursue the responsibility of relevant researchers and pharmaceutical company, the essential cause for such misconduct is the lack of rules to ensure the quality and reliability of academic trials, as well as the shortage of fundamental knowledge on clinical sciences and its methodologies. Particularly, credibility of data is not stipulated in the current clinical study guideline, allowing for the spread of studies with poor quality and/or malpractice. Under such conditions, we must be aware that the global standard for conducting clinical trials is ICH-GCP. Compliance with the guidelines is able to assure that the trial is valid and reliable. If so, the global reliance will be restored. ICH-GCP can be applied to all clinical trials even for academic purposes. Moreover, quality control and assurance of data are the basic requirements of clinical science, which are applied to all types of clinical studies. To meet the requirements, the study data should be strictly managed at independent data centers, and analyzed by dedicated experienced biostatisticians. Also, to increase transparency, information of the studies must be open to the public, and the relationship with the industry should be held accountable. In addition, for the proper execution of academic trials, a mechanism to avoid inappropriate interference by industry needs to be in place, as well as an education system for researchers. These issues need to be promptly addressed, as the prerequisites for reclaiming global reliance on clinical trials in the nation, in order to remain in the intense competition of clinical science and medical technology development.

Clinical Evaluation 2014; 31: 359-74

"No Control" Is Not an Option



Risk-based control model

Duke Clinical Research Institute

Why GCP Is Important?

■ Because:

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

Duke Clinical Research Institute

Principles of GCP

Duke Clinical Research Institute

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.

Duke Clinical Research Institute

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.

Duke Clinical Research Institute

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.

Duke Clinical Research Institute



Duke Clinical Research Institute

Principles of GCP

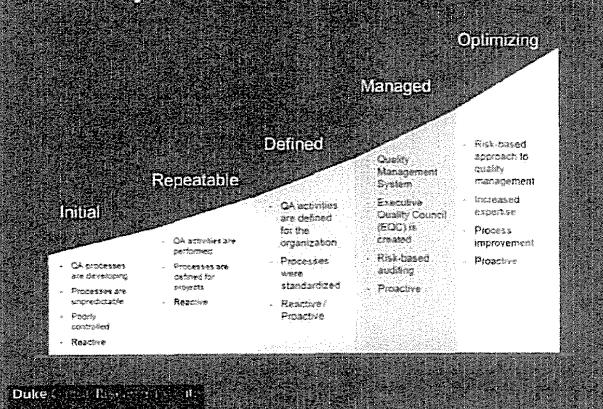
- **2.11** The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- **2.12** Investigational products should be manufactured, handled, and stored in accordance with 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.

Duke Clinical Research Institute

Quality System

Duke Clinical Research Institute

QA Maturity Model



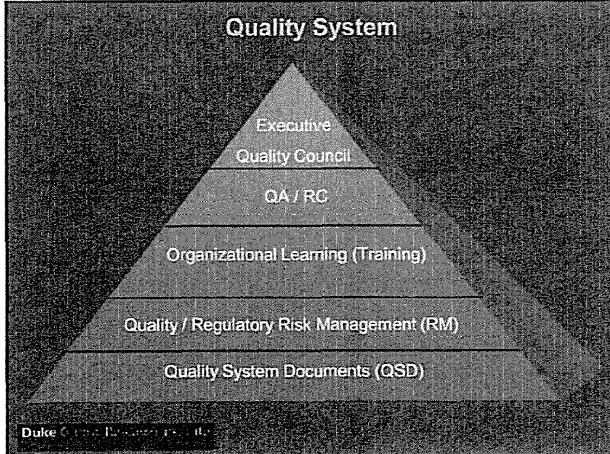
Duke Clinical Research Institute

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

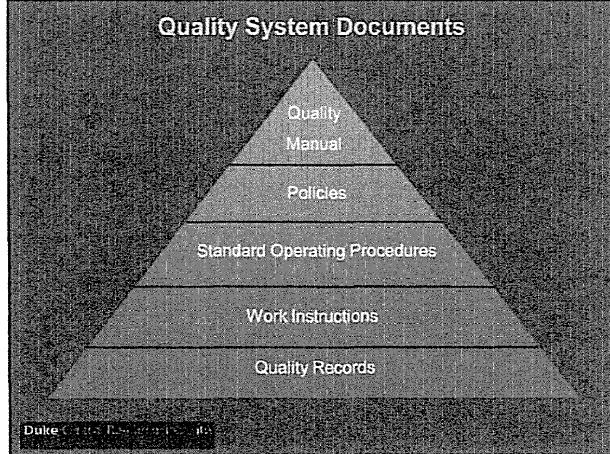
Duke Clinical Research Institute

Quality System



Duke Clinical Research Institute

Quality System Documents



Duke Clinical Research Institute



Duke Clinical Research Institute

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

Thank You

Duke Clinical Research Institute

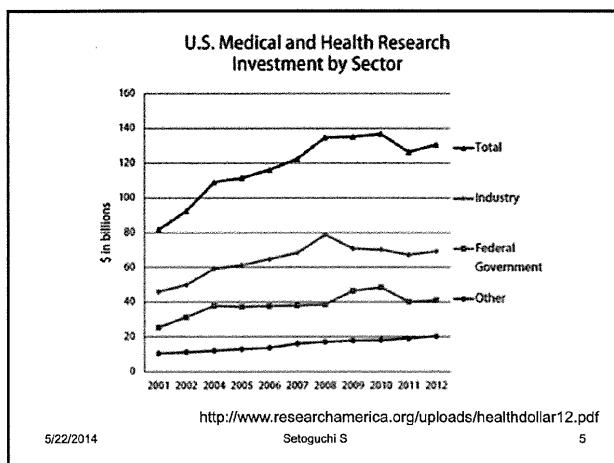


Duke Clinical Research Institute

研究者主導臨床研究 日米比較

いろいろな臨床研究

| USA | JAPAN |
|--|--|
| <ul style="list-style-type: none">\$130 billion dollars (約130億ドル) in 2012 per year including basic and clinical researchFunding sources<ul style="list-style-type: none">Industry>government>others | <ul style="list-style-type: none">?? 円 |
| | |



| | 2010 | '10-'11 Change | 2011 | '11-'12 Change | 2012 Estimate |
|--|---------------|-------------------|---------------|-------------------|------------------|
| 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 (bioterror) | 2,372 | +9.0% | 213 | +9.9% | 234 |
| Department of Agriculture (Agricultural Research Service, National Institute of Food and Agriculture, Economic Research Service) | 2,188 | +19.8% | 1,754 | +11.3% | 1,953 |
| National Science Foundation (biological sciences, engineering, behavioral sciences, computer and information sciences and engineering) | 1,753 | 0.4% | 1,760 | +1.7% | 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 (ocean air, clean water, health and human impacts, pesticides and toxic) | 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 | +5.8% | 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 (research, demonstration, evaluation) | .27 | +33.3% | 36 | +471% | 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% | 11,697 | 4.6% | 12,445 |
| State and Local Government (2011) | 3,847 | 5.7% | 3,854 | -0.9% | 3,819 |
| Independent Research Institutes (non-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 | 6.3% | 18,781 | 7.5% | 20,198 |

5/22/2014

Setoguchi S

8

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
 - データリンクージ、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

5/22/2014

Setoguchi S

9

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

5/22/2014

Setoguchi S

10

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

5/22/2014

Setoguchi S

11

レジストリ- 例



5/22/2014

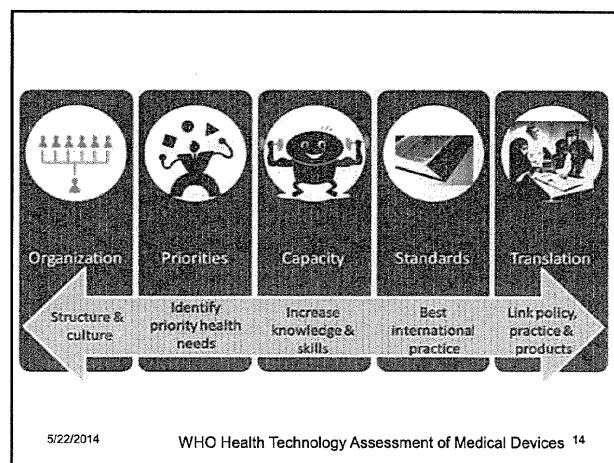
Setoguchi S

12

経験、人材 (データベース研究に関して)

| | |
|--|--|
| <p>USA</p> <ul style="list-style-type: none"> 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 | <p>JAPAN</p> <ul style="list-style-type: none"> 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? |
|--|--|

5/22/2014 Setoguchi S 13

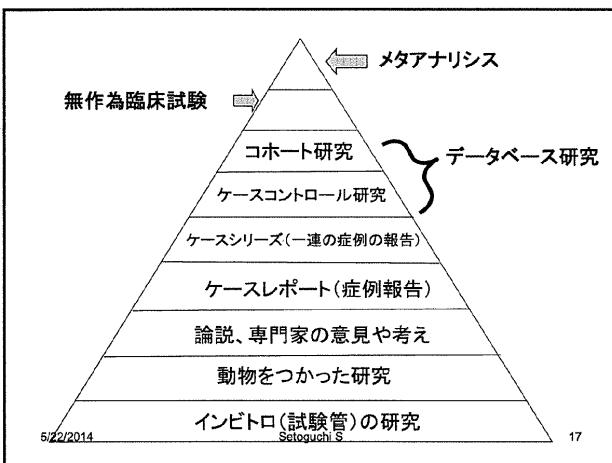


医療機器評価における データベースの役割

5/22/2014 Setoguchi S 15

市販前臨床試験と 医療機器の効果と安全性

5/22/2014 Setoguchi S 16



| RCTの長所と短所 | |
|-----------------------------------|--|
| 無作為臨床試験 | 長所 |
| 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、妊娠などが除外されやすい |
| | 通常の現場での医療とRCTの環境が異なる |
| | 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)では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 |

5/22/2014 Setoguchi S, NEJM 2009より抜粋、一部変更 18