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**Full Disclosure of the “Raw Data” of Research on Humans:
Citizens’ Rights, Product Manufacturer’s Obligations and the
Quality of the Scientific Database**

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Abstract

More work needs to be done across academic boundaries in the area of rights of study volunteers, consumers, and patients related to full and open disclosure of risk information related to medical products and the obligations of product manufacturers to provide this information about their medical products.

While emphasizing risk disclosure to patients in the patient-physician relationship through the concepts of consent and informed consent, society protects the product manufacturer in many ways from its obligations of full and open disclosure of risks related to its medical products. Here, for example, product manufacturers may insist that the academic research and medical institutions and their scientific investigators—involved in securing the study volunteers for study and obligated to carefully monitor all study volunteers during study participation—not disclose new risk information to the public about new drugs being tested on human research volunteers without full permission of the product manufacturer. Here, the product manufacturer assumes it has the legal right to restrict investigators’ and medical institutions’ disclosure of the risks—that these parties see occurring in the study participants who are under their care—through non-disclosure contracts.

This paper reviews the origins of study volunteer, consumer, and patient rights related to risk disclosure and the obligations of product manufacturers related to disclosures related to their medical products. Here, the citizen is the

subject of a research study who volunteers his or her participation in order to benefit present and future generations in the development of more accurate scientific knowledge. With this voluntary participation, that same study volunteer agrees to bear the risks of death and morbidity from adverse outcomes that befall him or her during the research study and bears the often heavier burden of risks and effects of unknown mechanisms of action from studies of newly developed drugs. The citizen is not only the study volunteer, but also the consumer and patient listening for new medical products that might be helpful to extend life or at least to improve the quality of life.

But what does it mean to say that the research study participant agrees to bear risks for the goal of development of scientific knowledge and what rights guarantee that the study sponsor, the product manufacturer, fulfills the requirements of free and open disclosure which is necessary for any development of scientific knowledge? In particular, what are the rights accorded to research study volunteers, consumers, and patients for free and open disclosure of risks related to newly designed medical products when product manufacturers' attempts to bypass their obligations of disclosing risk information to the public related to the new products under study in human volunteers as such risks become known during research trials involving humans? In the United States, the Freedom of Information Act may be used to attempt to garner raw data related to scientific studies from federal regulators, but where is the open disclosure of the raw data held by product manufacturers who are the primary repositories of data related to risk information from these research trials?

Research on medical product is dependent on research study participants' willingness to donate their time and effort and willingness to bear risks of research trial participation. The testing of new products (prescription medicine and medical devices) is always unpredictable. Higher degrees of unpredictability are always associated with those products with new designs with new mechanisms of action. "Unpredictability" refers to:

- The inability to estimate the chance (probability) that an adverse outcome will materialize in a study participant upon whom a new drug with a new mechanism of action is being tested
- The range of adverse outcomes that can occur to a participant
- The levels of severity of those adverse outcomes

The tasks of clarifying and communicating levels of unpredictability of a medical product to citizens are areas in need of more work across academic boundaries. More work also needs to be done across academic boundaries about rights of consumers, patients, and study participants related to full and open disclosure of risk information about medical products to citizens (1) as study participants bearing the risks of new medical products, (2) as patients who are asked to consider these products as part of their medical treatment. In order to achieve this goal of full and open disclosure of risks, society must focus on the obligations of product manufacturers to provide this type of disclosure about their medical products. I will argue that citizens are owed these rights because they are the study participants upon whom research is conducted in medical product testing.

Courts have given citizens rights to information in medical care and medical research through the respective doctrines of consent and informed consent. Consent and informed consent are legal doctrines developed by judges. They are made by judges when no such laws are created by legislatures. Consent and informed consent continue primarily as judge-made law in the four countries of our interest, namely Great Britain, the United States, Canada, and Australia. We will focus our review of consent and informed consent in medical care and medical research. Regarding the judge-made law of consent, we will focus on the decision making of the highest courts of Great Britain and Australia. Regarding the judge-made law of *informed* consent, we will focus on the decision making of federal court decisions in the United States and on decision making by the Supreme Court of Canada.

Published Data

With consent and informed consent, the term “data” is often considered in the form of “published data”, that is, the analyzed and interpreted data as they appear in summary form in the peer-reviewed medical-scientific literature (peer-reviewed literature). Such forms include numerical tables and graphic displays of data. An example of such a graphic display of data is the survival curves used to display information about survival over a period of five-years. The five-year survival curve is used to display survival at points in time one year, two years, three years, four years, and five years after treatment. Five-year survival curves have been used in medicine to portray survival of a patient given one treatment, versus those patients given an alternative treatment. The treatments of medical conditions that are often portrayed in terms of five-year survival curve comparisons include certain more-advanced cancers, like high-grade, high-stage lung cancer, or in more-advanced forms of heart disease, like grade 4 congestive heart failure.

Raw Data

Another category of data that is needed to complete our understanding of research trials is “raw data” or “primary data”. *Raw data* (or *primary data*) are the data that are collected during a research study and that are recorded in the research study’s database. Raw data in scientific studies take on two forms depending on the study hypothesis and study design: observational data and measurement data. *Pre-intervention observational data* are data obtained by directly observing the study participant at a designated time, T-0, before a medical intervention is applied to that participant. *Post-intervention data* are data obtained by again directly observing that same study participant at a designated time, T-1, after a specified medical intervention is applied to that participant.

Raw data need to be disclosed to citizens because raw data are the data derived from human study participants that are “non-manipulated”. Not all raw data are non-manipulated. There is always the possibility that raw data are manipulated as the data are acquired from observations and measurements and placed into the scientific database. For example, certain raw data may never be included in the scientific database because these data may show a product to be much less safe and less effective than the product manufacturer and the principal investigator would like to see with the product. But for our purposes in this paper, we will assume that the raw data are in fact non-manipulated data.

If citizens and parties interested in protecting citizens’ rights are given access to raw data, then the data can be “double checked” to determine what data are present in the database. Then the data can undergo “exhaustive analyses” to make certain that all information contained in the data derived from human study participants has been extracted and analyzed. With raw data, a physician, scientist, or statistician can always return to the database to see what the initial data showed before any analysis was conducted on the data, before any interpretation was made of those analyzed data, and before any conclusions were drawn from the analyzed and interpreted data.

‘Manipulated data’ are data that are changed in a database (or eliminated from inclusion in a database) to serve ends other than medical and scientific ends. Examples of ‘manipulated data’ used for non-scientific purposes are the data and descriptions of data that appear in direct-to-consumer advertising over the broadcast airways of television (DTC-broadcast). As of this writing, only two countries, the United States and New Zealand, have approved such advertising within their borders. Advertising messages in which data (or descriptions of data) are manipulated to sell the product are a

form of messaging within society that has been tolerated within many countries and even protected by federal governments as a freedom of commercial speech. This freedom of commercial speech is not unconstrained but typically allowed within certain boundaries. However, the precise boundaries of what can be said (and what cannot be said) in relation to the science of the medical product in commercial advertising, are not straightforward. In addition, the regulations which pertain to such advertising are not uniformly applied by federal regulators. The bottom line is that the primary purpose of any DTC-broadcast advertisement is not to meet the advertising goal of honest and complete disclosure to communicate scientific ideas to the public in the best of all possible ways. Rather, the goal of advertising is to sell the product being advertised.

We will begin our examination of full disclosure to the public with a review of the history of consent and informed consent in patient care in Great Britain, the United States, Canada, and Australia. In consent and informed consent in patient care, the primary consideration of the courts has been on the “invasive medical procedure”. In research informed consent and the information obtained from research trials on human study participants, our focus will be on one class of medical products, namely prescription medicines.

Accountability of Information

Scientific information related to health and disease in humans is based on the study of research participants volunteering their time, efforts, and willingness to bear risks of research trial participation. As such, there needs to be a special accounting of scientific information obtained from study participants and accuracy in communications within society. The following questions need to be raised in this regard:

- What information is now being provided by product manufacturers to patients, providers, and the public as scientific information?
- What is now *not* being provided to citizens (as consumers and patients) as scientific information?
- What are the different types of scientific information that need to be tracked over time in this new accountability?
- Where do the barriers related to the release of scientific information for decision making lie?

- What are the forms that scientific information must take when released to be used by the public and by experts?
- How is one to develop an assessment tool to measure the extent to which various forms of scientific information can achieve a level of accuracy and a level of understandability in communications to citizens for their decision making?

The basic question to be asked in relationship to information, trust, and accountability, is the following:

Can accountability of scientific information related to medical products within society be ensured without first assuring free and open disclosure of the “raw data” of science?

In the context of answering this question, citizens may need the help of interested experts—unrelated to industry and unrelated to government regulators—to help reexamine and reinterpret the “raw data” of science for citizens. This “double-checking” is needed to provide more surety to citizens that product manufacturers and regulators have made reasonable decisions in four areas: (1) the honesty in the formation of the initial dataset obtained from research on study participants; (2) the correct and optimal selection of the statistical and other analyses performed on the raw data; (3) the interpretations given the analyzed data; and (4) the conclusions drawn from the analyzed and interpreted data.

Rights to Information

Rights to information in patient care and biomedical and behavioral research exist as two distinct set of rights, namely rights in patient care and rights in research on humans.

In *patient care*, the first set of patient rights comes into discussion *before* the medical intervention is undertaken in medical care (consent and informed consent). In patient care, the second set of rights comes into discussion *after* the medical intervention is undertaken and successes or failure are obtained by the patient in the physician-recommended and patient-agreed-to medical intervention (presence or absence of negligence in the practice of medicine).

In *research on humans*, the first set of rights comes into discussion *before* the individual signs the informed consent form to agree to participate in a research study or research trial (research informed consent). This set of rights involves information of what the research study is about. This information

about the purpose or goal of a research study includes information about (1) the scientific hypotheses to be tested, (2) the risks of the study, (3) the alternatives to research participation, (4) who will pay for injuries sustained during research participation, and the like. In research on humans, a second set of rights hold *after* the research study is completed. This latter set of rights involves a question that has not been satisfactorily answered in contemporary society:

Who is to have access to the raw data obtained from human research participation in a situation where it is the study participant volunteering his or her time, effort, and willingness to bear risks of the study? Or better, who is the primary owner of the raw data (the observations and measurements pre- and post-research intervention) that exist only through the voluntary efforts of research study participants bearing the risks of research trial participation?

The rights accorded to humans in research trials are extensions of court decision making in the judge-made laws of consent and informed consent. The judge-made law of consent can be traced to England in 1767. We will first review the rights on consent and informed consent in patient care in Great Britain, the United States, Canada, and Australia, then we will review the rights of individuals recruited into research trials testing new study drugs.

Consent and Informed Consent: Patient Care

The notion of “consent” in patient care can be traced to the 1767 British court case, *Slater v. Baker & Stapleton* (*Slater v. Baker & Stapleton*, 95 Eng. 860, 2 Wils. KB 359, 1767). In this case, physicians were called in to court to testify whether it was the custom among physicians to secure their patient’s consent before undertaking an intervention on the patient’s behalf. The physicians testified that there was such a custom among physicians, and thus the professional standard of consent was born.

The term “informed consent” in patient care entered the judicial lexicon in the 1957 California appellate case, *Salgo v. Leland Stanford Junior University Board of Trustees* (*Salgo v. Leland Stanford Junior University Board of Trustees* 154 Cal. App. 2d 560, 317 P.2d 170, 1957). But the term itself can be traced to an amicus curiae brief submitted to the court by the American College of Surgeons (Katz, 2002, p. 60). Thus, the *Salgo* court assumed that the term — “informed consent” — provided by the American College of Surgeons in its amicus curiae brief referred to a custom or practice among surgeons. However, the brief itself did not detail to any extent the concept of informed

consent as presumably used by the American College of Surgeons. The *Salgo* court then used the term “informed consent” within its own statement of its judicial opinion on the obligations of physicians to provide an informed consent to patients before embarking on a medical intervention on the patient’s behalf. That is, the court stated that the surgeons should provide an “informed consent” to their patients in the same sense as the term was used in the amicus curae brief of the American College of Surgeons.

Thus, in the *Salgo* case, neither the brief nor the written court opinion developed the concept of “informed consent” to any extent. Both simply used the term. This use of the term by the California appellate court in its written opinion allowed the term’s entry into the judicial lexicon. Once in the judicial lexicon, the term “informed consent” could then be further developed, elaborated upon, and extended by other courts using the *Salgo* case as precedent.

“Professional” Standard of Disclosure (Patient Care)

The professional standard of consent founded in the 1767 case *Slater v. Baker and Stapleton* (*Slater v. Baker & Stapleton*, 95 Eng. 860, 2 Wils. KB 359, 1767) was further developed and was held as the only judicially-derived standard in consent or informed consent in Great Britain, the United States, Canada, and Australia until 1972. Under a professional standard, a physician must disclose to a patient what a physician-in-good-standing within a community of peers would disclose to his or her patients.

The professional standard is a physician-based standard. In the court room, the jury hears testimony from physicians, and the jury bases its judgment in a case on whether the physician in question disclosed to a patient as the physician’s peers would have disclosed to their patients.

“Reasonable Person” Standard of Disclosure (Patient Care)

In 1972, a landmark U.S. federal court case, *Canterbury v. Spence*, was heard in the District of Columbia (*Canterbury v. Spence*, 464 F.2d 772, D.C. Cir., 1972). This case soon became a key point in discussions of the developing doctrines of consent in the United Kingdom and New Zealand and the developing doctrine of informed consent in Canada.

In his written opinion in *Canterbury*, Judge Spottswood Robinson examined the data of a set of U.S. judicial written opinions of cases brought to court for adjudication by patients. In each case, a patient alleged that his or her physician did not secure the patient’s informed consent before proceeding

with a medical intervention in the patient's care. In each court case, the patient sustained a severe adverse outcome that the patient alleges is related to the medical intervention. And in each case, the patient argued that had the patient been informed about the chance that such an adverse outcome was possible in the medical intervention, the patient would never have given his or her permission to undertake that intervention. In this set of court decisions, Judge Robinson noted (1) the nature of the adverse outcome and (2) its chance of occurrence. Disclosure was required in two cases: the 3% chance of death, paralysis, or other injury and the 1% chance of loss of hearing. Disclosure was *not required* in three cases: a 1/800,000 chance of aplastic anemia, a 1.5% chance of loss of eye, and a 1/250-1/500 chance of perforation of an esophagus (*Canterbury v. Spence*, 464 F.2d 772, D.C. Cir., 1972, at p. 788, footnote 86).

From this set of illustrative informed consent cases, Judge Robinson argued that in each case the physician was alleged by the patient to have failed to disclose a risk of one type: a severe adverse outcome that had a low chance (probability) of occurring. Severe adverse outcomes included death, paralysis, loss of an organ (or loss of an organ's function), among other adverse outcomes. Judge Robinson argued that the professional standard as a rule of judgment in court decision making was inadequate. Instead, Judge Robinson argued that risks in informed consent should be disclosed under a *reasonable person standard of disclosure*. Under a reasonable person standard, a physician must disclose to a patient what a reasonable person in the position of that patient would have wanted to know about the risks of the physician-recommended medical intervention. The jury would be asked to consider whether the risks disclosed to the patient by the physician were risks that a reasonable person in that patient's position would have wanted to know before accepting the physician-recommended procedure.

The highest courts of Great Britain, Canada, and Australia each addressed Judge Robinson's approach in their decision making in different ways with the following results. The British House of Lords rejected Judge Robinson's reasonable person standard and maintained a professional standard (*Sidaway v. Board of the Governors of the Bethlem Royal Hospital and the Maudsley Hospital and Others*, 1 AC 871, 1985). The Supreme Court of Canada adopted Judge Robinson's reasonable person standard in informed consent (*Reibl v. Hughes*, 2 SCR 885, 1980). The High Court of Australia adopted Judge Robinson's reasonable person standard in consent (*Rogers v. Whitaker*, 175 CLR 479, 1992).

Framework of Information in Consent and Informed Consent in Patient Care

The following framework illustrates the information content of consent and informed consent in patient care across our countries of consideration (Table 1).

Table 1.

Information Content of Consent and Informed Consent: PARQ

- Procedure (P)
- Alternatives (A)
- Risks (R)
- Questions of the patient answered by the physician (Q)

The court framework for both consent and informed consent is primarily focused on *invasive medical interventions* including surgical operations, radiation therapy, and the like. Prescription medicines that are administered by invasive routes—for example, intra-arterially, intravenously, intramuscularly, among others—may also be heard in court in consent and informed consent, primarily because of the invasive route on administration of the medicine to the patient. Cases involving prescription medicines administered by mouth can typically also be brought against both the pharmaceutical manufacturer and the physician(s) in question.

Product Manufacturers’ Attempt to Opt Out of Disclosure Obligations to Patients: The Learned Intermediary Defense

In the United States, the manufacturers of prescription medicines attempted to opt out of direct risk disclosure obligations to patients. The product manufacturers used what has been called the “learned intermediary defense” in court to defend themselves against charges that they did not inform patients of the particular risks related to their medical products (*Sterling Drug v. Cornish*, 8th Cir., 1966). Using a learned intermediary defense, pharmaceutical manufacturers argued that the product manufacturer had obligations only to disclose risks of their medical product to physicians. Then, continuing the manufacturers' argument, it was the physician who then has the primary obligation to act as the "learned intermediary" between the product manufacturer and the patient. As the learned intermediary, the physician is to decide which of the medical product’s risks are to be disclosed to the patient in informed consent.

This defense by product manufacturers was questioned by the State Supreme Court of New Jersey (*Perez v Wyeth Laboratories Inc.*, Supreme Court of New Jersey, No. A-16-98, August 9, 1999). More recently, the learned intermediary defense was rejected by the Supreme Court of Appeals of West Virginia (*Johnson & Johnson v. Karl*, 2007 WL 1888777, West Virginia, June 27, 2007). In the latter case, the Supreme Court of Appeals of West Virginia argued that manufacturers of prescription drugs are subject to the same duties to warn consumers about the risks of their products as other manufacturers.

“Subjective Patient” Standard of Disclosure (Patient Care)

The subjective standard of risk disclosure that has been argued for by ethicists Ruth Faden, Tom Beauchamp, and Nancy King (Faden, Beauchamp, and King, 1978). The subjective patient standard was explicitly rejected by Judge Robinson in *Canterbury v. Spence*. Judge Robinson argued that such a subjective patient standard—relying solely on testimony from the patient-witness—shadowed by the occurrence of the undisclosed risks and thus placed the physician in jeopardy of the patient's hindsight and bitterness post-injury occurrence. Thus, Judge Robinson argued such a subjective patient standard was not suitable for court decision making in informed consent (*Canterbury v. Spence*, 464 F.2d 772, D.C. Cir., 1972, at pp. 790-791).

The Royal College of Surgeons Establishment of a Reasonable Person Standard of Disclosure in Great Britain

Michael Powers, Queen's Counsel, argues that although physicians in the United States are changing their practice by what the law demands, in the United Kingdom, the medical profession should be given credit for the changes in clinical practice that have driven the law on consent. In 1997, Powers notes that the Royal College of Surgeons had “effectively introduced its own ‘reasonable person standard’ into medical practice by reminding surgeons that they must convey sufficient information ‘in detail required by a reasonable person in the circumstances of the patient to make a relevant and informed judgment. (Powers, 2003, p. 735).”

Let us now review how elements of consent and informed consent related to invasive medical procedures in clinical care were expanded upon when informed consent was developed in research on humans, with special attention to human research drug trials of prescription medicines.

Informed Consent: Research on Humans

Within any country, the rights of the study participant (study subject, study volunteer) are discussed in various academic circles, from philosophy to sociology and public policy and from law to economics. Yet, little work has been done in examining the rights of the study participant in relationship to the definition of *research* within governments that have the duty to protect the rights of human study volunteers. Here, ethical assertions related to the rights of the study participants are grounded in and protected by the federal laws of each country.

The “Reasonable Volunteer” Standard of Disclosure (Research)

When informed consent was applied to research on human study participants In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the Belmont Report (*The Belmont Report: Ethical Guidelines for the Protection of Human Subjects of Research*, 1978) argued that neither the professional standard nor the reasonable person standard was to be considered adequate to use in research with human study participants. This National Commission held this position because, it argued, the patient in medical care is coming to the physician for care. For this national commission, any disclosure in clinical care would always be less than that required in research on study volunteers.

In research on humans, the individual is not coming for care but rather is being recruited as a study volunteer. As a volunteer, the research participant would be giving his or her time, effort, and willingness to bear the risks of research participation without any benefit to self resulting from his or her research participation. This type of voluntarism where one enters a research trial as a participant without surety of any chance of benefit was argued by this national commission to identify human study research participation as a unique experience in need of unique protection. Under a reasonable volunteer standard, the *Belmont Report* stated that:

the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they want to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation (*Belmont Report*, 1978, p. 11).

Yet, there are additional points that need to be included under a reasonable volunteer standard that go beyond the facts that that research participation is (1) not necessary for their care and (2) not fully understood as a medical intervention. This key point involves the research participant understanding

the definition of the term "research" itself and the reasons why research is undertaken.

The Definition of Research: "Generalizable Knowledge"

If the goal of the patient coming to the physician is medical care, what is the goal of the research study participant being recruited by a scientific investigator (or by his or her designee) into a research trial? The U.S. *Code of Federal Regulations* specifies the goal of research study participation in the definition of research itself. The U.S. *Code of Federal Regulations* defines *research* as:

a systematic investigation . . . designed to develop or contribute to generalizable knowledge. (U.S. *Code of Federal Regulations* 45.46.102.d)

The U.S. *Code of Federal Regulations*, however, does not further define what is meant by the phrase "generalizable knowledge". Jaakko Hintikka has argued that an attempt at gaining knowledge once reached often stops further inquiry. In Hintikka's words, "The notion of knowledge may or may not be a discussion-stopper, but it is certainly an inquiry-stopper." (Hintikka, 2007, at p. 26). But is this the case for the goal of generalizable knowledge? Although the U.S. *Code of Federal Regulations* does not define generalizable knowledge, we will view generalizable knowledge as comprising those results from research studies and research trials on humans—completed on a set of study participants at one site (or sets of participants at multiple sites)—that are then—through careful analyses and statistical and epidemiological argument—extended to other human populations as being applicable to these non-studied human populations. These extensions to other human populations are undertaken (1) in the interests of improving patient care and (2) in the interests of the developing better medical understanding. We will now consider how a framework for generalizable knowledge is constructed in our attempt to develop a scientific database of generalizable knowledge.

The Scientific Database of Generalizable Knowledge

We will use the term the "scientific database" to refer to the repository of generalizable knowledge secured from research on humans. Since research on study participants is a global scientific enterprise, it is reasonable to ask two questions:

- Where is the repository of generalizable knowledge? That is, where is this scientific database of generalizable knowledge derived from research study participants located?

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- What are the contents of this scientific database?

If one considers that generalizable knowledge is contained in the set of all scientific papers published in the peer-reviewed scientific and medical journals, then one has the following framework for the structure of generalizable knowledge based on the general contents of a peer-reviewed scientific article (Table 2).

Table 2.

Framework for Generalizable Knowledge Based Upon the Contents of a Peer-Reviewed and Published Scientific Medical Article

- Study hypothesis
- Study design (study methods)
- Data (observational and measurement)
 - Summaries in tabular or graphical formats
- Results of statistical data analyses
- Interpretations of analyzed data
- Conclusions drawn from analyzed data

The scientific database of generalizable knowledge could be interpreted as containing that set of scientific articles as submitted to and published in the peer-reviewed scientific medical literature. But is this approach to the scientific database sufficient for what will be considered generalizable knowledge? The answer here is no, because each scientific article is a “summarized version” of the analyzed raw data. As a summarized version of analyzed raw data, each of the above elements of a scientific article is often given—within the context of that particular scientific article—a much-too-abbreviated portrayal of what the actual scientific hypothesis is, the problems encountered in implementing the research study, the problems interpreting the analyzed data, and the like.

The next question takes the following form: What would be needed to improve understanding of each peer-reviewed published article? A key part of this improved understanding includes the actual discussions of the *alternatives* to each of the components of a research study, that is, what were the other scientific hypotheses considered and rejected and how did this scientific hypothesis rise as the one to be tested? Similarly, we would need to see the discussions related to alternative study designs, alternative observations and measurements, alternative statistical analyses, alternative interpretations, and alternative conclusions to be drawn. Some of this information would be contained in the scientific protocols submitted to the institutional review boards that would be evaluating the protocol and its informed consent form for approval as a research study to be conducted within the institutions over which the IRB had decision-making authority.

The Final Missing Component of the Scientific Database: Raw Data

Although adding the above clarifying information to the scientific database would definitely improve our understanding of research study, we would still be missing one component of that scientific database. This final component is required because nothing we have so far considered would allow the essential ingredient of any scientific information platform that would allow such information to be considered generalizable knowledge. This final component is the ability to reanalyze the raw data that were obtained from the research participants in the research trial. The ability to reanalyze data by others offers the following benefits. First, reanalysis reduces conflict of interest in the choice of analyses to be conducted on the data to determine issues like statistical significance. Second, reanalysis allows an increased surety that the data—after reanalysis and reinterpretation—have been exhaustively analyzed and interpreted as much as is allowable by (1) the statistical power of the study and (2) the number of individuals selected in the study population. Third, exhaustive reanalysis allows the opportunity to extract and answer all the scientifically-important questions that can legitimately be answered by the data in the research study within the constraints of (1) protection of human study participants and (2) the original design of the study. Fourth, reanalysis offers the potential of developing new insight into a medical-scientific topic and thus a better selection of research study hypotheses that are tested in humans in future research studies. (See, for example, D'Agostino, 2004).

The essence of "generalizable knowledge" can be best captured in two descriptions. First, it is as conflict-free as humanly possible. That is, issues such as financial conflict of interest have been eliminated as a possible factor in how study data are interpreted and conclusions are drawn about a set of

raw data. Second, the original raw data have been exhaustively analyzed so the study participants' volunteered time, effort, and bearing of risks are not wasted as a human resource.

We now review recent attempts by U.S. state supreme courts to reconstruct the scientific database. These attempts by U.S. state supreme courts approach the reconstruction of the scientific database by rejecting the learned intermediary defense of product manufacturers.

Example of Court Attempts at Reconstruction: Court Rejection of the Learned Intermediary Defense

The advent of direct-to-consumer advertising in the United States has prompted two state supreme courts to argue that the “learned intermediary” defense is no longer to be considered acceptable. Both state supreme courts base their arguments in the allowances that product manufacturers have taken upon themselves in their advertising of their medical products, particularly prescription medicines, over broadcast airways of television and radio directly to consumers (*Perez v. Wyeth Laboratories, Inc.*, Supreme Court of New Jersey, 1999; *State of West Virginia ex rel. Johnson & Johnson Corp. v. Hon. Mark A Karl*, Supreme Court of Appeals of West Virginia, 2007). Today, as we noted above, only two countries have legalized direct-to-consumer advertising within their borders: the United States (Donohue, Cevasco, and Rosenthal, 2007) and New Zealand (Dens, Eagle, and De Pelsmacker, 2008).

Both the Supreme Court of New Jersey and the Supreme Court of Appeals of the State of West Virginia rejected the learned intermediary standard within their states as being made irrelevant by the approaches product manufacturers were taking to advertise their products directly to consumers and patients over broadcast airways (DTCA-broadcast). On the one hand, pharmaceutical manufacturers were denying—through their use of the learned intermediary defense—that they had direct disclosure obligations to inform consumers and patients of the risks of the prescription medicines. On the other hand, pharmaceutical manufacturers in the United States were directly advertising these same prescription medicines to consumers and patients with partial disclosures of risks in ads over broadcast (television and radio) airways. In these direct-to-consumer broadcast ads, the medical product itself was argued to be misrepresented by the manufacturer and advertiser in that the risks of product were often understated. That is, in DTCA-broadcast ads, product manufacturers were not only advertising to consumers and patients, but the manufacturer’s advertisements were misrepresenting the product being advertised to the public (Brown, 2009).

Misrepresentations in DTC-Broadcast ads and DTC-Print Ads

DTC ads can be found in two forms: (1) broadcast advertisements over television and radio and (2) print advertisements in journals, magazines, and newspapers. Misrepresentations related to advertised prescription drug can take on many forms in both broadcast and print ads.

In advertising over the broadcast airways of television, an advertisement can pitch a drug as a treatment for “weakness”, but the drug is intended to help only patients with specific types of causes of anemia. Let us consider two examples.

- A television broadcast ad pitches a drug to treat “weakness” to a general population of television viewers without further specification of the cause of the weakness that the drug may help treat should be considered a “misrepresentation” of the drug in the broadcast advertisement.

The term “weakness” without a specification of the cause of that weakness the drug has been approved to treat is misrepresenting the use of the drug to the television audience.

- A television broadcast advertisement promoting a drug used to treat erectile dysfunction as having the risks of change in vision and change in hearing in the ad should be considered an “understatement” and “misrepresentation” of the risks involved with the drug if the drug is associated with the risks of blindness and deafness.

In advertising in print medium, DTC-print ads can also take many forms. For example, Gregory Abel and colleagues reviewed DTC-print ads for bleeding disorder products in a patient-directed magazine (Abel and colleagues, 2008, p. 1680). The authors found 39 unique advertisements for 12 products. After analysis, the authors found that about twice the amount of ad text was devoted to benefits compared to risks and adverse outcomes. In addition, the researchers found that according to the Flesch Reading Ease Score (FRES), the rating of the text related to the risk and adverse outcome presentation was “more difficult to read” than the benefits section in the print ads appearing in the patient-directed magazine. When product manufacturers attempt to maintain the DTC-ads contain “information”, and not advertising, studies such as that conducted by Gregory Abel and colleagues show otherwise.

“Raw Data” and the Quality of the Research Study from Which the Study Was Obtained

In the above study of print ads, Gregory Abel and colleagues found that about two-thirds of the advertising claims they studied were considered by a majority of experts to be based on “low-quality scientific evidence”.

The question of whether the evidence derived from a research study is of high quality is a question that starts with the quality of the raw data. The question of whether raw data are of high-quality needs to be examined in two areas, namely 1) the quality of the observations and measurements of the data and (2) the quality of the study hypothesis and study design. High-quality raw data are not simply defined in reference to the data that were observed, measured, and collected. High-quality in relation to raw data is also defined and judged by (1) the scientific hypothesis that determined what data were sought out to be observed, measured, and collected and (2) the original study methods used to acquire the data.

The “Raw Data” of Science Related to Medical Products

The full and open disclosure of the “raw data” of science (and its inclusion in the scientific database of generalized knowledge) is needed at minimum to allow interested parties access to more information than is now provided by pharmaceutical manufacturers. Today, pharmaceutical manufacturers provide elements of summarized data derived from research studies in published medical journals and on Web sites open to the public in the form of tables and graphs. But what is really needed is to allow interested parties the opportunity to reanalyze the data exhaustively. This exhaustive accounting of research data is needed to provide the best data analyses, best data interpretations, and best conclusions to be drawn from analyzed data for inclusion in the scientific database. Science is not simply the conduct of a new research trial and the inclusion of elements of that research trial in the scientific database as the endproduct of research. “Confirmatory studies” also need to be carried out. Additional studies in the hands of other scientific investigators in different institution are needed to “confirm” the result of earlier studies. But in each case—original study and confirmatory study—what is needed in each case is the raw data for exhaustive analysis by independent parties.

But a real question remains: Are the raw data enough or is still more clarifying information needed for the scientific database of generalizable knowledge? Many decisions about observations and measurements are made

before the data point enters the data sheet. The underlying questions related to the decision of whether or not to include an element of data into a dataset is of the following type:

Did the research participant really develop adverse outcome, AO-1, when started on the new study drug, D, in the research trial?

Let us examine this question for the case where AO-1 is Stevens Johnson Syndrome (SJS). SJS is a non-immediate allergic reaction that can be induced by a new study drug. SJS includes a spectrum of manifestations, typically affecting the skin and mucous membranes. SJS is a systemic disorder with the potential for severe morbidity and even death. Besides being caused by a first time exposure to a new study drug, SJS is also associated with many prescription medicines already approved and on the market. In addition, SJS can be associated with infections and malignancies. Let us examine the above question in the case where AO-1 is SJS and D is a drug being tested for its abilities to control seizures in humans (a newly developed anti-seizure medication).

Our question now becomes:

Did the research participant really develop Stevens Johnson Syndrome (SJS) when started on the new study drug for seizure control?

The product manufacturer would prefer that a case of SJS not be associated with its product because it wants to advertise the product as not associated with SJS. Yet, the patient and his or her neurologist need to understand whether the new drug in question is or is not associated with SJS to see if the patient is willing to accept the risk of developing SJS when agreeing to accept the anti-seizure drug in his or her care. To answer the questions of the patient and the physician completely enough to allow a medical decision to be made on the part of the patient related to taking this anti-seizure drug, the patient and the physician need to understand the answers to the following questions related to SJS and its measurement in the research studies that were undertaken on the product:

- What were the criteria used to define a case of SJS in the research study?
- Were the definitional criteria used to characterize SJS too strict (excluding study participants who did have SJS but were excluded as cases of SJS within the research trial) or too loose

(including study participants who did not have SJS but were included as cases of SJS within the research trial)?

- Was a skin biopsy required in the criteria in the research trial before SJS was counted as occurring in a study participant? Or was a clinical diagnosis of SJS without skin biopsy used as the defining criterion of SJS? In this latter case, SJS would be included as a data point in the dataset of risks related to the new study drug without a skin biopsy ever being performed?
- If a skin biopsy was employed to attempt to diagnose SJS, two additional questions will need to be asked and answered, namely (1) what were the false-positive and false-negative rates of SJS biopsy results, and (2) how skilled was the practitioners or researchers (2.1) who performed the biopsy and (2.2) who interpreted the biopsy results?

Although we have illustrated raw data issues about SJS above, any observation or measurement in a research trial related to the identification of an adverse outcome as a risk of a prescription medicine needs to be scrutinized to a similar depth. This scrutiny is needed to assure understanding of how each of the points above related to definition of adverse outcomes, the inclusion and exclusion criteria uses in determining whether an adverse outcome is study-related, and the like were treated in the medical research study in question.

N-of-1 Trials in Patients

New drug trials on humans often do not discover the severe adverse outcome at low chance (probability) of occurrence associated with the new study drug. These severe adverse outcomes will only come to be identified after the newly approved prescription drug is prescribed in patient care. The reasons for this failure of discovery during the research trials relates to three points.

- Research on human in drug trials is typically based on drug trials studying about 6,000 participants. For example, drug studies that are done on 6,000 study participants will not necessarily identify the severe adverse outcome that will be identified in the population when the drug is approved and prescribed in patient care. Once approved, prescribed in patient care, and taken by the patient over time, a newly approved drug that had zero instance of the severe adverse outcome during its drug trials will now after use in the population be seen as

having an occurrence rate of that severe adverse outcome in 1 in 10,000 or 1 in 20,000 individuals when used by patients in their medical care.

- Most new drug trials do not study patients with multiple medical conditions and on multiple prescription medicines. Most new drug trials are conducted on healthier individuals with fewer co-morbidities so it will be easier to ascribe an adverse outcome occurring in a study participant as due to the study drug.

One motivation in developing exclusion rules in a study is to simplify the study by (1) excluding individuals who have additional diseases in addition to the disease that is being studied, and (2) excluding individuals as participants who take multiple medications. These exclusion-approaches are intended to simplify the assignment of blame to the study drug as the “cause” of an adverse outcome in a study participant. By excluding individuals with multiple diseases, one does not have to worry as much about one of the individual’s other diseases (alone or in combination with the study drug) as causing the adverse outcome in the participant in question. By excluding individuals on multiple medications for the same medical condition (or for many medical conditions), one does not have to consider one of the individual’s other drugs (or a study drug-patient drug interaction) as the cause of the adverse outcome. However, the use of extensive exclusion criteria does not help identify the risks of the new study drug, because too many exclusion criteria end up with an over-simplified study population.

“Too Many Exclusion Criteria” End Up With an “Over-Simplified Study Population”

Given the above points that are part of current research trials on prescription medicines on humans, it is easy to understand why the clinical drug trials before the approval for sales and marketing of a new drug do not exhaustively characterize the new study drug that is approved for sales and marketing. To more fully characterize the new study post-approval, we need N-of-1 trials to identify the severe adverse outcome at a low chance of occurrence that is associated with the drug (Tsapas and Matthews, 2008; Askew, Schluter, Claravino, and Del Mar, 2008; Larson, 1990). The less-than-complete investigation of drugs in human study participants means that the citizens in the patient population of any country are unwitting study participants in informal (and never specified to the patient) N-of-1 trials in which experimentation on drugs in the population goes on long after the drug has been approved for sales and marketing. Thus, these citizens of the population are unwittingly study participants in informal research trials undertaken in one-on-one patient care. This point further extends the

reasons why citizens have the right to full disclosure related to the benefits and risk identified in human research study participation of medical products of all types, including prescription medicines, in two ways. First, citizens are formal study participants during the drug trials leading to the new drug's approval. Second, citizens as patients are study participants in informal N-of-1 trials as the now-approved drug is prescribed in patient care.

It is also important to note that N-of-1 trials can be formally conducted after the new drug is approved and prescribed in practice. More research needs to be undertaken on the formal N-of-1 trial in contemporary research on humans on medical product after they have been approved for marketing (Tsapas and Matthews, 2008; Askew, Schluter, Claravino, and Del Mar, 2008; Larson, 1990).

Future Directions of Trust and Accountability in Medical Products

It is fair to say that new study drugs with new mechanisms of action are the best example of a class of drugs where new risks—undiscovered in research trials that yield a drug's approval for sales and marketing in the population—will be identified only when the drug is prescribed to more patients in the population in the medical care of those patients. Yet, the principles and questions we have reviewed can be applied to any new medical product—a new prescription drug, a new medical device, a new medical diagnostic or screening test—allowing us an opportunity to develop a sturdier framework of trust and accountability for the scientific database than we now have.

Areas Where Future Solutions Should Be Looked For

There is a need in contemporary society to better protect the integrity of the scientific database of research derived from human study participants. The scientific database needs to include both (1) “raw data” from research trials and (2) the “definitions” (and “criteria”) needed to interpret why particular data types were selected and other data types rejected in research trials. Such added precision to the contents of the scientific database of generalizable knowledge will allow for better patient care decision making in the present and better development of research hypotheses and research designs in the present and future.

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