医薬品の安全対策等における医療関係データベースの活用方策に関する懇談会～勉強会～

日時：平成21年11月19日（木）
　　18：00～20：00
場所：厚生労働省6F　共用第8会議室

議事次第：

1　開会

2　議題
　有識者からのヒアリング

3　閉会

医薬品の安全対策等における医療関係データベースの活用方策に関する懇談会～勉強会～

配付資料一覧

開催要綱

構成員名簿

資料1：有識者からのヒアリング

Using large linked healthcare databases for medical product safety assessment

参考資料1：Striking the right balance between privacy and public good (Lancet, vol. 367, p275)

「医薬品の安全対策等における医療関係データベースの活用方策に関する懇談会」
開催要綱

1 目的

「薬害再発防止のための医薬品行政等の見直しについて(第一次提言)」(平成 21 年 4 月 30 日)において、医薬品の安全対策の強化において、各種データベースについての活用基盤の整備が求められてきたところである。同時に、データベースの種類や内容及びそれらがどのように安全対策等に活用できるのかについての検討が必要との指摘もなされている。

これらを踏まえ、「医薬品の安全対策等における医療関係データベースの活用方策に関する懇談会」を設置し、各種データベースの安全対策への活用方策等について議論を重ね、報告書として提言をとりまとめることを目的とする。

2 検討事項

(1) 諸外国での医療関係データベースの活用状況等
(2) 医薬品の安全性等の評価の各目的に応じた医療関係データベースの種類・内容の活用の方策
(3) 医薬品の評価に活用するための技術的な課題
(4) 個人情報の保護、研究倫理
(5) 情報の利用・活用に必要とされ、利用者が備えるべき情報基盤
(6) その他

3 構成員等

(1) 懇談会は、別紙の構成員により構成する。
(2) 懇談会に座長を置き、座長は副座長を指名できるものとする。また、座長は懇談会の議事を整理する。
(3) 懇談会は、必要に応じて、構成員以外の専門家から意見を聴くことができる。

4 運営

(1) 懇談会は、厚生労働省医薬食品局長が、構成員等の参集を求め開催する。
(2) 検討会は原則公開するとともに、議事録を作成し、構成員の了解を得た上で公表する。
(3) その他、必要な事項は、座長が検討会の了承を得てその取り扱いを定める。

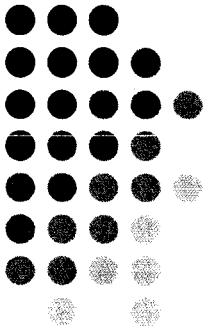
5 庶務

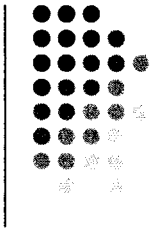
懇談会の庶務は、安全対策課が関係課室の協力を得て行う。

資料 1

Using large linked healthcare databases for medical product safety assessment

K. Arnold Chan 陳建煒 , MD, ScD, FISPE
Harvard School of Public Health
&
i3 Drug Safety





Potential Conflict of Interest

- Adjunct Associate Professor, Harvard School of Public Health
- Part time employee of i3 Drug Safety
- Co-editor of a book, no royalty received
- Public health worker

Outline

- Some examples of using large healthcare databases for public health research
- Ethical principles in biomedical research
  - Special considerations about observational studies conducted with large healthcare databases
- Using large healthcare databases
  - UK, Scandinavian countries, USA
- Scientific and practical issues

Current Medical Research and Opinion 2009; 25: 1019-27

- The report was sponsored by the manufacturer of exenatide

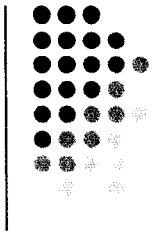
BRIEF REPORT

Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide

David D. Dore[a,b], John D. Seeger[a,c] and K. Arnold Chan[a,c]

- The exendatide vs. metformin/glyburide comparison was initiated after exenatide approval
- Data system allows evaluation of all potential outcomes that resulted in ICD-9 diagnosis codes
- Address an important public health question

Using databases for drug safety



FDA News

FOR IMMEDIATE RELEASE

September 17, 2007

Media Inquiries:
Sandy Walsh, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

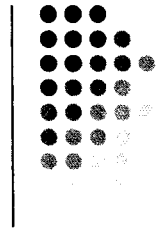
AHRQ and FDA to Collaborate in Largest Study Ever of Possible Heart Risks With ADHD Medications

Two U.S. Department of Health and Human Services agencies will collaborate in the most comprehensive study to date of prescription medications used to treat attention deficit hyperactivity disorder (ADHD) and the potential for increased risk of heart attack, stroke or other cardiovascular problems.

Researchers supported by the Agency for Healthcare Research and Quality and the U.S. Food and Drug Administration will examine the clinical data of about 500,000 children and adults who have taken medications used to treat ADHD, to determine whether those drugs increase cardiovascular risks.

Using databases for drug safety

JAMA 2004; 292: 2585-90



Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs

David J. Graham, MD, MPH
Judy A. Staffa, PhD
Deborah Shatin, PhD
Susan E. Andrade, ScD
Stephanie D. Schech, MPH
Lois La Grenade, MD, MPH
Jerry H. Gurwitz, MD
K. Arnold Chan, MD, ScD
Michael J. Goodman, PhD
Richard Platt, MD, MSc

Context Lipid-lowering agents are widely prescribed in the United States. Reliable estimates of rhabdomyolysis risk with various lipid-lowering agents are not available.

Objective To estimate the incidence of rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination, in the ambulatory setting.

Design, Setting, and Patients Drug-specific inception cohorts of statin and fibrate users were established using claims data from 11 managed care health plans across the United States. Patients with at least 180 days of prior health plan enrollment were entered into the cohorts between January 1, 1998, and June 30, 2001. Person-time was classified as monotherapy or combined statin-fibrate therapy.

Main Outcome Measure Incidence rates of rhabdomyolysis per 10 000 person-years of treatment, number needed to treat, and relative risk of rhabdomyolysis.

Results In 252 460 patients treated with lipid-lowering agents, 24 cases of hospi-

Using large databases to evaluate the effectiveness of a black box warning

Contraindicated Use of Cisapride

Impact of Food and Drug Administration Regulatory Action

Walter Smalley, MD, MPH
Deborah Shatin, PhD
Diane K. Wysowski, PhD
Jerry Gurwitz, MD
Susan E. Andrade, DSc
Michael Goodman, PhD
K. Arnold Chan, MD, DSc
Richard Platt, MD, MS
Stephanie D. Schech, MPH
Wayne A. Ray, PhD

Context Cisapride, a gastrointestinal tract promotility agent, can cause life-threatening cardiac arrhythmias in patients susceptible either because of concurrent use of medications that interfere with cisapride metabolism or prolong the QT interval or because of the presence of other diseases that predispose to such arrhythmias. In June 1998, the US Food and Drug Administration (FDA) determined that use of cisapride was contraindicated in such patients and informed practitioners through additions to the boxed warning in the label and a "Dear Health Care Professional" letter sent by the drug's manufacturer.

Objective To evaluate the impact of the FDA's 1998 regulatory action regarding contraindicated use of cisapride.

Design and Setting Analysis of data for the 1-year periods before (July 1997-June 1998) and after (July 1998-June 1999) the regulatory action from the population-based, pharmacoepidemiology research databases of 2 managed care organizations (sites A and B) and a state Medicaid program (site C).

Participants Patients with at least 180 days of prior enrollment in 1 of the 3 sites who were prescribed cisapride at least once in the period before (n=24 840) or after (n=22 459) regulatory action. Patients could be included in both cohorts.

Main Outcome Measures Proportion of cisapride users in each period for whom cisapride use was contraindicated by the product label, based on computerized patient medical encounter records.

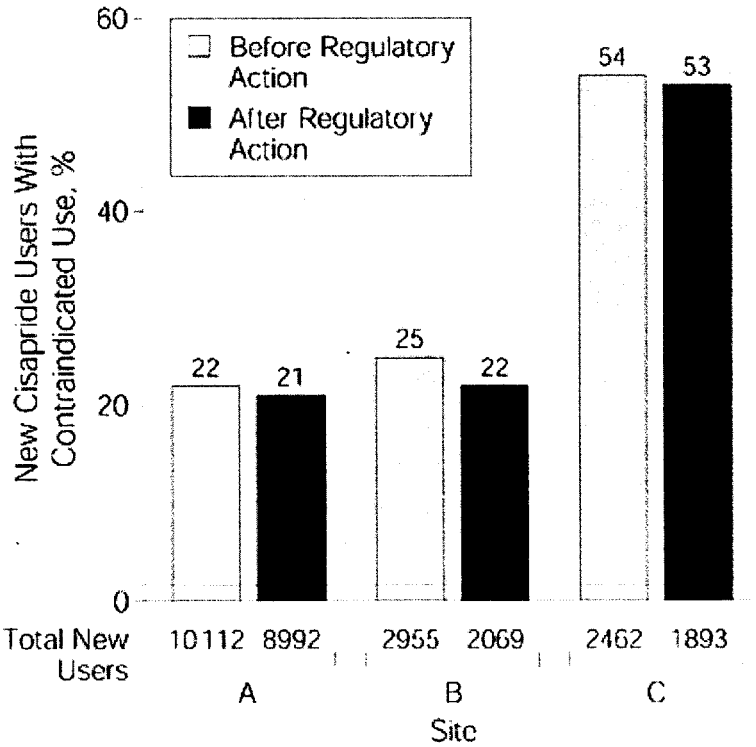
Results In the year prior to regulatory action, cisapride use was contraindicated for 26%, 30%, and 60% of users in study sites A, B, and C, respectively. In the year after regulatory action, use was contraindicated for 24%, 28%, and 58% of users, a reduction in contraindicated use of approximately 2 per 100 cisapride users at each site. When the analysis was restricted to new users of cisapride after regulatory action, only minor reductions in contraindicated use were found.

Conclusion The FDA's 1998 regulatory action regarding cisapride use had no material effect on contraindicated cisapride use. More effective ways to communicate new information about drug safety are needed.

JAMA. 2000;284:3036-3039 www.jama.com

CISAPRIDE IS A GASTROINTESTINAL tract promotility agent that was first marketed in the United States in August 1993 with a label indication for nocturnal heartburn.[1] Use grew rapidly so that in 1995 there were approximately 5 million outpatient cisapride prescriptions filled in the United States.[2] However, by this time, the Food and Drug Administration (FDA) had received 34 cases of torsade de pointes and 23 of prolonged QT interval in cisapride users, including 4 deaths.[3] Since many of these cases were in patients taking drugs that inhibited the cytochrome P450-3A4 enzymes

Black box warning did not work for cisapride (*JAMA* 2000; 284: 3036-9)



Using database for safety surveillance

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; 16: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1509

ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], K. Arnold Chan MD, MPH, ScD[3,4], Robert L. Davis MD, MPH[5], David Graham MD[6], Parker T. Pettus MS[1,2], Susan E. Andrade ScD[2,7], Marsha A. Raebel PharmD[2,8], Lisa Herrinton PhD[2,9], Douglas Roblin PhD[2,10], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,7], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

A recent article published online at Medical Care

- http://journals.lww.com/lww-medicalcare/Abstract/publishahead/Active_Influenza_Vaccine_Safety_Surveillance_.99875.aspx

ORIGINAL ARTICLE

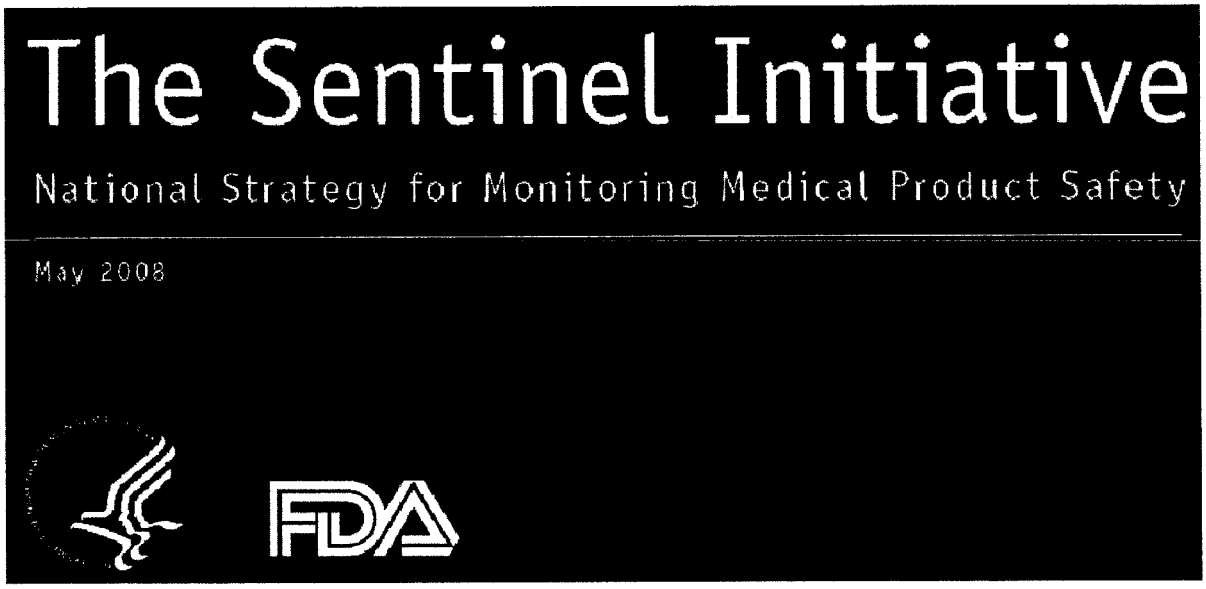
Active Influenza Vaccine Safety Surveillance

Potential Within a Healthcare Claims Environment

Jeffrey S. Brown, PhD,† Kristen M. Moore, MPH,*† M. Miles Braun, MD, MPH,‡ Natat Ziyadeh, MA, MPH,§ K. Arnold Chan, MD, ScD,§¶ Grace M. Lee, MD, MPH,*‖ Martin Kulldorff, PhD,* Alexander M. Walker, MD, DrPH,¶** and Richard Platt, MD, MSc*†*

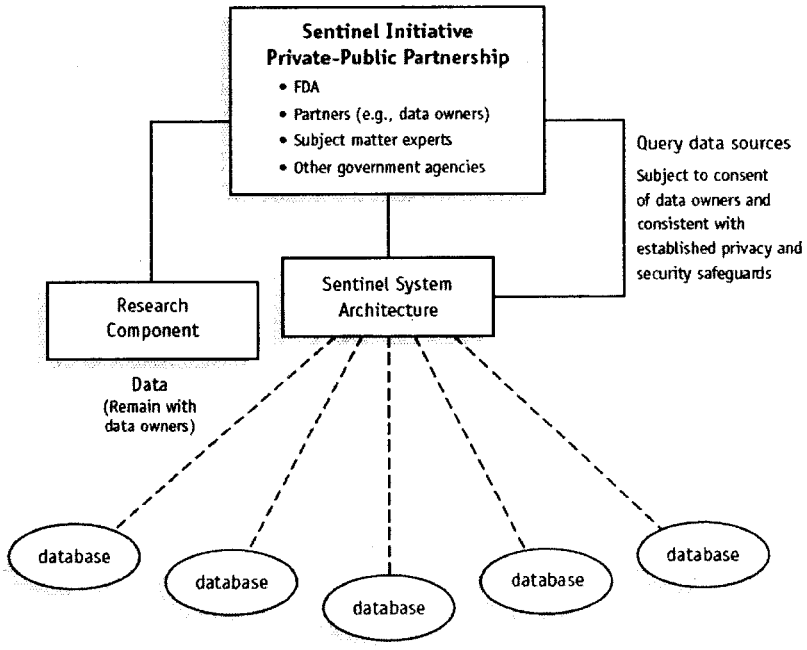
FDA Sentinel Initiative

- http://www.fda.gov/oc/initiatives/advance/sent



According to the FDA Sentinel Initiative

A Potential Organizational Structure for the Sentinel Initiative/System



Using databases for surveillance

- New England Journal of Medicine 2009; 361: 645-647

Perspective

AUGUST 13, 2009

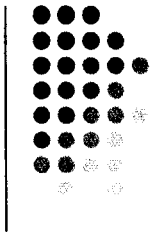
The New Sentinel Network — Improving the Evidence of Medical-Product Safety

Richard Platt, M.D., M.Sc., Marcus Wilson, Pharm.D., K. Arnold Chan, M.D., Sc.D., Joshua S. Benner, Pharm.D., Sc.D., Janet Marchibroda, M.B.A., and Mark McClellan, M.D., Ph.D.

General ethical principles in human research (from a U.S. perspective)

- Respect for Persons / Autonomy
- Beneficence / Non-maleficence
- Justice
- Based on these principles, specific guidelines have been developed
  - Intervention studies
    - Good Clinical Practice and others
  - Observational studies
    - Primary data collection
    - Utilize secondary data

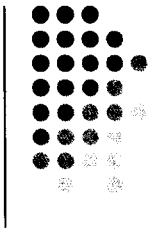
Different types of research, different types of ethical considerations



- Basic / mechanistic
  - Animal rights and welfare
- Clinical trials
  - Autonomy – informed consent
- Observational studies
  - Autonomy – authorization to use health records

- Is there a cultural component in ethical considerations?

The U.K. perspective

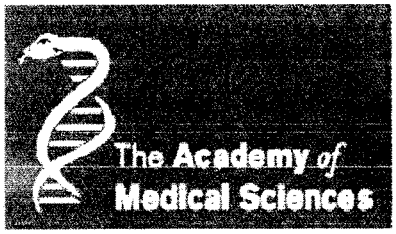


- Striking the right balance between privacy and public good. Lancet 2006; 367: 275

  "... the tension between the vital need to respect the privacy of patients and the important task of medical research using large population datasets."
  - Autonomy vs. Beneficence
  - Justice
    - Everyone, including study subjects, may benefit

A U.K. report in 2006

www.acmedsci.ac.uk/index.php?pid=99&puid=62



Personal data for public good: using health information in medical research

1. Interpreting the legal framework
2. Improving regulatory processes
3. Developing good practice in research using personal data, including issues related to anonymisation and consent
4. Harnessing the opportunities of the NHS National IT programme
5. Engaging the public

www.sciencemag.org/cgi/content/summary/sci;301/5630/163?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=denmark+epidemiology&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT

- Science 2003; Vol. 301. no. 5630, p. 163

NEWS FOCUS

EPIDEMIOLOGY:

The Epidemiologist's Dream: Denmark

Lone Frank

Epidemiologists in Denmark finished enrolling a cohort of 100,000 pregnant women into a mother-and-child research project last September and expect to finish collecting data from the children over the next year. The entire survey--which is large for this country of 70,000 annual births--is to be completed in 2005 for about $15 million, a tiny fraction of what the cost would be in the United States.

Wettermark, Furu, Andersen, Martikainen, & Bergman

24th International Conference on Pharmacoepidemiology & Therapeutic Risk Management
Copenhagen, Denmark
August 17-20, 2008

Symposium 19 August

The Nordic Countries as a cohort

ALS and statines: Rapid Response analyses

Three related topics in database research in the U.S.A.

- Privacy
  - Right to be left alone
  - Derived from the Autonomy Principle
- Confidentiality
  - Legal requirement
  - Breach of confidentiality may result in substantial damage to individuals
    - Financial
    - Social stigma and discrimination
- Data security
  - Information Technology standard to prevent breach of data

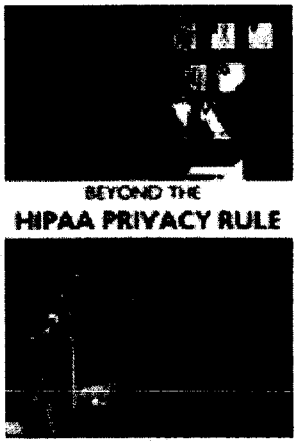
U.S. legislations

- Health Insurance Portability and Accountability Act (HIPAA)
  - Provisions for public health research with large linked health care databases
- American Recovery and Reinvestment Act (ARRA)
  - Security standard for electronic records

The consumers' view?

- U.S. Consumer Reports 2000 Aug issue, P 26
  - "Patients are well served if doctors and hospitals have fast access to accurate records."
  - "With proper safeguards against re-identification, analysis of government, hospital, and health-related databases yields a gold mine of information on public-health trends and the effectiveness of various types of care."
- Lancet 2006; 367: 275
  - "The Academy's report points to a paucity of evidence about patients' preferences for and attitudes towards participating in research, and calls for more involvement with the public to get a fuller and more accurate picture of their views."

Institute of Medicine Report in 2009



Sharyl J. Nass, Laura A. Levit, and Lawrence O. Gostin, *Editors*

Committee on Health Research and the Privacy of Health Information:
The HIPAA Privacy Rule

Board on Health Sciences Policy

Board on Health Care Services

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

- The committee's conclusion is that the HIPAA Privacy Rule does not protect privacy as well as it should, and that, as currently implemented, the Privacy Rule impedes important health research.
- Privacy Rule in the U.S. is a work in progress.

A common misconception – data quality

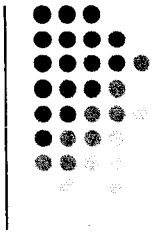
- Desire for perfect data may become the enemy of public good
  - Do not throw away the baby with the bathwater
- Jan P Vandenbroucke. Lancet 2004; 363: 1728-31

VIEWPOINT

When are observational studies as credible as randomised trials?

- What is the hierarchy of evidence?

My own thoughts on how to put ethical principles into practice



- Competent Privacy Board / Institutional Review Board / Human Subjects Committee review
- Legislation to provide the legal framework
- Training of investigators and research staff
- Utilize Information Technology to protect confidentiality without losing efficiency
- Open dialogue with all stakeholders
  - Investigators
  - Patients / consumers

参考資料 1

Striking the right balance between privacy and public good

On Jan 17, the UK's Academy of Medical Sciences issued a report, *Personal data for public good: using health information in medical research*, on the use of individual medical information for research purposes. The report highlights the tension between the vital need to respect the privacy of patients and the important task of medical research using large population datasets.

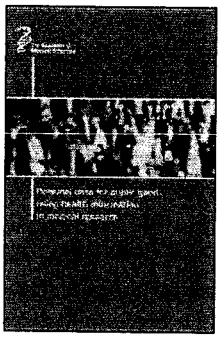
Growing concerns about privacy have spawned a great many laws and regulations governing the use of personal data, as spelled out, for example, in the UK's Data Protection Act and the EU Clinical Trials Directive. These regulations are complex in themselves, but the various ways in which they are interpreted increase complications for researchers, with the result that important and worthy projects can be long delayed or blocked entirely.

Similar concerns have been raised in the USA since the implementation in 2003 of the Health Insurance Portability and Accountability Act (HIPAA), which established standards for the confidentiality of identifiable health information. HIPAA's "common rule" governs research and specifically requires written informed consent from patients, even for so-called de-identified data for projects that combine quality improvement (QI) with research (these had not generally required consent in the past). Some US researchers have argued that HIPAA regulations can inhibit research and increase its cost, or skew data collection and therefore bias the results.

Likewise, the Academy's report argues that overregulation and overly cautious interpretation of regulation is stifling important research. It points to landmark epidemiological work—such as Sir Richard Doll's 1947 finding of the link between smoking and lung cancer—that would not have been possible without a large database of patients' records.

The UK is particularly well placed to undertake database research because large numbers of people use the National Health Service (NHS) and electronic medical records are starting to be widely used. The obstacles in the way of potentially important medical advances are therefore all the more frustrating.

To remedy these problems, the Academy's report makes recommendations, which *The Lancet* strongly endorses, in five areas. First, it claims that identifiable data can be used if the research to be undertaken is necessary and balances privacy concerns with public benefit. The report also recommends simplifying the process of assessing proposals so that researchers can get clear and timely decisions about their projects, all of which should be done under a code of practice, to be developed. It suggests that immunity from liability for data controllers should be considered, and recommends that the needs of researchers, not just those of practitioners, should be incorporated into ongoing development of the information technology programme of the NHS. Finally, patients, in formal groups and among the general public, must be engaged in discussion and debate. A group that has been established as a temporary statutory body, the Patient Information Advisory Group, should be thoroughly reconfigured, with one of its key roles being active facilitation of research.



For the **AMS report** see http://www.acmedsci.ac.uk/p47.html

More generally, the public needs to be engaged about how medical records are used and how research is done. The Academy's report points to a paucity of evidence about patients' preferences for and attitudes towards participating in research, and calls for more involvement with the public to get a fuller and more accurate picture of their views. One bioethicist, John Harris (University of Manchester, UK), has even argued that patients are morally obliged to participate in research projects, as a "mandatory contribution to public goods", at least for research that is aimed at preventing serious harms and providing important benefits. Harris also claims that in the absence of knowledge about an individual's actual preferences, it is justifiable to assume that a person would want to participate in research. Such "opt-out" schemes have been proposed as default options for database study recruitment.

Better public education about how research works and about the benefits that can accrue from investigation of population data is urgently needed, as is the need to convey the message that advances in diagnostics and therapeutics are being held up by bureaucratic regulation. When patients are convinced that their personal information is being used under rigorously controlled conditions and in accordance with best research practices, they are likely to agree to give up a small amount of individual privacy for the greater societal good that can come from population research. The future of our health depends on it. ■ *The Lancet*