

Public Health Research Ethics: Clinical Registries and Informed Consent

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Abstract

Epidemiologic studies using data collected through disease surveillance or clinical registries improve public health practice. Principles of human research ethics such as the Belmont report and the Declaration of Helsinki have been developed to prevent harm from medical experiments. Those who prepared these principles may not have imagined that the day would arrive when information technology would be so widely available and endemic chronic diseases would become one of the major interests of public health. Some key questions that have now become growing areas of interest include: How to deal with epidemiologic studies which impose minimal risk but which require access to medical records or personal information; how to balance the public good that will result from large epidemiologic studies and protection of privacy In this master's paper, I reviewed the historical development of research ethics, informed consent, and protection of privacy related to health information, and how they affect the conduct of epidemiologic studies. I discussed the application of research ethics principles and proposed better ways to solve the ethical dilemma between protection of privacy and pursuing the public good through epidemiologic studies, especially using data from medical records and clinical registries.

As a result of this review and in consideration of dilemmas regarding the protection of patient privacy and the need for efficient access to data, I developed a set of eight proposals for the ethical use of existing data in medical records or clinical registries in epidemiological and other public health studies.

1. Introduction

Epidemiologic study using data collected through disease surveillance, routine clinical practice, or clinical registries improves public health practice. In the era of Evidence Based Medicine, interventional studies such as randomized controlled trials (RCT) have been viewed as higher rank in hierarchies of evidence; however, RCT is not suitable study design to identify the cause of diseases or incidence of adverse effect or long term outcome in real world settings. Well designed observational studies “produce a more complete picture of the potential benefits and harms of clinical decisions for individual patients or health systems.” (Lindsay, 2007; Ayanian, 1999; Black, 1996; Hoppe, 2009; Haynes, 1999)

Research using population case registries are an essential component of epidemiologic and genetic research, and have helped to identify genetic and environmental contributions to the etiologies of various diseases and the knowledge of long-term prognosis (Simon, 2000; Kendler, 1994; Black, 1985). Some of the advances in understanding of diseases which were made possible through epidemiological studies using medical records include association of cigarette smoking and bladder and lung cancer and coronary heart disease (Gordis and Gold, 1980; Coleman, 1992). Furthermore, the advance of information technology, availability of electronic medical record, and development of sophisticated analytic programs have expanded the potential area of knowledge discovery and public health practice.

Dramatic advances of information technology and its use on health care and public health enabled efficient and effective use of health related information to improve practice as well as research. However, public concern on protection of privacy in

medical research has created several regulations on the use of health related information such as the Health Insurance Portability and Accountability Act (HIPAA) and “The Privacy Rule” (to be described further later in this paper). Such regulations, aimed to protect human rights, may threaten the welfare of society through impeding the conduct of epidemiological studies which should improve the quality of medical care and public health practice. The first cancer registry in Hamburg, Germany, suffered from unintended effect of Privacy laws. It has been collecting data on all cases of cancer for more than 50 years helping practitioners make treatment decisions and counsel with patients; however, the number of cancers reported to the cancer registry in Hamburg fell from 10,000 per year to just two cases in 1980-1981 (Dudeck, 2001; Ingelfinger, 2004; Parkin, 2006)

Ethical conduct of research is essential both in clinical trials and public health research, and acquisition of informed consent from study participants has been standard practice in clinical studies; many basic principles of research ethics described in Declaration of Helsinki, and the Belmont Report have been developed to protect human research subjects from unethical human subjects research. At that time, harm from unethical research was mainly physical harms. Few people could have imagined the availability of modern information technology and endemic of chronic diseases. It was not until 1990’s that use of internet and electronic medical records became popular. It was after 1990 that there was wide spread acceptance that public health practice include chronic disease prevention and medical care (Turnock, 2009).

Rise of Information technology is remarkable, which benefits many areas of public health and health care. At the same time, it has significant threats to privacy; personal

health information can be easily accessed, copied, and transported (Myers, 2008). For example, Behlen et al. reported that they could identify one specific person from the University of Chicago Hospital by combining birth data and residence ZIP code (Behlen, 1999).

How to balance the public interest and individual privacy, and conduct ethical research which uses personal health information with minimal risk and maximum privacy protection has been one of the key issues today. This paper overviews the historical perspectives of human subjects research ethics, informed consent, and protection of health information privacy, and the influence of research regulation on epidemiologic studies. I will discuss issues of related to the balance between the public good and privacy, requirements of waiver of informed consent, and propose some guidance to use data from existing medical record or clinical registries. Unless otherwise indicated general statements regarding regulations, history and research examples relate to the U.S.A.

2. Methods

To address these issues I have conducted a literature review and web-based search regarding epidemiologic studies using health record and informed consent. Key words I used for literature search included “clinical registries”, “cancer registration”, “medical record research”, “public health research ethics”, and “informed consent”. I also analyzed collected information to develop an ethical framework on clinical registries and informed consent. Definitions of terms such as epidemiology, registry, public health practice and research, are described in a glossary.

3. History of Research Ethics and Informed Consent

3.1 The history of research ethics and regulations

I will overview the history of research ethics and regulations before discussion further about necessity of informed consent in epidemiological studies.

The current ethical framework for human subject research was developed after the World War II, with reflection on several unethical examples that occurred prior to that time. The Nuremberg War Crime Trials were held in the southern German city of Nuremberg, the site of large Nazi Party conventions during the WWII in order to prosecute war criminals and Nazi medical scientists for war crimes and crimes against humanity. The absence of laws or regulations for human subjects research at that time led to the formulation of the formulation of Nuremberg Code in 1947, a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp detainees. The Nuremberg Code contains ten principles, such as voluntary informed consent and absence of coercion (Nuremberg Code, 1949; US DHHS, 2008), and it provided new standards of ethical medical behavior for the post World War II human rights era. Principles from the Nuremberg Code, summarized by Lynn et al. were shown in the Appendix1.

The Declaration of Helsinki was developed by World Medical Association in 1964, which reinforced the principles of the Nuremberg Code and established new rules for human experimentation. It emphasized that “In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.” (WMA, 1964)

The development of ethical guidelines did not abolish unethical conduct of human subject research. Dr. Henry Beecher, Professor of Anesthesiology at Harvard University, published an article titled “Ethics and clinical research” in *New England Journal of Medicine* in 1966, which cited 22 representative examples from over 200 unethical medical experiments (Erler, 2008; Beecher, 1966; Lerner, 2004). He demonstrated that unethical conduct of human subjects research was not confined to the barbaric practices of Nazi physicians, but that even physician–scientists in renowned universities had conducted unethical research.

A blatant example was the Tuskegee study, which was reported first in the *Washington Star* on July 25, 1972 and then published in the *New York Times* on July 26, 1972 (Heller, 1972). The Tuskegee syphilis study was conducted, with the support of the US Public Health Service, between 1932 and 1972; 399 African American men with syphilis were left untreated to clarify the natural course of syphilis. Even after the effective treatment was available, they were intentionally left untreated. The Tuskegee study led to the creation of the National Research Act in 1974 and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979 (US DHHS, no date.).

The National Commission published several reports including reports entitled *Ethical Principles and Guidelines for the Protection of Human Subjects*. This was popularly called the Belmont Report, named after the conference center in Elkridge, a small town near Baltimore, Maryland. The Belmont Report identifies three fundamental ethical principles for all human subject research – respect for persons, beneficence, and

justice, which remain the basis for the human subject protection regulations (US DHHS, no date)

Based on the Belmont Report and other work of the National Commission, DHEW (Department of Health, Education, and Welfare) revised and expanded its regulations for the protection of human subjects. When DHEW became DHHS (Department of Health and Human Services), the regulations are codified at 45 CFR part 46, often called the "Common Rule." The regulations found at 45 CFR part 46 are based in large part on the Belmont Report and were written to offer basic protections to human subjects involved in both biomedical and behavioral research conducted or supported by HHS (US DHHS, 2008)

The U.S. Food and Drug Administration (FDA) does not use the Common Rule; instead, separate rules applying to clinical trials regulated by FDA are contained in 21 CFR Parts 50 and 56, and were originally adopted in 1980 (Bertholf, 2001; US DHHS FDA, 2009).

The National Research act in the U.S. also requires the establishment of Institutional Review Boards (IRBs) at institutions receiving U.S. federal grants. An IRB is a board or committee formally designated by an institution to review and monitor research involving humans as subjects. Its main responsibility is to protect the rights and welfare of human subjects and to evaluate risks/benefits and ethical component of the research, and as such, an IRB has the authority to approve, require modifications in, or disapprove research proposals.

International guidelines on ethics of human subjects' research had been developed in the late 1940's. The Council for International Organizations of Medical

Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949, and has more than 55 international and national members, representing a significant proportion of the world's biomedical scientific community (CIOMS, no date). The objectives of CIOMS include facilitation and promotion of international activities in the field of biomedical sciences, and CIOMS has contributed to the programs of bioethics, health policy, drug development and use (CIOMS, no date). In 1982, CIOMS proposed *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, and the latest version revised in 2002 is *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002) .

Recognizing the need of ethical guidance for public health research, CIOMS published *International Guidelines for Ethical Review of Epidemiological Studies* in 1991. Increased attention to the ethical conduct of research, and greater awareness of health-related information and protection of privacy have led CIOMS to revise the *International Ethical Guidelines for Epidemiological Studies* in 2009.

In Japan, the legal regulatory requirement for human subjects' research, which is called Good Clinical Practice, is limited to clinical trials for the purpose of new drug applications. It was formulated in 1997. The *ethical guidelines for genomic research* in 2001 was the first among several guidelines on the conductance of human subjects' research. However, absence of legal binding force, and inconformity between guidelines have been the matter of debate. Furthermore, no regulations or guidelines exist for the human subjects' research for behavioral science.

3.2 Current status of protection of Privacy and Human subject research

The advances and increased utilization of information technology in health care settings and growing public concern about privacy and protecting personal health information promoted the U.S. Congress to set a national standard for electronic transfers and security of health data. Electronic medical records systems have a double edge; they can promote efficient medical practice and medical and epidemiological studies while they can also cause serious harm, if the proper privacy protections are not in place. Disclosure of health data can cause discrimination or stigmatization, which may lead to the loss of insurance, promotion, education, or employment.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) had three objectives: to make insurance portable between jobs, to provide tax provisions to make insurance portable, and to simplify administration of electronic health information (Horning,2009; Nosowsky, 2007). The HIPPA Privacy rule created confidentiality standards. The Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule”) establishes, for the first time, a set of national standards for the protection of certain health information (US DHHS, 2007). Although a major goal of the Privacy Rule is to properly protect the individual’s health information while allowing the flow of health information needed to provide and promote high quality health care and to protect the public's health and well being, some concerns on its impact on clinical research have been raised before and after the enactment of Privacy rule. Failure to comply with HIPAA can result in civil and criminal penalties; maximum penalty for HIPAA violation is \$50,000 per violation, with an annual maximum of \$1.5 million (AMA, 2010) .

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances set forth in the Privacy Rule.

Similar regulations and laws concerning the protection of privacy can be seen in other countries. The European Commission (Currently European Union) implemented the Data Protection Directive in 1995, which regulates the processing of personal data within the European Union. Personal data may only be transferred to third countries if that country provides an adequate level of protection (Article 25, 95/46/EC; Gershon, 2008). For example, unless Japan ensures adequate level of protection, personal data would not be transferred to Japan, which will adversely affect commerce. This accelerated the formulation of law on privacy in Japan, and Act on the Protection of Personal Information (APPI) was passed in 2003.

Use of patients' information for practice and research purposes is exempted from Japanese Privacy Law, to respect for the Academic freedom assured in the Constitution. Use of private health information is regulated by Ethical guidelines for epidemiological and clinical researches, and approval of the study and approval of waiver of informed consent are determined by IRB. Maximal fine for violation of Japanese Privacy Rule is 300,000 Japanese Yen or approximately \$3,000.

The Personal Information Protection and Electronic Document Act, which was passed in 2000 in Canada, addressed important privacy and confidentiality issues in medical research.

4. Regulations and systems to protect research participants

Independent ethical review can function as a safeguard to human subjects; it can also ensure public accountability that people who enroll in trials will be treated ethically (Emanuel, 2000; Emanuel, 2009). Institutional Review board is a committee which reviews the research protocol, approves or disapproves the research project, monitors the progress of the research, and has authority to terminate the research if needed. The term “IRB” is used in the U.S.A, whereas Research Ethics Committee or Research Ethics Board is often used in other countries. In this paper, I use the term “IRB”. The function and structure of IRBs are described in the Common Rule; the federal policy requires that an IRB have a minimum of five members including a chairperson, a scientific member, a nonscientific member, a lay person not affiliated with the institution, and a practitioner. The composition of the IRB must provide the professional competence required for reviewing research to determine whether the research fulfill ethical standards.

Types of IRB review are classified to full, expedited, and exempt. Human subjects research with minimal risk can be exempted from IRB review; examples include the observation of public behavior, the collection of not-sensible anonymous surveys of non-vulnerable individuals, and analysis of existing non-identifiable data (US DHHS, 2009).

Research that does not qualify for exemption but has minimal risk and fits at least one of the allowable categories may be reviewed by expedited procedures. An expedited review procedure can be carried out by the IRB chair person or by more

experienced IRB member designated by the chair person. Categories of research qualified for expedited review are listed at relevant site.

Voluntary informed consent is one of the fundamental issues in research ethics, especially in biomedical research including randomized controlled trial using interventional procedures or medication. The principle of consent protects individual's right not to be harmed. Researchers must always respect the autonomy of human subjects who participates in research. Difficult issues arise in the concept of informed consent in observational epidemiological studies which pose little or no intervention to study subjects, and I will discuss these issues in detail.

5. Protection of research participants and Informed consent

5.1 Epidemiological study issues

Epidemiological studies using clinical registries and medical records are indispensable and valuable to detect the cause of the disease, and to assess the performance and effectiveness of treatments. Linkage of multiple databases can enhance the quality of research, but the requirement of de-identification of the data or individual consent for the use of data in clinical registries and medical records will significantly affect the quality of the study. Especially, the quality of large scale epidemiological studies such as population-based cancer registries will be significantly flawed; it is impossible to obtain informed consent from all participants and selection bias is inevitable if the research is conducted using only participants with consent.

Several studies showed that privacy legislation and its conservative interpretation by IRB affected the validity of the research in observational studies. Statistically

significant differences between participants and non-participants in research that used medical records are termed as “authorization bias” by Jacobson et al. (Jacobsen, 1999)

The pregnancy Exposure and Preeclampsia Prevention Project (PEEP) is a prospective study of women followed throughout pregnancy to determine the cause of preeclampsia. Recruitment suddenly declined from 12.4 women per week pre HIPAA to as low as 2.5 women per week post HIPAA (Nosowsky, 2007; Ness, 2005). Similarly, a study using Michigan Acute Coronary Syndrome Registry has also shown the decline of consent to follow up: 96.4% in the pre HIPAA period to 34.0% in the post HIPAA period (Armstrong, 2005).

In the Canadian Stroke Registry (CSN), obtaining written informed consent for participation led to significant selection bias. The Registry of the Canadian Stroke Network (RCSN) is a clinical database of patients with acute stroke patients seen at selected acute care hospitals across Canada (Tu, 2004). The in-hospital mortality rate was much lower among participants (6.9 percent) than among those who declined to give consent (21.7 percent). The result of this study may underestimate the risk of death among stroke patients, and if used for public policy or therapeutic guidelines, can mislead the practice affecting millions of people with stroke or high risk of stroke.

In a Scottish intracranial vascular malformation study, differences were observed between adults who consent to participate in observational record-based research and those who do not, or cannot consent. Participants were 187 adults were asked consent of the study at the time of their first diagnosis of a brain arteriovenous malformation. Consenters were significantly more likely to receive interventional treatment, and their survival was significantly better than non-consenters. Analysis of the whole cohort

shows that the presentation with intracranial hemorrhage confers high a higher risk of subsequent hemorrhage, while analysis using data of consenters does not (Al-Shahi, 2005).

A Systematic review of 17 studies was conducted to determine whether informed consent introduced selection bias in prospective observational studies using data from medical records. Authors found differences in outcomes between participants and non-participants in all 17 studies. Requirement for written informed consent for the use of identifiable data in medical record or registries can bias disease registries, epidemiological studies, and health service research (Kho, 2009).

In Italy, basic indicators such as neonatal and infant mortality stratified by birth weight and gestational age are no longer available at national level due to the prohibition of linkage of private health information even between public institutions (Cuttini, 2009)

Requirement of individual informed consent for the secondary use of clinical registries or medical records will significantly influence clinical and public health research and health service research, resulting in the decline of quality of health services people will receive.

Another concern is the undue burden of financial and human resource required for the pursuit of individual consent. National survey of British public's view on use of identifiable medical data by the National Cancer Registry shows that 72% of all responders considers the confidential use of personal, identifiable patient information by the National Cancer Registry for the purpose of public health research and surveillance not to be an invasion of privacy (Barett, 2006). However, Japanese public's view is

more stringent; the public opinion poll on health conducted by the Mainichi Newspaper showed that 62% of responders consider that “case should be registered only when patients give consent”, and 15% answered that “cancers should not have to be registered.” (Suda, 2007). Questionnaire survey conducted by Matsuda et al. showed that 43% considers the registration without individual explanation to be violation of privacy regardless of the strictness of the data protection (Matsuda, 2010).

5.2 Ethical framework of participants’ protection and informed consent in U.S. epidemiological studies

One of the greatest obstacles of high-quality epidemiological observational studies is to gain approval of access to medical record and health information. Requirement of informed consent for studies using existent data such as those of medical record are not uniform among states and institutions. Federal regulations require that no investigator may involve a human being as a subject in research unless legally effective informed consent has been obtained. However, an IRB may waive the requirements to obtain informed consent in two conditions; the first is for governmentally approved study of a “public benefit or service program” that “could not practically be carried out without the waiver”. The second is when the IRB finds and documents that; the research involves no more than minimal risk to the subjects; the waiver or alteration will not adversely affect the rights and welfare of the subjects; the research could not practicably be carried out without the waiver or alteration; and whenever appropriate, the subjects will be provided with additional pertinent information after participation (US DHHS 45CFR46.116(d), 2009)

For many epidemiological studies using clinical registries, informed consent can be waived to conduct epidemiological studies using personal health information. The rationale for the waiver of consent is as follows; 1) waiver of consent will not harm the participants 2) waiver of consent will not violate either privacy or right to control 3) some epidemiological studies can be regarded as public health practice, not pure scientific research. I will discuss the above issues as well as presumed, blanket consent.

5.2.1 Examples of waivers of privacy rules

Current guidelines and rules for human subject research ethics are created by reflection of unethical medical experiment during World War II and other examples, noted above, during the mid 20th century. The code of medical and research ethics generally gives high priority to individual autonomy, which mandated individual informed consent for the use of private information. However, priority of individual autonomy over public interest is not necessary prima-facie, especially in the field of public health. Disclosure of private information or isolation (restriction of transport) may be required to prevent outbreak of infectious disease in communities. Assessment of quality improvement in some public health practices requires access to private health information. Growing needs for advanced ethics framework for public health research and practice are expressed in several sources in the public health literatures (Kass, 2001; Gruskin, 2002; Buchanan, 2008; Myers, 2008; Wartenberg, 2010).

5.2.2 Waiver of consent does not violate privacy

A waiver of consent for epidemiological studies using private health information in medical records or clinical registries is not violating privacy and can be justified under certain conditions.

According to Introna, there are three categories of privacy definitions: privacy as no access to the person or the personal realm; privacy as control over personal information and privacy as freedom from judgment or scrutiny by others (Introna, 1997; Whitley, 2009).

De-identification can protect the third definition of privacy, but still violated the first two definitions. If the private information is considered as private property, the person owns his/her private health information, access to private health information can be regarded as violation to privacy. And use of such information without owner's permission will violate the second definition of privacy, the right to control. For example, a heavy smoker may not allow his/her personal information to be used in research which may prove the harm of smoking, leading to public policy regulating smoking.

Miller uses the analogy of land ownership to solve these questions (Miller, 2008). Access to and use of medical records can be compared to trespassing on one's land. Even so, Miller argues that limitations on property rights are generally accepted both to prevent harm to others and to promote the common good. Environmental regulations limit people's right to use their homes and land in a way that is a nuisance to their neighbors. Property owners are obliged to pay real estate taxes. Then, a waiver of consent for certain epidemiological studies involving access to personally identifiable data is accepted as long as the proposed research is socially valuable and there are severe practical impediments to soliciting consent or requiring consent would be likely to

compromise the scientific validity, and consequently the value of research, and adequate safeguards for access by researchers are implemented to minimize the intrusion on privacy.

We need to balance basic principles of research, respect for autonomy, non-maleficence, beneficence, and justice. Limiting respect for autonomy can be justified when other ethical principles need to be respected. The principle of justice or fairness demands access and use of personally identifiable data without consent to conduct research which answers socially valuable questions. Fairness limits “free riders” who will benefit from result of studies for which they refuse to participate. Balancing public goods and privacy is necessary, and the importance of public purpose should not harm research participants. Strict safeguard measures need to be practices such as the demonstration of an important public purpose for research, de-identifying the data when possible, and mandating strict standards for protecting the private data (Miller, 2008).

It is critical to address who determines whether the research has an important public purpose; rather than the local IRB who may not always have expertise in reviewing epidemiological studies, a central IRB with members of public health professionals and representatives of the society should play an important role in determining the value of such studies.

Recent advances in information technology can protect privacy in research using electric database. Several studies demonstrated the effectiveness of advanced data mining, anonymization techniques to protect privacy (Malin, 2005; Agrawal, 2007). Agrawala et al reported an integrated set of technologies called "the Hippocratic

Database" which manages disclosure of electronic health records in compliance with data protection laws without impeding the legitimate flow of information (Agrawal, 2007).

5.2.3 Issue of blanket consent

Blanket consent, advance consent, or presumed consent should not replace individual consent. Blanket consent is a consent in which patients are asked to give when they enter a new health plan or are admitted to hospital. At the inception of the human subjects research, participants may be asked to give a blanket consent for secondary use of data collected during the study. Data and information collected during the study, with tremendous efforts and funding, as well as goodwill of participants, is a valuable asset for the improvement of public health. Accessing former participants or patients to ask for consent may pose additional violation of privacy, annoyance, or financial burden to the society which funds public health research. For example, in the registry of the Canadian Stroke Network, estimated cost spent on consent-related issues was \$ 500, 000 (Canadian dollars) for 7,108 eligible patients (Tu, 2004).

Blanket consent should not replace individual consent; it not only poses ethical ambiguity but also technical difficulties. Asking someone to give consent to future unknown studies is not fair. Appelbaum expressed doubt as to whether meaningful consent can be offered without knowing the purpose of the study, data to be collected, or who will be collecting the data (Appelbaum, 2001). Receiving such consent only indicates that the participant trusts the well intent of the researcher or does not care at all. Such consent should not guarantee researchers to have unconditional access to private health information. Furthermore, use of broad consent has technical difficulties

as well; when collecting large database, it is extremely difficult and costly for researchers to effectively exclude those data to which participants did not give consent.

For ethical use of private health information data as well as secondary use of collected data, oversight and approval of waiver of consent by IRB or equivalent committee is preferable. Expedited or full review by IRB can assure that the study has significant public health value and adequate safeguard for protection of privacy is conducted.

5.2.4 Importance of continuous effort to promote public recognition of epidemiological studies

Continuous effort to promote participation rate and public recognition and approval of epidemiological studies should be encouraged.

Lack of trust or understanding of medical and public health research among the public can result in low participation rate or low consent rate. In one study using telephone interview in Pennsylvania, 25% said they would not be willing to participate in medical research and 29 % indicated uncertainty about participation (Trauth, 2000). However, in genetic research in the Framingham Heart Study, percentages of participants who consented to collection of DNA and to various uses of their genetic information between 2002 and 2009 were above 95%. The researchers considers that the high consent rates are partly due to researchers' ongoing efforts to maintain communications with participants and to keep them informed about research activities and procedures (Levy D. 2010). Fostering mutual understanding and cooperation

between researchers and public should be the basal ground of public health practice and research.

5.3 International and national guidelines

Recognizing that ethical guidance was needed for public health research, international and national ethics guidelines on epidemiological research have been developed. Among them, I will cite two guidelines, CIOMS and the Japanese guideline, and review how they consider the issue of informed consent in epidemiological studies.

CIOMS guidelines state that “for all epidemiological research involving humans the investigator must obtain the voluntary informed consent of the prospective subject.” However, “waiver of individual informed consent is to be regarded as exceptional, and must in all cases be approved by an ethical review committee unless otherwise permitted under national legislation that conforms to the ethical principles in these Guidelines.” (CIOMS p.35, 2009) CIOMS guidelines comments issues on the use of medical records and biological specimens collected for other purposes. “Records and specimens taken in the course of clinical care, or for an earlier study, may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed.” (CIOMS p.39, 2009)

Other categories of epidemiological studies for which consent may be waived include: the use of personally non-identifiable materials; the use of personally

identifiable materials with special justification; studies performed within the scope of regulatory authorities; studies using health-related registries that are authorized under national regulations; and cluster-randomized trials. (CIOMS p.40, 2009)

In Japan, *Ethical Guidelines for Epidemiological Research* were published in 2002, and later revised in 2009. As for informed consent, it states “Ordinarily, informed consent should be obtained from research subjects according to the following rules.” Like other ethical guidelines, Ethics review committee has authority to give waiver of consent in certain conditions which include:

- 1- The epidemiological research involves no more than minimal risk to the subjects;
- 2- The relaxation, waiver or deviation will not adversely affect the interests of the subjects;
- 3- The epidemiological research could not practically be carried out without the relaxation, waiver or deviation;
- 4- Whenever appropriate, any of the following measures shall be taken:

A. The population in which the subjects are included shall be informed about the details of collection and use of human biological materials and information, including collection methods;

B. Research subjects shall be provided with pertinent information after participation, as soon as practically possible (group briefings are also acceptable);

C. Where human biological materials and information are collected or used continuously for a long period of time, reasonable efforts shall be taken to make all relevant details known to the public by disseminating pertinent information including the methods of collection and use;

5- The epidemiological research is recognized as having great social importance.

Regarding observational research using only existing materials, informed consent does not necessarily need to be obtained from research subjects. However, for these types of research, researchers shall publish all relevant details regarding the study to be carried out (Japanese government, 2009).

6. Proposal to promote ethical public health researches using existing medical records

To promote ethical and effective epidemiological studies using clinical registries and medical records, development of standard guidelines on ethical conduct and reviewing the process of epidemiological studies, and structuring skilled IRB system is mandatory.

6.1 Development of standard guidelines of ethical conduct and reviewing the process of epidemiological studies

Several proposals and guidelines have been presented to solve the dilemma of public good and protection of privacy in conducting epidemiologic study, including studies using data from clinical registries. Dissemination of these guidelines among researchers, IRB, and the public will solve some barriers to ethical conduct of research.

IACR (International Association of Cancer Registry) developed guidelines on confidentiality for population-based cancer registration. Recognizing that the principles of informed consent is not practicable in much of the population-based public health research in which cancer registries participate, where the whole population is under study, IACR developed detailed guidelines which help to take balance between the right to privacy for the participating individual and the right of fellow citizens who will benefit

from the knowledge discovered by the cancer registration (IARC, 2005). These guidelines not only facilitate studies using cancer registration but also studies of other diseases.

The Institute of Clinical Evaluative Science of Canada proposed safeguards to ensure confidentiality of personal health data (ICES, 2005. Appendix 1).

Kho et al suggested five strategies to minimize the impact of bias from informed consent: a waiver of consent from research ethics boards and explicitly outline procedures to protect privacy and confidentiality, some suggestions if a waivers is not possible, education at clinicians, researchers, and research ethics boards on conditions under which studies can proceed without individual consent, standardize reporting of methods used to seek informed consent, and increase awareness by clinicians and researchers of potential impact of selection bias introduced by informed consent (Kho, 2009, Appendix 2)

6.2 Role of IRB in epidemiological studies

CIOMS guidelines, Japanese guidelines, and current regulations in the Common Rule and the Health Insurance Portability and Accountability Act (HIPAA) permit waivers of informed consent in epidemiological studies under certain conditions. It is the responsibility of IRB to critically examine the balance between public goods and privacy to determine whether waiver of consent is justified for the proposed epidemiological study. Even for the Registry of the Canadian Stroke Network (RCSN), waiver of consent could have been justified if IRB determined that subjects would be exposed to no more than minimal risk, and the recruitment of individual consent would make the

conduct of the research impracticable. Since RCSN is an observational study using a de-identified minimal data set and data were encrypted, password-protected, securely housed and analyzed, waiver of consent seems justified. However, informed consent has been required for many clinical registries and epidemiological observational studies.

The imprecise criteria for waivers of authorization and use of traditional framework of research ethics caused the different interpretation, leading to conservative and strict regulation on minimal risk studies using routinely collected data.

Whether the acquisition of medical record data can be regarded as “minimal risk” not requiring informed consent varies among states and institutions. Strict interpretation may require individual informed consent whereas other interpretation may give waiver of consent. A study conducted in Canada showed that large variation exists across sites in the requirement for consent for research involving access to medical records. Forty seven percent of Research Ethics Boards (REBs) required individual patient consent, while 38% did not require consent (Willison, 2008). The American Society of Clinical Oncology (ASCO) Cancer Research Committee conducted study to assess the attitudes of cancer researchers and compliance officials regarding compliance with the US Privacy Rule, and found disagreements between researchers and compliance officials. (Goss, 2009). Requirement for research ethics committee varies among different countries. Hearnshaw compared requirements of research ethics committees in 11 European countries for non-invasive interventional study. Three countries including UK required approval, four countries required committee’s check for decision of exempt, while four countries did not require approval from research ethics committee for the same protocol. (Hearnshaw, 2004)

Inconsistency among review boards cause delay in approval of access to data. In UK where researchers are required to apply to the Patient Information Advisory Group (PIAG) for permission to access medical records without written permission, considerable delays in approval were found; Metcalfe conducted a study to examine the time needed to receive permission for low risk research using routinely collected identifiable health information without informed consent, and found that it took eight months to receive permission to access basic identifying information on individuals registered at general practice, and 18 months to receive permission to access clinical information in medical records. (Metcalfe, 2008)

When researchers need to access records for which consent has not been provided, such as the secondary use of routinely collected data, waiver of consent should be determined by an IRB, and not by other review board such as patient advocate group or medical records review board proposed by Dr. Goldman, Chairman of American Psychiatric Association (Goldman, 2001). Dr. Goldman proposed that waiver of consent should be approved by medical records review boards because IRB may be susceptible to institutional pressure to approve research proposals. I opposed to this view; it may bring more confusion among researchers and review board members, adding more burdens to review board member as well as to the society which needs to spend more time and money to educate review board members. IRB should take the role to review and approve access to data in medical record and registries for public health researchers.

One of the causes of inconsistency among IRB decision lies in the advance and specialization of science. No one IRB member can review and make a critical decision

in every field of discipline; it is far beyond one's ability to understand the scientific value, methodology, and social influence of a particular research. Use of central IRB skilled with public health and epidemiological studies together with local IRB may help facilitate ethical, rational, and scientific review of epidemiological studies. The scientific and social value the research may bring will be adequately judged by central IRB, which is composed of scientist, public health professionals, representatives of public policy maker, and representatives of population for which the research is targeting. To prevent potential harm the research poses in certain geographic or cultural area, local IRB should also participate in reviewing process; however, to prevent redundant reviewing and to lessen the burden to the local IRB, reviewing at local IRB can be conducted as expedited review if central IRB approves the research. If local IRB faces difficulty in judging the scientific or social benefit the research may bring, local IRB should contact central IRB for clarification. These collaborative works will facilitate consistent review, educate IRB members, and contribute to the dissemination of knowledge of research ethics among researchers and IRB member.

Inconsistency among IRBs and complicated, and sometimes bureaucratic reviewing process can cause delay of approval of the study, which can peril the public goods. Continuous education and development toward IRB members and research on research reviewing process and research ethics should be emphasized.

6.3 Proposal to promote public health research using data in medical records or clinical registries.

Based on the review of U.S., Japanese and other international standards and guidelines that have been presented in this paper I propose following guidance to promote public health research using data in medical records or clinical registries, with careful consideration of ethical and privacy issues and the current use of IRBs worldwide.

- 1) All patients or potential participants of future studies should receive sufficient information that his or her private health information could be used for future observational studies, and that the access to those data will be allowed only after careful review of the IRB, and that their privacy and confidentiality will be strictly protected and that he or she can opt-out the study.
- 2) Government, organizations, and health institutes need to educate public about the importance of public health research and procedure to provide researcher's access to data in medical record and clinical registries.
- 3) Researches who wish to use existing data in medical record or clinical registries should request a waiver of consent from an IRB, by providing a detailed research protocol, reasons why informed consent would not be available, and procedures to protect the privacy and confidentiality of each patient. An IRB can allow permission to access to data if it finds the research is public health research which brings benefit to the society, and waiver of consent is justified, and that the procedure to protect the privacy and confidentiality is valid.
- 4) Researchers who use private health information for public health research should exert maximum effort to protect confidentiality of research subjects.

- 5) For prospective collection of data, researchers are encouraged to attempt to receive individual consent; however, if it is not feasible, researchers can collect and access data if those data can be regarded as routinely collected data in standard practice.
- 6) Researchers need to inform the public about the ongoing studies so that patients can opt-out any time.
- 7) Continuous education toward public, researchers, and IRB members should be emphasized.
- 8) Explicit guidelines and rules about the use of data in medical records and clinical registries should be developed and disseminated.

Conclusion

I reviewed the ethical framework and current practice of epidemiologic studies which use data from existing medical records or clinical registries and the requirement of informed consent in such studies, and clarified the potential causes of confusion between the goals of epidemiologic research and the purposes of informed consent and other privacy protections. As a result of this review and in consideration of dilemmas regarding the protection of patient privacy and the need for efficient access to data, I developed a set of eight proposals for the ethical use of existing data in medical records or clinical registries in epidemiological and other public health studies.

Provision of education on research ethics to the general public, researchers, and IRB members is a cornerstone in the advancement of quality research. Fostering public views that participation in public health research is both a right and duty for members of

a society, to promote welfare of the public, is needed. It is also critical to develop a culture among researchers that the acquisition of public trust through the conduct of ethical public health research is a prerequisite for high quality clinical and public health research.

Appendix 1

Principles from the Nuremberg Code (1947)

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should produce results for the good of society that are not obtainable by other means of study.
3. Research with human subjects should be based on the results of animal experimentation and knowledge of the disease or other problem so that the results justify the research.
4. To the extent possible there should be no unnecessary physical or mental suffering or injury.
5. Research should not be conducted if there is an expectation that death or disability will occur unless the experimental physicians also serve as subjects.
6. The degree of risk must be in balance with the possible benefit from the research.
7. Research should only be conducted in facilities that are adequate for the study and will not cause injury, disability, or death.
8. Researchers and other study personnel need to be qualified to perform their roles.
9. Subjects may end their participation in the research if they chooses to do so.
10. Researchers should be prepared to terminate the study at any time if they believe that continuing the study will place the subject in danger of injury, disability, or death.

(Table from Lynn and Nelson, 2005)

Appendix 2

Safeguards to ensure confidentiality of personal health data used by the Institute for Clinical Evaluative Sciences

- De-identification of data or, if de-identification cannot occur, the substitution of an encrypted unique numeric identifier for personal identifiers by a designated data custodian
- Designation of a privacy officer to implement and monitor compliance with all security and confidentiality policies and practices
- Stringent physical and electronic security of data
- Limitation of physical and electronic access to the data
- Cultivation of an atmosphere of respect for privacy and confidentiality, inclusion of confidentiality and data protection obligations in employment contracts, requirements for employees to sign confidentiality pledges yearly and to receive adequate and ongoing training
- Implementation of strict policies and procedures to handle, access, use, disclose, retain and destroy data
- Established penalties for unauthorized attempts to access or disclose data, or to re-identify de-identified data
- Assessment of potential privacy and confidentiality risks for every observational study
- Limitations on data use to a need-to-use basis
- Controls on disclosure of study results including the stipulation that only aggregate results are allowed to be reported

- Regular reviews and audits, transparency to the public, firm oversight and approval by independent parties
(ICES, 2005)

Appendix 3

Five suggested strategies to minimize the impact of bias from informed consent

1. Request a waiver of consent from research ethics boards and explicitly outline procedures to protect the privacy and confidentiality of each patient
2. If a waiver is not possible then:
 - Collect a minimum dataset of key prognostic variables on all eligible people identified through screening
 - Complete a preliminary analysis comparing participants and non-participants on key prognostic variables at predetermined times
 - Revise the strategy for recruitment as necessary
3. Aim education at clinicians, researchers, and research ethics boards on conditions under which studies can proceed without individual consent
4. Standardize reporting of methods used to seek informed consent
5. Increase awareness by clinicians and researchers of the potential impact of selection bias introduced by informed consent and implications for interpretation of the study

(Kho, 2009)

Appendix 4

ETHICAL GUIDELINES FOR EPIDEMIOLOGICAL RESEARCH

17 June 2002

Japanese Ministry of Education, Culture, Sports, Science and Technology

Ministry of Health, Labour and Welfare

CHAPTER 3. INFORMED CONSENT

SECTION 7. PROCEDURES FOR OBTAINING INFORMED CONSENT

Ordinarily, informed consent should be obtained from research subjects according to the following rules.

Where it is infeasible to observe these rules due to such reasons as methodology or purpose of the research, nature of research subjects, or the like, exceptions to the Guidelines may be permitted only when approval of both the ethics review committee and the institute head have been secured.

Ethics review committees shall make certain that all of the following conditions are met in research proposals, whenever relaxing, waiving or deviating from the general rules for obtaining informed consent:

- 1- The epidemiological research involves no more than minimal risk to the subjects;
- 2- The relaxation, waiver or deviation will not adversely affect the interests of the subjects;

3- The epidemiological research could not practically be carried out without the relaxation, waiver or deviation;

4- Whenever appropriate, any of the following measures shall be taken:

A. The population in which the subjects are included shall be informed about the details of collection and use of human biological materials and information, including collection methods;

B. Research subjects shall be provided with pertinent information after participation, as soon as practically possible (group briefings are also acceptable);

C. Where human biological materials and information are collected or used continuously for a long period of time, reasonable efforts shall be taken to make all relevant details known to the public by disseminating pertinent information including the methods of collection and use;

5- The epidemiological research is recognized as having great social importance.

Regarding observational research using only existing materials, informed consent does not necessarily need to be obtained from research subjects. However, for these types of research, researchers shall publish all relevant details regarding the study to be carried out.

(Ministry of Education, Culture, Sports, Science and Technology,

Ministry of Health, Labour and Welfare. Japan, 2002)

Glossary

Epidemiology

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and application of this study to control of health problems.” (John Last, Dictionary of Epidemiology, 4th edition)

Public Health Practice

Public Health Practice is an activity to protect the public’s health through epidemiological investigations, surveillance, programmatic evaluations, and clinical care for populations. (Perlman, 2008)

Public Health Research

Public Health Research is an activity to design and conduct of studies involving human subjects or the purpose of generating knowledge that often benefits those beyond the participating community bearing the risk of participation (Perlman, 2008)

Registry

A register is an ordered collection of records, for instance of births or of deaths.
A registry is an organized system to develop, maintain and use one or more registers, for example a national registry may keep the registers of births and deaths. By extension the institution responsible for the system is also called a registry (e.g., a cancer registry) (CIOMS, 2009).

REFERENCES

Agrawala, R., Johnson C. (2007). Securing electronic health records without impeding the flow of information. *International journal of medical informatics*, 76, 471-479.

Al-Shahi, R., Vousden, C., & Warlow, C. (2005). Bias from requiring explicit consent from all participants in observational research: prospective, population based study. *BMJ*, 331, 942.

AMA HIPAA Health Insurance Portability Accountability Act. HIPAA Violations and Enforcement. Retrieved June 29, 2010 from <http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/hipaahealth-insurance-portability-accountability-act/hipaa-violations-enforcement.shtml>

Appelbaum, P.S.(2001). Dr. Appelbaum Replies. *American Journal of Psychiatry* 158,1745-1746

Armstrong, D., Kline-Rogers, E., Jan,i S.M. et al. (2005). Potential impact of the HIPAA privacy rule on data collection in a registry of patients with acute coronary syndrome. *Archives of Internal Medicine*, 165, 1125-1129.

Ayanian J.Z. (1999). Using administrative data to assess health care outcomes. *European Heart Journal*, 20, 1689–1691.

Barrett, G., Cassell, J.A., Peacock, I.L. et al. (2006). National survey of British public's view on use of identifiable medical data by the National Cancer Registry. *BMJ*. 332, 1068-1072

Beecher, H.K. (1966). Ethics and clinical research. *New England Journal of Medicine*, 274, 1354-1360.

Behlen, F.M., Johnson, S.B. (1999). Multicenter Patient Records Research: Security Policies and Tools. *Journal of the American Medical Informatics Association*. 6, 435-443.

Bertholf, B.L (2001). Protecting Human Research Subjects. *Annals of Clinical and Laboratory Science*, 31, 119-127

Belmont Report. (1979). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report :Ethical Principles and Guidelines for the Protection of Human Subjects of Research. April 18, 1979. Retrieved June 29, 2010 from

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

Black, D.W., Warrack. G., and Winokur. G. (1985). The Iowa record-linkage study, III:excess mortality among patients with “functional” disorders. *Archives of General Psychiatry*, 42, 82-88.

Black, N. (1996). Why we need observational studies to evaluate the effectiveness of health care. *BMJ*, 312, 1215-1218.

Buchanan, D.R. (2008). Autonomy, paternalism, and justice: ethical priorities in public health. *American Journal of Public Health*, 98, 15-21.

Byerly, W.G. (2009). Working with the institutional review board. *American Journal of Health-System Pharmacy*, 66, 176-184.

CIOMS. (no date). The Council for International Organizations of Medical Sciences. About Us. Retrived June 29, 2010 from http://www.cioms.ch/about/frame_about.htm

CIOMS. (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Retrieved June 29, 2010 from http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm

CIOMS.(2009). International Ethical Guidelines for Epidemiological Studies. Geneva, WHO Press

Coleman, M.P., Muir, C.S., and Menegoz, F. (1992). Confidentiality in the Cancer Registry. *British Journal of Cancer*, 66, 1138-1149.

Cuttini, M., Saracci, R. (2009). Commentary: Can we facilitate the ethical approval of international observational studies? *International Journal of Epidemiology*, 38, 1108-1109.

The European Union Privacy Directives (EU) . Retrived June 29, 2010 from <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:NOT>

Dudeck, J. (2001). Informed consent for cancer registration. *Lancet Oncology*, 2, 8-9.

Emanuel, E.J., Wendler, D., and Grady, C. (2008). An ethical framework for biomedical research. In Emanuel, E.J. et al. (Eds), *The Oxford Textbook of Clinical Research Ethics*. (pp.130). New York, NY: Oxford University Press.

Emanuel, E.J., Wendler, D., Grady, C. (2000). What makes clinical research ethical? *JAMA*, 283, 2701-2711.

Enfield, K.B., Truwit, J.D. (2008). The purpose, composition, and function of an IRB: balancing priorities. *Respiratory Care*, 53, 1330-1336.

Erler, C.J., Thompson, C.B. (2008). Ethics, Human rights, and clinical research. *Air Medical Journal*, 27, 110-143.

Gershon, A.S., Tu JV. (2008). The effect of privacy legislation on observational research. *Canadian Medical Association Journal*, 178,871-873

Goldman, M.P. (2001). Use of Psychiatric Records. *American Journal of Psychiatry*, 158, 1744-1745.

Gordis, L. (1991). Ethical and professional issues in the changing practice of epidemiology. *Journal of Clinical Epidemiology*, 44, Suppl 1, 9S-13S.

Goss, E., Link, M.P., Bruinooge, S.S. (2009). The Impact of the Privacy Rule on Cancer Research: Variations in Attitudes and Application of Regulatory Standards. *Journal of Clinical Oncology*, 27, 4014-4020.

Gruskin, S. (2002). Ethics, Human rights, and public health. *American Journal of Public Health*, 92, 698.

Haynes, B. (1999). Can it work? Does it work? Is it worth it? *BMJ*, 319, 652-653.

Hearnshaw, H. (2004). Comparison of requirements of research ethics committees in 11 European countries for a non-invasive interventional study. *BMJ*, 328, 140-141.

Hoppe, D.J. Schemitsch, E.H., Morshedet, S. et al. (2009). Hierarchy of Evidence: Where Observational Studies Fit in and Why We Need Them. *Journal of Bone and Joint Surgery, American Volume*, 91 Suppl 3, 2-9.

Horning, S.J. (2009). Cancer Research and Privacy: The Problem with Being Joined at the Hip. *Journal of Clinical Oncology* , 27, 3879-3880.

IARC. (2005). Guidelines on confidentiality for population-based cancer registration. *European Journal of Cancer Prevention*, 14, 309-327.

Ingelfinger, J., Drazen, J.M. (2005). Registry Research and Medical Privacy. *New England Journal of Medicine*, 350, 1452-1453.

Institute for Clinical Evaluative Sciences. Privacy code: protecting personal health information at ICES. Toronto: The Institute; 2005. Retrived June 29, 2010 from www.ices.on.ca/file/ACF20B.pdf<<http://www.ices.on.ca/file/ACF20B.pdf>>

Introna, L.D. (1997). Privacy and the computer: why we need privacy in the information society. *Metaphilosophy*, 28, 259-275.

Jacobsen, J., Xia, Z., Campion, M.E. et al. (1999). Potential effect of authorization bias on medical record research. *Mayo Clinic Proceedings*, 74, 330-338.

Jean Heller. New York Times Page 1. July 26, 1972

Kass, N. (2001). An Ethics Framework for Public Health. *American Journal of Public Health*, 91, 1776-1782.

Kendler, K.S., McGuire, M., Gruenberg, A.M. et al.(1994). An epidemiologic, clinical, and family study of simple schizophrenia in County Roscommon, Ireland. *American Journal of Psychiatry*, 151, 27-34.

Kho, M.E., Duffett, M., Willison, D.J. et al. (2009). Written informed consent and selection bias in observational studies using medical records: systematic review. *BMJ*, 338, 866.

Lerner, B.H. (2004). Sins of omission: Cancer research without informed consent. *New England Journal of Medicine*, 351, 628-630.

Levy, D., Splansky, G.L., Strand, N.K. et al.(2010). Consent for genetic research in the Framingham Heart Study. *American Journal of Medical Genetics*, 152A, 1250-1256.

Lindsaya, R. (2007). Beyond clinical trials: The importance of large databases in evaluating differences in the effectiveness of bisphosphonate therapy in postmenopausal osteoporosis. *Bone*, 40(Supplement 2), S32-S35.

Lynn, M.R., Nelson, D.K. (2005). Common (Mis) Perception about IRB review of human subjects research. *Nursing Science Quarterly*, 16, 264-270.

Malin, B.A., Sweeney, L. (2005). A secure protocol to distribute unlinkable health data. *AMIA Annual Symposium Proceedings*, 485-489.

Matsuda, T., Marugame, T., Ajiki, W, Sobue, T. (2010). Do the Japanese feel more suspicious about cancer registration than the British? *Cancer Epidemiology*, 34, 122-130.

Metcalfe, C., Martin, R.M., Noble, S. et al. (2008). Low risk research using routinely collected identifiable health information without informed consent: encounters with the Patient Information Advisory Group. *BMJ*, 34, 37-40.

Miller, F.G. (2008). Research on medical records without informed consent. *Journal of Law, Medicine, and Ethics*, 36, 560-566.

Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare. Ethical Guidelines for Epidemiological Research. 2002. Retrieved June 29, 2010 from <http://www.niph.go.jp/wadai/ekigakurinri/ethical-gl/guidelines.htm>

Myers, J., Frieden, T.R., Bherwani, K.M. et al. (2008). Privacy and public health at risk: public health confidentiality in the digital age. *American Journal of Public Health*, 98, 6793-801.

Ness, R.B. (2005). A year is a terrible thing to waste: early experience with HIPAA. *Annals of Epidemiology*, 15, 85-86.

Nosowsky, R., Giordano, T.J. (2007). The HIPAA Privacy Rule: Implications for Clinical Research. *Annual Reviews of Medicine*, 57, 575-590.

Nuremberg Code.(1949). "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office.

Parkin, D.M. (2006). The evolution of the population-based cancer registry. *Nature Reviews Cancer*, 6, 603-612.

Perlman, D. (2008). Public health practice vs research: Implications for preparedness and disaster research review by state health department IRBs. *Disaster Medicine and Public Health Preparedness*. 2, 185-191.

Simon, G.E., Unutzer, J., Young, B.E. et al. (2000). Large medical databases, population-based research, and patient confidentiality. *American Journal of Psychiatry*, 157, 1731-1737.

Suda, M. (2007). Expectation for cancer control measures progress. Mainichi Newspaper, October 19, 2007

Tannen, R. L, Weiner, M. G, Xie, D. (2009). Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. *BMJ*, 338, b81-b81

Trauth, J.M., Musa, .D, Siminof, f L. et al. (2000). Public attitudes regarding willingness to participate in medical research studies. *Journal of Health Policy*, 12, 23-43.

Tu, J.V., Willison, D.J., Silver, F.L, et al. (2004). Impracticability of Informed Consent in the Registry of the Canadian Stroke Network. *New England Journal of Medicine*, 350, 1414-21.

Turnock, B.J. (2009). Core Functions and Public Health Practice. In *Public Health. What it is and how it works*. Fourth edition. (pp.222). Massachusetts.:Jones and Barlett Publishers.

U.S. Department of Health and Human Services.(no date). National Institute of Health. Regulations and Ethical Guidelines. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. Retrieved June 29, 2010 from <http://ohsr.od.nih.gov/guidelines/belmont.html>

U.S. Department of Health and Human Services. (2003). Standards for Privacy of Individually Identifiable Health Information. Retrieved June 29, 2010 from <http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/introduction.html>

U.S. Department of Health and Human Services. (2007). National Institute of Health. HIPAA Privacy Rule. Retrieved June 29, 2010 from <http://privacyruleandresearch.nih.gov/>

US DHHS. (2008). Office for Human Research Protections (OHRP):OHRP 45 CFR part 46 Frequently Asked Questions (FAQs). Retrieved June 29, 2010 from <http://www.dhhs.gov/ohrp/45CFRpt46faq.html>

U.S. Department of Health and Human Services. (2009). Code of Federal Regulations. Title 45 public welfare Part 46 protection of human subjects. Revised January 15, 2009. Retrieved from <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

U.S. Department of health and Human Services. Food and Drug Administration (2009). CFR-Code of Federal Regulations Title 21. Part 50 Protection of Human Subjects. Retrieved June 29, 2010 from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=50>.

U.S. Department of Health and Human Services. Food and Drug Administration (2009). CFR-Code of Federal Regulations Title 21. Part 56 Institutional Review Board.

Retrieved June 29, 2010 from

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm?cfrpart=56>

Wartenberg, D., Thompson, W.D. (2010). Privacy versus public health: the impact of current confidentiality rules. *American Journal of Public Health*, 100, 407-412.

Whitley, E.A. (2009). Informational privacy, consent and the "control" of personal data. *Information Security Technical Report*, 14, 154-159.

Willison, D.C., Emerson, C., Szala-Meneok, K.V et al. (2008). Access to medical records for research purposes: varying perceptions across research ethics boards. *Journal of Medical Ethics*, 34, 308-314.

World Medical Association. (1964). The Declaration of Helsinki. Retrieved June 29, 2010 from <http://www.wma.net/en/30publications/10policies/b3/index.html>