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Bioethical Issues in Pharmacoepidemiologic Research

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Because the bioethical issues involved in pharmacoepidemiologic research are closely related to changing patterns of drug usage and changing technologies of surveillance and data analysis, it is impossible to understand them without attention to historical and sociological perspectives. The field of pharmacoepidemiology emerged as a result of broader recent developments in medical therapeutics, concomitant with the expansion and refinement of the field of bioethics. Some key bioethical principles relevant to pharmacoepidemiologic research have remained significant over time; others have only gained attention in recent years. This chapter briefly introduces historical and sociological dimensions of pharmacoepidemiology from an international perspective, with an eye to commonalities and differences in national variations in ethical approaches to the field.

On the most common level, it is widely believed that pharmacoepidemiologic studies should create data that benefit public health, improve drug safety, and ensure efficacy. The protection of research subjects' rights and safety, their wellbeing, dignity, autonomy and privacy, as well as the reliability and robustness of generated data are relatively universal normative cornerstones of pharmacoepidemiology ethics. The same goes for the injunction that objectives and results of pharmacoepidemiologic research should be independent from economic and promotional interests of pharmaceutical companies or device manufacturers. Yet these principles are not simple to implement systematically at an international level. In this chapter, we explore the emergence and conduct of pharmacoepidemiologic research in three major global settings in which the field developed (North America, Europe, and East Asia) and some of the key challenges, tensions, and trends in historic and current international ethical policies relating to pharmacoepidemiology.

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Clinical Problems to be Addressed by Pharmacoepidemiologic Research

Emergence, Changing Methods, and Moral Stakes of Pharmacoepidemiology in 20th Century North America

In 1962, a series of epidemiological reports initiated by the German physician Widukind Lenz connected a recent increase in phocomelia, a birth defect which resulted in grossly visible limb deformities, with maternal use of the popular new antinausea medicine Contergan® (thalidomide) [1–4]. Images of thalidomide children became an international symbol of the ethical failure of the medical profession and the regulatory state to protect vulnerable populations from the harmful effects of widely marketed new drugs. Contergan had been extensively marketed to physicians and consumers alike, and its premarket testing and postmarket promotion had emphasized its remarkably *nontoxic* safety profile by available standards of clinical pharmacology [5,6]. As Lenz's work was read internationally, his careful use of the correlative techniques of infectious disease epidemiology within the terrain of prescription drug use documented not only the unseen dangers of newly marketed drugs but also the need for a new discipline of pharmaceutical epidemiology to scour observational data for therapeutic effects and adverse reactions that could clearly be associated with drug use in clinical practice [7,8].

The recognition that the risks of new drugs could be better understood when they were consumed by broad numbers of patients had been evident long before Lenz's epidemiology of thalidomide-associated phocomelia. Indeed, the history of federal drug regulation in the United States can be recounted as a succession of measures taken in response to dangers of drugs that became apparent after widespread consumption by the general public [9–11]. However, until the 1960s the Food and Drug Administration (FDA) had very limited authority in the postmarket regulation of drugs. The agency had neither direct means to control physician prescriptions nor resources to gather data on prescribing of newly marketed drugs. While the Committee on Pharmacy and Chemistry of the American Medical Association (AMA) nominally maintained more influence in both arenas, it depended entirely upon voluntary physician reports, and Committee members complained loudly that the system itself was doomed to failure; as one report noted, "physicians reported only a small fraction of all cases and the total number of patients receiving a drug was unknown" [12].

The 1962 Kefauver–Harris Amendments, passed largely on the strength of popular moral outrage over thalidomide, demanded that pharmaceutical manufacturers establish records and make reports to the FDA of "data relating to clinical experience and other data or information, received or otherwise obtained" [13] for all new drugs. By 1967, the agency had developed a protocol requiring manufacturers to seek and report any reported or published case reports related to putative side effects of their products. Any novel or unexpected adverse effect was to be reported to the agency within 15 days; other information "pertinent to the safety or effectiveness of the drug" was to be reported quarterly for the first year after approval, twice in the second year, and annually thereafter. Yet this kind of information could become actionable only after years of case reports, and then only if one of the relatively few FDA staffers took an active interest in pursuit of a specific question of drug harm.

The hospital became the center of early programs of pharmacoepidemiologic surveillance. By 1964, the FDA and AMA had built a surveillance program involving more than 600 hospitals, which became the focus of early pharmacoepidemiologic research by Johns Hopkins University's Leighton Cluff, Harvard University's Thomas

Chalmers, and Tufts University's Hershel Jick [14–18]. Yet the data were still only as good as the reporting physicians' records [19]. As Leighton Cluff noted, an early validation system of reporting efforts at the Johns Hopkins Hospital "proved completely unsatisfactory for detecting drug reactions …during recent daily intensive surveillance of one hospital service, four times as many reactions were detected than had been reported on the cards from the entire hospital" [19]. Would-be epidemiologists of adverse drug effects needed a way to circumvent the physician as reporting device and the digitization of data provided an appealing solution. Cluff's attempts at computerized drug monitoring involved the creation of three linked datasets for every drug received by every patient in a dedicated hospital ward [20]. D.J. Finney, another early theorist of computerized drug monitoring, expressed these data sets as a linked "P-D-E system," in which P(atient) population data would be systematically gathered within a set geographic or hospital catchment area, the D(rug) data would include records of all relevant prescriptions, and E(vent) collection would record all untoward reactions potentially attributable to the drugs prescribed [20].

Proponents of drug monitoring imagined a linked system of inpatient surveillance wards circling the globe, which could act as pharmacovigilance sensors, detecting early signals of possible drug harms and providing descriptive data regarding their frequency, severity, and relative strength of association. Finney predicted that surveillance would change pharmacoepidemiology from a reactive into a proactive field. Allowing that "much is due to Lenz for his discovery in 1961 [that thalidomide was associated with phocomelia]," he also boasted that "a *monitor* could have signaled a warning 1½–2 years earlier" [20]. Automated inpatient surveillance systems liberated pharmacoepidemiology from the "weak link" of the reporting physician [20]. With public and private support from the United States Public Health Service and the Pharmaceutical Manufacturers Association, Dennis Slone, Hershel Jick, and Ivan Borda demonstrated the feasibility of implementing an automated hospital-based drug monitor system in 1966 [21]. Based at the Lemuel Shattuck Hospital, the Boston Collaborative Drug Surveillance Program bypassed the physician by hiring a drug surveillance nurse "whose primary role is the acquisition of accurate data" [21,22]. The Boston team became a model for an automated drug surveillance program that functioned "largely independent of clinical judgment in establishing a connection between a drug and an adverse event" [23].

Early results showed that drug-related events were both more frequent and less severe than had previously been anticipated. More than one-third of patients on the Shattuck wards experienced at least one drug-associated adverse reaction during the first year of study [24]. By 1967, the Boston group had established a numerator/denominator approach for comparing drug usage between long-term and acute hospitals through a network of five hospitals in Boston [25]. By 1968, over 2500 patients had been entered and discharged from the surveillance system, with over 26 000 monitored drug exposures, representing more than 700 individual drugs [22]. Commonly prescribed drugs, such as digoxin and heparin, could be reported in detail, yielding novel information related to their clinical pharmacology and their interactions with other drugs [26–28]. The system enabled the observation of not only obvious drug reactions (such as a rash) but also other clinical events (such as heart attacks or kidney failure) that could only be associated with drugs by careful epidemiologic surveillance.

As the Boston Collaborative Drug Surveillance Program escalated its activities and exported its methods to other sites, these new data provoked a series of drug scandals that emphasized both the utility and the limitations of

the new forms of pharmacovigilance. Clioquinol, an antiinfective that had been in use since the 1930s, was found to be associated with subacute myelooptic neuropathy in 1970, over three decades after its initial introduction. An association between the synthetic estrogen diethylstilbestrol (DES) and a rare form of cervical clear cell adenoma was reported in 1971, with evidence of a 20-year latency period between use of the drug and detection of the cancer [29]. The beta-blocker practolol became the focus of a scandal after it was associated with a potentially fatal inflammation of the skin and soft tissues (oculomucocutaneous syndrome) some five years after its broad release on the British market. These examples simultaneously elucidated the scientific and ethical necessity for drug surveillance units and underscored the impossibility of inpatient surveillance systems to capture drug–disease associations in which three decades or more might pass between drug exposure and adverse events. As Jick warned, in a systematic proposal for the theory and design of the emerging field of pharmacoepidemiology, the ability to study "drug–illness relations" required distinct methods depending on the time course and prevalence of prescription-related adverse events. High-frequency events in high-prevalence diseases could be detected swiftly by case report, low-frequency events in high-prevalence diseases required careful active ongoing surveillance, and low-frequency events in low-prevalence diseases might simply never be adequately described [23]. Many early pharmacoepidemiologic researchers viewed scientific quality and ethics as complementary: more rigorous data collection of drug-related events carried ethical benefits by enhancing medical practitioners' capacity to "do no harm" to patients. As early pharmacoepidemiologic work also coincided with the development of bioethics as a field, critical principles of informed consent, external review of research protocols, and protection of patient privacy began to influence pharmacoepidemiologic investigators' thinking in the US and internationally.

To address the growing problems of drug safety, prescription surveillance needed to extend outwards: spatially, from the monitored wards of the hospital to the messier universe of outpatient care; temporally, from links visible in days or weeks of measurable hospital time to the longer stretches of months and years required to understand the impacts of chronic medication use; and thematically, from the isolated connection of drug and disease to the study of all steps of diagnosis, prescription, adherence, consumption, and presentation that might extend in between. In the United States, this project would find its boldest form in the Joint Commission on Prescription Drug Use, formed in response to a press conference held by Senator Edward Kennedy in November 1976, at which he announced that the new science of drug utilization studies had provided irrefutable evidence that prescription drugs were ill-used in American society [30]. Kennedy called for Congress to work with the medical profession and the pharmaceutical industry to sponsor a public–private body of expertise whose explicit purpose would be to establish a postmarket surveillance system for prescription drugs [31]. As the Commission would note in its final report, the purpose of systematic prescription surveillance was "not merely to learn 'something' about a drug but to glean information that is useful in improving the rational use of drugs" [31].

Conceived as a public–private venture, the Commission ran from 1976 until 1979 and issued its final report in the first month of 1980. The Commission worked to integrate the social, epidemiological, marketing, and policy interests in prescriptions as a source of data. Initially, the prospects for a harmonization of these four perspectives seemed auspicious. At the first meeting, Howard L. Binkley, Vice President for Research and Planning of the Pharmaceutical

Manufacturers Association, provided a description and critique of presently available sources of data on trends in the prescribing and dispensing of prescription drugs, with an emphasis on how market research data could be linked to broader systems of private and public claims and outcomes data [31]. Yet as the Commission assessed its findings by 1979, it became clear that although several datasets existed, no individual dataset contained enough information to deliver sufficient granularity to allow the full assessment of drug use in outpatient practice.

The Commission began to interview hybrid data sources that illustrated new links between the public and private nature of prescriber data sets. Fledgling HMOs such as Kaiser Permanente and the Group Health Cooperative of Puget Sound developed in-house proprietary databases that linked both prescription claims and outcomes data in the same place [31]. Exploratory work by Hershel Jick following the use of the blockbuster antiulcer drug Tagamet® (cimetidine) in Puget Sound pharmacies suggested that this approach could be quite promising [32]. Another hybrid form was introduced by Noel Munson, a spokesman from Prescription Card Services (PCS), a private prescription data company that acted as a "fiscal intermediary" for public payment groups like Medicare and Medicaid and other groups that paid for prescription drugs. But these individual companies (e.g., PCS) appeared to code their data according to their own proprietary software [31]. Even within the Medicaid system, the promise of effortless data linkage remained a dream in the late 1970s, complicated by wide state-by-state discrepancies in patterns of coding, storing, and retrieving prescription data [31].

If the 1980 publication of the Joint Commission report represented a high point of collaboration between market researchers, epidemiologists, policy reformers, and sociologists in imagining an early "big data" universe for therapeutic surveillance, it also represented a dream of collaborative work that would soon dissipate. Like many other grand designs for federally sponsored health programs conceived in the later 1970s and proposed in the early 1980s, its speculative structures would never materialize, its measures would be left unfunded, and subsequent calls for a center for postmarketing surveillance would be repeated, and unfunded, every few years for several decades. Only in the past decade, with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), would a substantial US public investment be made in the construction of a linked public prescription database for pharmacoepidemiologic research, with the creation of the FDA's new automated pharmacovigilance program, the Sentinel Initiative, which officially launched in 2016 (see Chapter 25).

European Pharmacoepidemiologic Trends and Ethics

In Europe, several nations with centralized national health systems like England and Sweden created prescription surveillance systems by the second half of the 20th century. Scandinavian countries in particular had long histories of centrally organized pharmacy records and more tightly controlled national formularies of allowable drugs [33]. Moreover, the World Health Organization had set up a regional European Drug Utilization Group in Oslo which held a prominent conference on the overprescribing of prescription drugs in 1969 [34] and then proceeded to develop methods of comparing utilization across drug classes and across national pharmacy standards [35]. Ironically, even in countries such as Sweden, much of the prescription data came from the private sector [33,36,37]. Still, pharmacoepidemiologic research in Europe continued to receive substantial public support throughout the 1970s, 1980s, and 1990s.

The founding of the European Medicines Agency (EMA) in 1995 was a crucial step toward a pan-European supervision of medicines. The

decentralized agency is critical to the European Medicines Regulatory Network (EMRN), partnering with the European Commission (EC) and national authorities of European Economic Area (EEA) member states (the Heads of Medicines Agencies [HMA] network). The EMRN's main objective is to achieve a consistent approach to medicines regulation across the EU. In collaboration with network partners, the EMA oversees the scientific evaluation, safety and efficacy monitoring of human (and veterinary) medicines in the EU. For most innovative medicines, including those for rare diseases, a central assessment and marketing authorization coordinated by the EMA is compulsory. In cases of human medicines, the EMA's Committee for Medicinal Products for Human Use (CHMP) carries out a scientific assessment, based on which the EC decides whether to grant marketing authorization. Once granted, such a centralized marketing authorization is valid across the EU. Predominantly, though, medicines in the EU are authorized by member states' national authorities.

Shared, key ethical requirements in European pharmacoepidemiologic research came to include beneficence, transparency, scientific independence, and integrity. Yet, inconsistent application and authorization procedures for clinical studies in European Union (EU) and European Economic Area (EEA) member states have long been criticized. This also applies to pharmacoepidemiology and pharmacovigilance. Especially for multinational, noninterventional studies (NIS), it has been lamented that "… a patchwork of regulations and codes of conduct have to be followed" [38].

Partly in response to some of these issues, since the early 2000s new EU regulations, directives, and guidelines have been introduced. These aim to facilitate ethical, effective pharmacoepidemiologic practices in and across different member states. Currently, crucial regulatory changes are under way that will affect pharmacoepidemiology and pharmacovigilance in the EU.

The EU pharmacovigilance legislation aims to minimize risks and harms posed by adverse drug reactions (ADRs). Its implementation is overseen by the EMA, EU member state authorities, and the European Commission (EC). Key legal documents for the pharmacovigilance legislation and pharmacoepidemiologic studies are EU Regulation No 1235/2010 and Directive 2010/84/EC [39]. In effect, the regulation outlines measures for safeguarding patients' safety and rights and asserts the crucial role of healthcare professionals in reporting ADRs. It moreover acknowledges the necessity to develop EU/EEA-wide "… harmonized guiding principles for, and regulatory supervision of, postauthorization safety studies that are requested by competent authorities and that are noninterventional, that are initiated, managed or financed by the marketing authorization holder" [39]. Among other deliverables, the regulation established the EudraVigilance database as a main platform for the obligatory reporting of ADRs by marketing authorization holders and respective national authorities.

In response to the benfluorex scandal, the legislation was amended in 2012. Servier Pharmaceuticals' Mediator® (benfluorex), marketed as an add-on for diabetes and hyperlipidemia, was under pharmacovigilance investigation in France since 1998. It was found that the drug caused cardiovascular complications in 2003. In response, Servier did not reapply for marketing authorization in Spain and Italy, effectively withdrawing the product from the market in those countries. However, benfluorex continued to be available and approved for diabetes treatment in France and other countries until 2009, when its authorization was fully revoked; its efficacy was found to be limited and it risked causing cardiac valvulopathy [40]. Subsequently, EU Regulation No 1027/2012 and Directive 2012/26/EC were published, amending the 2010 EU pharmacovigilance legislation. The amendments especially addressed the issue that safety measures for medicinal products

need to be implemented consistently and in a timely fashion in all member states where respective products were authorized.

The benfluorex scandal points to broader challenges regarding pharmacovigilance and pharmacoepidemiologic research in the EU: regulations and guidelines need to be applied across multiple states and to different actors, including national marketing authorization holders and applicants. While the legislation outlines fairly broad objectives, responsibilities, and issues, these are specified in concrete deliverables. One of these deliverables was the founding of the EMA Pharmacovigilance Risk Assessment Committee (PRAC) which monitors and assesses drug safety in the EU. Moreover, it initiated the development of the EMA's Good Pharmacovigilance Practices (GVP) guideline (described later in this chapter).

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established in 2006 and is coordinated by the EMA. It is an expertise and resource network focused on pharmacoepidemiology and pharmacovigilance in Europe. It consists of partners that are public and not-for-profit organizations, including research and pharmacovigilance centers, university hospitals, healthcare database hosts, and electronic registry sponsors. For-profit organizations, such as contract research institutions, may only participate if they conduct pharmacoepidemiologic and/or pharmacovigilance studies commissioned by third parties. While pharmaceutical companies are not eligible for becoming ENCePP partners, the network provides relevant resources and allows for these companies to be involved in public document reviews.

The ENCePP offers crucial guideline documents for pharmacoepidemiology and pharmacovigilance: a Code of Conduct; the ENCePP Checklist for Study Protocols; and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology. The Code lays down rules and principles aimed at ensuring transparency and scientific independence. While adherence to the Code is voluntary, it is required to receive the ENCePP Seal. Conditions for receiving the Seal are, among others, that a study is entered in the EU PAS Register and that it is of scientific and public health relevance, rather than mainly pursuing results which may promote certain medicinal products. The Checklist is meant to ensure that studies adhere to epidemiological principles, while also considering methodological transparency and the need for public outreach.

East Asian Pharmacoepidemiologic Trends and Ethics

East Asia has made major contributions as the field of pharmacoepidemiology has grown, producing a very robust body of pharmacoepidemiologic research that has expanded in recent decades. Researchers in South Korea, Japan, and Taiwan have linked into comprehensive data systems on insurance claims created through universal insurance coverage of these entire national populations. To help protect patient privacy, these databases have been made available for drug safety research only to researchers in nonprofit organizations who must apply and undergo ethical review [41].

The Korea Food and Drug Administration (KFDA) launched an adverse drug reaction (ADR) reporting system in 1988, although the reporting rate was initially very low. In 2004, the KFDA mandated that pharmacists and pharmaceutical companies report adverse drug reactions. The KFDA also established regional pharmacovigilance centers in university hospitals that now provide nearly complete coverage of the country. The KFDA funded a pharmacovigilance research network (PVNet) among these centers, and researchers in the network use their data for studying adverse events. The Korean national health insurance database also contains all information on insurance claims

made and prescriptions for approximately 50 million Koreans, and this has been used for pharmacovigilance [41].

In Japan, drug manufacturers are required to report adverse drug reactions to the Pharmaceuticals and Medical Devices Agency (PMDA). A partial adverse drug reaction dataset is available to researchers through the PMDA website. Healthcare professionals report adverse drug events to the Ministry of Health, Labor and Welfare. Japan made its national insurance claims database available for drug safety researchers in 2011. The database covers the entire population of 128 million and includes basic patient characteristics, drug prescription and dispensing, medical procedures, hospital admission, and annual health check data (for some patients) [41]. To protect patient privacy, Japan's national database is usually not available for purchase and may only be shared in some cooperative research projects [42]. The Japanese government has also created the Medical Information for Risk Assessment Initiative (MIHARI) to access data from different sources and create a central database with a common data format [43].

Taiwan requires mandatory reporting of serious adverse reactions by medical institutions, pharmacies, and drug and device companies, as well as obligatory safety reports for newly marketed drugs over a five-year surveillance period. In Taiwan, the National Adverse Drug Reactions Reporting System has been the primary source for postmarketing surveillance of adverse drug events. Taiwan's single-payer National Health Insurance (NHI) program was created in 1995 and covers more than 99% of the population. The NHI Research Database is thus a highly comprehensive dataset including basic patient data, care record and expenditure claims, and pharmaceutical reimbursements. There are also subject datasets available to researchers on topics such as traditional Chinese medicine, cancer, diabetes, dental, catastrophic illness, and psychiatric care. Patients and medical facilities are deidentified for pharmacoepidemiologic research use of the NHI Research Database [41]. To protect patient privacy, researchers using Taiwan's NHI Research Database also receive data for 10% or less of the population. Ethical policies for data privacy stipulate that no individual-level data can be shared with researchers from other countries [42].

China and other East Asian countries also have been creating national healthcare claims databases [44]. In China, the Shanghai Center for Adverse Drug Reaction Monitoring has operated a drug surveillance and evaluation system since 2001 that works with patient information from 10 Shanghai hospitals [43]. The Asian Pharmacoepidemiology Network (AsPEN) was recently established as a multinational research network for pharmacoepidemiological research that promotes international communication among academia, government, industry, and consumers. The network functions to promptly identify drug safety issues [44].

Pharmacoepidemiology ethics in East Asia are similar in many ways to those of Western countries, including features such as institutional ethical review and guiding principles such as beneficence, justice, autonomy, and data privacy. However, experts on East Asian bioethics also have recognized some distinctions. For example, scholars have contended that much East Asian bioethical thinking reflects value systems that emphasize the family and public interest ahead of the individual rights of the liberal subject that characterize much of Western bioethics. The family is often depicted as responsible for taking care of members who become sick, and medical decision making has often been family based. Some also have noted a plurality of ethical perspectives within East Asia, contending that a simple Eastern and Western bioethical dichotomy of communitarian versus individualistic values would be overly simplistic. Others have viewed bioethics as a Western entity, promoting the development of

Asian bioethics based more on the traditions, philosophies, religions, and perspectives of the region's cultures [45]. Future policies should consider these issues as core principles for pharmacoepidemiologic research ethics are discussed.

Methodologic Problems to be Solved by Pharmacoepidemiologic Research

More work remains to establish international ethical policy harmonization while also promoting practices that support cultural variation in ethical values. Yet, as pharmacoepidemiological practices developed in different national contexts that have been incorporated into increasingly globalized flows of pharmaceuticals and pharmaceutical-related information, a number of ethical principles and practices have been adopted widely across international settings in efforts to establish consistent pharmacoepidemiologic methodology.

The expansion of the field of pharmacoepidemiology has coincided with the establishment and institutionalization of the discipline of bioethics. Numerous critical ethical concepts took hold early in pharmacoepidemiology and have remained significant over time. For example, privacy of medical data is a historically consistent value guiding the ethics of global pharmacoepidemiologic research. Pharmacoepidemiologic research protocols and/or database designs also often have been subjected to review by institutional review boards as external review has become increasingly widespread for biomedical research since the second half of the 20th century, although there is variation in the nature of this review. For example, some pharmacoepidemiologic research has been reviewed by institutional or national ethics boards, as well as by privacy boards [46]. Some countries also do not require ethical review for deidentified datasets [47].

Informed Consent

Informed consent became increasingly valued as a critical standard of international research ethics following its establishment as a cornerstone of the 1964 Declaration of Helsinki, a ground-breaking statement of international human experimentation ethics [48]. However, the role of informed consent has been perceived differently in interventional versus noninterventional research studies. Many ethicists of international human subject research have argued that since pharmacoepidemiologic research involves relatively low risks to participants, patient consent is necessary only for studies that involve contact with patients/research subjects, such as for direct intervention or prospective gathering of information. There has been a broad acceptance among ethicists allowing researcher access to identifiable medical records for pharmacoepidemiologic research without explicit individual subject authorization [46]. Research has also found that public opinion has echoed the views of professional ethicists that pharmacoepidemiologists should be permitted to use identifiable patient records, without patient consent, to study drug safety as long as existing ethical guidelines and relevant laws are followed [49].

A number of nations, however, require explicit informed consent from each study participant, and there are also international variations in requirements for electronic consent versus hard copy written consent. Ethical regulatory disharmony causes differences in study conduct between countries and increases the cost of assembling multinational data. This poses challenges for conducting large international studies capable of detecting rare events. Additionally, requirements of explicit individual informed consent are problematic in that they can corrupt data by preventing a postmarketing pharmacoepidemiologic study from detecting fatal or serious events since people who have died are unable to provide informed consent [47].

Thus, it is unsurprising that ethicists weighing risks and benefits have tended to contend that individual consent is not essential for use of patient records in pharmacoepidemiologic research.

However, over time it has become normative that pharmacoepidemiologists also must meet certain requirements when conducting research in which participant consent is waived. These requirements often include that the use of protected health information involves no more than minimal risk to patients, the research could not be effectively conducted without access to the protected health information and/or the waiver of individual consent, the privacy risks to individuals are reasonable in relation to any value to the individuals of the knowledge expected to result from the study, there is a sound plan to protect patients from improper use or disclosure of their information, there is a plan to destroy identifiers at the earliest opportunity consistent with the research, and the data will not be shared with external parties to the research [46].

Recent attention has been given to waiver of patient informed consent to use data on substances of abuse or drugs that carry social stigma. Patient privacy is essential in these areas of research; however, requiring informed consent for each patient or allowing retraction of sensitive drug information from patient records leads to partial datasets that impede the ability of researchers to study the impact of these substances on patient health outcomes. The negative consequences of failing to collect sound pharmacoepidemiologic data on the health effects of these substances are likely worse than the relatively minimal risk associated with waiver of patient consent. However, in such circumstances, the highest precautions should be taken to protect patient privacy, such as deidentifying data through secure codes or potentially having extra ethics training requirements for all researchers using data on stigmatized or abused substances. (See Chapter 28 for further discussion of pharmacoepidemiology research on drugs of abuse.)

Ethics of Surveillance

Surveillance has long provoked public concern regarding privacy, confidentiality, and autonomy. This is relevant to postmarketing surveillance, since health information is seen as highly sensitive and personal. Thus, pharmacoepidemiologic researchers need to balance possible risks to a larger population against the harms concerning individuals, such as a possible infringement of privacy. While privacy is highly important to the ethics of pharmacoepidemiologic research, privacy is not an absolute value, nor does it seem to have been perceived as such in public health surveillance history. Rather, privacy is one of multiple values that are balanced in public health surveillance [50]. It has been argued that ensuring privacy is part of the broader value of protecting autonomy. Yet other key principles to be balanced in pharmacoepidemiologic research include beneficence to promote research that adds to the existing knowledge base of medicine to improve patient health and prevent mortality; nonmaleficence, or the prevention of patient harm; and justice, which manifests as the fair distribution of research burdens and benefits among people [51].

Risks of surveillance can be minimized through confidentiality and data anonymization. Such strategies are ethically imperative, since they safeguard individuals' rights, privacy, autonomy, and dignity. Applying the highest ethical standards and communicating with the public about potential criticism are also important for a positive public perception of pharmacoepidemiology.

While there have been some disagreements, international ethics policies have developed some common stances toward ethical review of drug surveillance. Certain pharmacoepidemiologic research tends to qualify as exempt from ethics board review or qualifies for expedited review by an ethics board chair or a designated member. For studies in which it is not possible for investigators to identify individual patients, ethics board review is often not required. For example, the US 45 Code of Federal Regulations 46.101

exempts from institutional review "research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects" [52]. In many countries, research is also often eligible for expedited review if it poses no more than minimal risk to patients and involves a retrospective analysis of existing records. Still, ethics review policies vary internationally and by institutional practice, depending *inter alia* on respective national/state regulations, posing challenges for global collaborative studies [53]. This may lead to inconsistent risk–benefit assessments and variations in balancing subjects' protection (e.g., regarding safety and privacy) against public health interests.

The European Medicines Agency's guideline on Good Pharmacovigilance Practices (GVP) provides a useful differentiation between "active surveillance" and "passive surveillance." Active surveillance is defined as a continuous, systematic process of monitoring adverse events in a population. For example, a risk management system may be put in place which allows for the active surveillance of patients receiving a medicinal product. Another active surveillance option would be the monitoring of laboratory reports to detect adverse events. Active surveillance may be part of interventional or noninterventional studies (NIS). Passive surveillance, based on patients' spontaneous reporting, for example, is commonly seen as less effective, because it runs the risk of delivering less comprehensive data [54].

Ethical Benefits of Pharmacoepidemiologic Research for Data Integrity

From a broader ethical perspective, it is increasingly clear that the expansion of pharmacoepidemiological research can provide added benefits to drug research by detecting groups at risk for adverse events. Thus, the field can play an important role in reducing drug safety data inequalities. For example, expanding drug outcomes data for groups such as minorities or small/rare genetic subpopulations who may have treatment outcome variations that can only be identified and/or adequately quantified and measured through large postmarketing pharmacoepidemiologic studies may provide substantial benefits for members of these populations. There are also limited data on the efficacy and safety of drugs in children due to the fact that historically, children have often not been included in randomized controlled trials (RCTs). Pharmacoepidemiologic research helps to fill these research gaps [55]. However, it would be ethically problematic for pharmacoepidemiology to be relied on solely to provide missing data on children, minorities, or other subgroups in lieu of RCTs, particularly in cases when RCTs could produce more robust data.

Further, pharmacoepidemiologic studies are usually conducted after drug approval, and there is high variability in the frequency and design of postmarketing pharmacoepidemiologic research [56]. Such studies are not necessarily required, and so are not a consistently reliable source of information on drug outcomes among diverse demographic groups. Clinical trials are usually required for drug approval and are thus a mechanism for ensuring broader implementation of policies requiring the inclusion of diverse research subjects [48]. Ultimately, consistent with recurring concerns over ethical practices in pharmacoepidemiologic research in general, ethicists have noted that pharmacoepidemiology related to subpopulations would benefit from a more explicit legal ethical framework, particularly to clarify ethical requirements for data sharing [57].

Problems of Conflicts of Interest for Drug Industry Research

Academia–industry collaborations have become a critical area of concern for the ethics of pharmacoepidemiologic research, particularly in

recent decades as pharmaceutical profits have soared and the stakes have been raised for the outcomes of research on drug safety and efficacy. There is an inherent conflict of interest in research that is funded by drug companies to assess their own products. Academic settings in which researcher success and advancement depend on obtaining external funding also can exacerbate the ethical problems resulting from direct relationships between drug companies and the pharmacoepidemiologists evaluating their products. Investigators in such environments are under professional pressure to secure funding, and in a climate of heightened competition for public funding sources, an academician who establishes a positive working relationship with a pharmaceutical research sponsor may increase his/her chances of obtaining future funding from that sponsor.

This creates an incentive, whether subconscious or acknowledged, for researchers to conduct studies that sponsoring drug companies will find favorable. Indeed, studies have shown a trend toward more favorable efficacy results and conclusions for industry-sponsored drug research than research sponsored by other sources, finding a bias in industry-funded research that cannot be otherwise explained by standard assessments of risk of bias [58,59]. There are a number of feasible solutions to address the ethical conflicts of interest in industry-funded research.

Currently Available Solutions

Good Pharmacoepidemiology and Pharmacovigilance Practices

The International Society for Pharmacoepidemiology (ISPE) has created Guidelines for Good Pharmacoepidemiology Practice (GPP), which provide a model for key pharmacoepidemiologic research ethics policies. The guidelines recommend that researchers include a description of quality control procedures; plans for protecting human subjects; confidentiality provisions; ethical conditions under which a study would terminate; the use of Data Safety Monitoring Boards where appropriate; institutional review board and informed consent considerations in accordance with local laws; research study registration; and plans for disseminating study results [60]. However, ISPE GPP policies are nonbinding and therefore do not resolve concerns regarding national variations in ethical oversight and requirements by regulatory agencies for postmarketing pharmacoepidemiologic work [47].

European Union policies provide a useful example of transnational efforts at regulatory standardization of good pharmacovigilance practices. EU documents concerning biomedical research in general and pharmacoepidemiologic research commonly speak of two types of clinical studies, broadly speaking: interventional, that is, experimental, and noninterventional, sometimes called observational research. On the one hand, pharmacoepidemiologic research relies on noninterventional study designs such as case–control or cohort studies. On the other hand, interventional RCTs are an important element of postmarketing pharmacoepidemiology studies (see Chapter 32).

The EMA defines Good Pharmacovigilance Practices (GVP) as "a set of measures drawn up to facilitate the performance of the safety monitoring of medicines in the European Union" [54]. It includes chapters on pharmacovigilance processes as well as product- and population-specific considerations. For EU pharmacoepidemiologic postauthorization safety studies (PASS), module VIII is particularly relevant. PASS may be interventional or noninterventional. Although the module touches upon interventional studies too, emphasis is put on noninterventional PASS.

In accordance with the EU pharmacovigilance legislation, the GVP stipulates that the EMA needs to ensure that protocols and abstracts of PASS results are published. While the primary/

lead investigator is responsible for the information provided, the registration may be made by, for example, research center staff or representatives of pharmaceutical companies funding a study. Where possible, this should be done before the study commences. Practically, registration and publication are processed through the EU postauthorization study (PAS) register, hosted by the ENCePP [61]. As the ethics review procedure and requirements for respective committees depend on national legislation, information on individual application procedures is not included in the GVP. While there is no EU regulation or directive for NIS, interventional studies are covered in the Clinical Trials Regulation.

In the European Union, methodological, ethical, and legal requirements for pharmacoepidemiologic research hinge significantly on whether a study is categorized as a "clinical trial" or as "noninterventional/nonexperimental." Both categories are defined as "clinical studies" aimed at discovering or confirming the (adverse) effects of medicinal products [62]. For pharmacoepidemiologic studies involving clinical trials, the introduction of the EU Clinical Trials Regulation (CTR) No 536/2014 will be decisive [63].

The CTR was adopted on 16 April 2014 and entered into force on 16 June 2014. According to the EMA, it will come into application in late 2019, starting a transition period of three years [64]. It is meant to harmonize research practices and to ensure the highest methodological and ethical standards across all EU as well as EEA EFTA member states. To what extent it will deliver on these promises is under discussion [65,66]. The regulation replaces the Clinical Trials Directive 2001/20/EC which is said to have "… failed to achieve its goal of simplifying the scientific and ethical review of clinical trials in the EU" [67].

Moreover, the ENCePP had problematized the NIS definition given in the 2001 directive. The ENCePP raised the issue that the definition was not sufficiently specific and created uncertainty as to what counts as NIS or RCT. Pharmacoepidemiologic prospective case–control studies – like the IPPHS investigation of primary pulmonary hypertension (PPH) occurrence in association with anorectic agents – would classify as a clinical trial according to the 2001 directive. Its ambiguous NIS definition was thus criticized for impeding the conduct of pharmacoepidemiologic studies [68].

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology (Revision 6, July 2017) lays down rules and principles for transparency and scientific independence. Chapter 9 of the Guide deals with ethical aspects of pharmacoepidemiology, focusing on patient and data protection (9.1) and scientific integrity and ethical conduct (9.2). It identifies key values based on documents such as the ADVANCE Code of Conduct for Collaborative Vaccine Studies, the GPP of the International Society for Pharmacoepidemiology, and the Good Epidemiology Practice (GEP) guidelines of the International Epidemiological Association. The Guide highlights that "principles of scientific integrity and ethical conduct are paramount in any medical research" and points out that the above-mentioned ENCePP code of conduct "… offers standards for scientific independence and transparency of research in pharmacoepidemiology and pharmacovigilance" [69]. In addition, it highlights core values, such as best science, strengthening public health, and improving transparency, as stressed by the ADVANCE Code of Conduct. It also emphasizes the need for ensuring scientific autonomy, beneficence, nonmaleficence and justice, according to the four general ethical principles defined in the GEP guidelines.

Protections Against Conflicts of Interest for Drug Industry-Sponsored Research

While industry-sponsored research creates real challenges for conflicts of interest, industry also has an interest in maintaining public trust in product integrity, as well as in compliance with

regulatory ethical and methodological requirements to obtain drug approval. Thus, there is some incentive for industry to address concerns about conflicts of interest. The Board of Directors of the International Society for Pharmacoepidemiology has published a set of principles for academia–industry collaboration that can be helpful in managing industry conflicts of interest. It includes the importance of transparent research agreements, open and complete disclosure of conflicts of interest, registration of research protocols in public sites such as the ENCePP registry or ClinicalTrials.gov, compliance with local laws, clarity on confidentiality of proprietary information while also ensuring reporting of all relevant and important information to regulators, the potential value of having a steering committee and/or an independent advisory committee to the research, and an obligation to disseminate and publish research findings of potential scientific or public health importance irrespective of results [70].

While all these principles are helpful in managing financial conflicts of interest, they do not eliminate the inherent problem of drug companies having a stake in the outcomes of research that they sponsor or the ethical concerns associated with the power dynamics of industry directly funding investigators as described above. To eliminate these underlying ethical problems, the direct relationships in which companies fund individual investigators to assess specific products would need to be severed. Alternative models that eliminate these ethical conflicts can be easily envisaged. For example, the British Drug Safety Research Unit (DSRU), an independent charity supported by the National Health Service, conducts publicly funded pharmacoepidemiologic research [43]. Still, the organization conducts a large amount of research funded by unconditional donations from pharmaceutical companies. However, the companies have no control on the conduct or the publication of studies conducted by the DSRU [71] which helps to mitigate the pressure of inherent conflicts of interest in industry-funded research.

Given that industry funding may lead to biased study results, a comprehensive solution could build from the DSRU model, for example by requiring sponsors of new drugs to contribute an unconditional fee to drug regulators that would fund pharmacoepidemiologic research. By making such contributions mandatory rather than voluntary, investigators could conduct studies without concern as to whether results may influence future industry donation decisions. In the US, for example, the expansion of the FDA's Prescription Drug User Fee could easily establish a fund for pharmacoepidemiologic research.

The Future

The ethical conduct of pharmacoepidemiologic studies is of crucial importance for subjects' safety, health, and wellbeing. Moreover, it is decisive for the public perception of pharmacoepidemiology. Research in this field is rooted in the moral obligation to preempt or at least minimize medicine-related harms and health hazards. Implementing highest ethical standards helps to avoid potential damage to the public image of the field and public trust in claims of pharmacoepidemiological research as a disinterested form of expert knowledge. Such damage may be related to research practices compromised by economic interests or misconduct of the pharmaceutical industry. Thus, scientific integrity, independence, and transparency will continue to be crucial for the ethics of pharmacoepidemiologic research.

Even in the recent past, regulatory amendments relevant to pharmacoepidemiology and pharmacovigilance were often triggered by scandals, although a dream to make pharmacoepidemiology a proactive rather than a reactive field can be traced back to the 1960s if not earlier. Adjusted, new, and emerging regulations and guidelines aim at promoting ethical

pharmacoepidemiologic research that effectively identifies and reports ADRs, thus allowing for timely responses. New policies must also be more thoroughly transnational and attentive to global variations in ethical beliefs. A main challenge is and will continue to be to translate inevitably general documents into practical instructions and relevant local practices.

In the future, national regulatory authorities, universities, and research centers will continue working to align requirements towards coherent pharmacoepidemiologic research ethics. It is to be expected that further regulatory efforts will be invested in streamlining requirements for ethics review boards and ethical guidelines for noninterventional studies, especially across the EU. Although recent regulations and directives in the EU hope to address several pressing issues, many of these are complicated anew by the UK's announced withdrawal from the EU. This has already triggered practical changes, such as the relocation of the European Medicines Agency from London to Amsterdam in March 2019. Moreover, legal uncertainties are increasing [72], as it has been disclosed by the UK Department for Exiting the European Union that the post-Brexit guidelines for clinical studies in the UK may deviate from EU legislation [73].

Transparency has been stressed as a key element for ensuring ethical pharmacoepidemiologic practices. Moreover, data sharing is pivotal for effective pharmacoepidemiology and pharmacovigilance. At the same time, researchers are required to safeguard subjects' privacy and dignity. Developments such as the open data movement on the one hand and regulations aimed at protecting individuals' privacy on the other hand put researchers in a difficult position. At an increasing rate, there is a tendency to require public accessibility of scientific results and even data. Simultaneously, privacy concerns and potential regulations may pose challenges for data (re-)use in pharmacoepidemiologic studies [74].

Heightened attention has already been paid to the environmental, polluting effects of pharmaceutical residues. Regulatory documents, such as the EU pharmacovigilance legislation, acknowledge that "the pollution of waters and soils with pharmaceutical residues is an emerging environmental problem" [39]. Research examining the adverse effects of pharmaceuticals on the environment has been labeled *pharmacoenvironmentology*. With its focus on the environmental impact of drugs given at therapeutic doses, it is considered part of pharmacovigilance [75]. Assuming that environmental issues will continue to be high on the political and scientific agendas, pharmacoepidemiologic expertise will be increasingly needed to assess medicines as pollutants. In this context, pharmacoepidemiologists will need to employ and expand their methodological repertoire for studies investigating medicines' adverse effects on the environment. This development might also imply an amplified need for novel, interdisciplinary research collaboration involving pharmacoepidemiologists.

Such collaboration is also characteristic for another emerging intersection, between pharmacoepidemiology, computer, and data science. Research at the intersection of digital services, big data, and public health is a potentially promising but precarious field. It has been demonstrated that emerging digital data sources like social networking sites can function as complementary resources for pharmacoepidemiology. The use of such data sources, often referred to as a type of big data, is atypical for pharmacoepidemiologic studies but may become more common in the future. Research drawing on big data may take place outside medical departments or hospitals, for example being conducted by data scientists. Big data and emerging data science approaches have created new possibilities for pharmacoepidemiologic research. For example, Freifeld *et al*. used data from the social networking site and microblogging service Twitter to monitor ADRs [76].

The term *big data* has become associated with various leaks and scandals. The UK Science and Technology Committee concluded in a 2015 report that data misuses and leaks have led to public skepticism concerning the use of big data [77]. Not only such negative connotations, but also scientific concerns regarding users' consent, autonomy, and privacy raise ethical questions about big data research. Pharmacoepidemiologic research involving big data requires careful ethical considerations for the individuals generating such data, for example users of social networking sites. Moreover, pharmacoepidemiologists need to consider the biases inherent to digital data sources: such bias can be caused by big data retrieved from populations that do not allow for generalizations. For instance, since individuals included in a digital data sample may represent only those using an expensive/innovative technical device or service, these users could be on average younger or above average in access to health-promoting resources [78]. In addition, the quality of such data may differ from other sources of data (e.g., medical records).

Research involving these alternative sources of data is subject to different laws and regulatory frameworks when conducted in different global settings. For the US, access to health-relevant information via social networking sites such as Facebook is at present legally possible, due to the lack of protection for health-relevant data retrieved outside the traditional healthcare and research system. With regard to medical privacy, the Electronic Frontier Foundation (EFF) points out that social networking sites and other online services compromise US citizens' control over their health data:

> The baseline law for health information is the Health Insurance Portability and Accountability Act (HIPAA). HIPAA offers some rights to patients, but it is severely limited because it only applies to an entity if it is what the law considers to be either a "covered entity" – namely: a health care provider, health plan, or health care clearinghouse – or a relevant business associate (BA). [79]

This also implies that content such as Facebook or Twitter data, despite their actual use as health indicators, are currently not protected under the HIPAA. Yet, although arguably unlikely, this may change in the future. In addition, scientists should not conflate legal with ethical requirements.

With regard to biomedical research, it has been pointed out that the ethical implications of big data research are, at least partly, uncharted territory. Additional ethical considerations for pharmacoepidemiologic research involving big data are thus needed. This applies to the autonomy of data subjects but also to new corporate stakeholders and public–private partnerships. The latter may not merely involve pharmaceutical companies or device manufacturers. Internet and technology corporations may also play a role and require ethical as well as legal oversight, since they control access to digital data that could further complement pharmacoepidemiology in the future.

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