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Challenges in the Ethical Review of Research Involving Complementary and Integrative Medicine

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Abstract

Complementary and integrative medicine (CIM) involves using practices outside mainstream Western medicine, often derived from Eastern traditional medicine, and combining those practices with Western medicine. Conducting CIM research that is necessary to determine whether particular interventions are beneficial and safe will involve a set of ethical challenges. Institutional review boards (IRBs), also known as research ethics committees or research ethics boards, are responsible for determining that research studies involving human subjects appropriately address ethical and regulatory concerns inherent to the research. Like other research with human subjects, research involving CIM is subject to ethical review and ongoing oversight by an IRB. IRBs are often challenged by the review of CIM. These challenges include accounting for cultural differences and the interests of competing stakeholders. In this report, we describe these issues that were the focus of a workshop that was part of an international conference held in Seoul, Korea, on April 4, 2015.

Keywords

complementary and alternative medicine, ethical review, Korea, traditional medicine

Complementary and alternative medicine includes using "health care approaches developed outside of mainstream Western, or conventional, medicine," some of which are derived from Eastern traditional medicine, whereas integrative health generally "involves bringing conventional and complementary approaches together in a coordinated way."[1] Collectively, these may be considered as complementary and integrative medicine (CIM). Conducting research involving CIM to determine whether particular interventions are beneficial and safe involves some ethical issues. Institutional review boards (IRBs), which are also known as research ethics committees or research ethics boards, are responsible for determining that research involving human subjects appropriately address ethical and regulatory issues inherent to the research. Like other research with human subjects, research involving CIM is subject to ethical review and ongoing oversight by an IRB. IRBs are often challenged by the review of CIM. These challenges include accounting for cultural differences, understanding the interests of competing stakeholders, and applying ethical standards.

In this report, we describe the proceedings of a workshop focused on IRB oversight of CIM research that was conducted at the Global Clinical Research Summit 2015, hosted in Seoul, Korea, by the Comprehensive and Integrative Medicine Institute (CIMI) of Daegu Catholic University Medical Center and Daegu University Medical Center (http://www.globalsummit.or.kr/program.jsp). The goal of CIMI is to develop an environment where allopathic Western medicine and Korea's traditional medicine are provided to patients in a single venue as part of a coherent plan of care. The challenges to achieving this goal in South Korea are similar to those faced in other locales, although what constitutes "conventional" and "traditional" medicine may be different. In particular, the current environment in South Korea provides little opportunity for collaborative care between providers of conventional and traditional medicine; South Korean traditional medicine has no established infrastructure or standards for research to establish safety and efficacy for its interventions, much less the use of those interventions in combination with conventional medical diagnoses, drugs, and devices; and standards of evidence are different in the two systems. Similarly, CIMI is primarily concerned with the health care

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delivery system in South Korea and finding a means of addressing these issues in its particular context. However, these issues are widespread, and it is conceivable that the solutions identified in South Korea would be applicable in other contexts trying to integrate the delivery of effective conventional medicines and devices with traditional medicine.

Of note, the context of the workshop determined the meaning of many of the terms used in this report: *conventional medicine* in South Korea is allopathic medicine in the Western tradition, whereas *traditional medicine* is primarily Korean and Chinese traditional medicine, although traditional practitioners in South Korea are adopting nonindigenous methods and interventions they believe will help their patients.

Cultural Differences

The conventional medical environment is currently dominated by calls for evidence-based medicine, comparative effectiveness research, and learning health care organizations. In the US, the conventional medical community is struggling to balance the results from clinical trials with individual physician experience in the face of scrutiny by payers for justification of clinical choices. Concurrently, patients are increasingly using therapies that come from different traditions and at times asking their doctors to ''integrate'' such practices into their care plans.

Practitioners of traditional medicine face a corresponding insistence on the need for evidence to support their practices. Traditional medicine approaches that claim to take advantage of the body's natural ability to heal, and that are less reliant on expensive technology or patented drugs, can look like attractive options not only to patients, but also for payers and policymakers. However, the quality of evidence demonstrating safety and effectiveness for these therapeutic approaches is largely anecdotal, at least by Western scientific standards. There is no obvious characteristic of traditional medicine that would exempt it from the same scientific assessment being increasingly required for conventional medicine.

Regardless of how the ''evidence base'' for traditional medicine is developed, the integrated delivery of Western and traditional medicine poses additional challenges. Given that nonconventional therapies will continue to be used by patients and any conclusive demonstration of their value (in a scientific sense) is likely years away, how can a health care delivery system competently and safely advise patients and provide care? Integrating delivery of different medical traditions will also require overcoming significant cultural differences regarding conceptions of disease, health, medicine, research, and evidence.

Coming from either a conventional or traditional medicine culture it is all too easy to cast the other as simply wrong. Conventional medicine typically assumes that traditional medicine is ''unscientific'' and unproven. Traditional medicines may be seen as at best harmless and at worst interfering with delivery of effective conventional therapy. Conversely, traditional medicine may characterize Western medicine as being concerned about treating symptoms, not people; as ignoring the body's innate ability to heal; as minimizing the differences between individuals; as being unaware of the importance of ''balance'' to health; and as disregarding traditions based on centuries or millennia of practical knowledge.

It is critical to recognize that these perspectives embody alternative epistemological bases and understandings of how individuals relate to their world from their broader philosophical traditions, as well as different professional norms. Despite the different perspectives of practitioners of conventional and traditional medicine, in some settings both patients[2] and physicians[3,4] are seeking to combine these healing traditions. Each tradition brings value. For example, conventional allopathic medicine illustrates the necessity of using well-developed scientific methods and traditional medicine underscores the importance of considering health as a matter of balance for the whole person. To ignore these perspectives risks missing the opportunity to provide optimal care to patients. Striving to reach consensus about the need for data and how best to obtain it is essential in order to help evaluate CIM for evidence of true benefit and safety through research.[5]

Lessons From History

Conducting CIM research requires balancing the ethical obligations to patients and the desire to advance understanding through research. Historically, physicians would try to strike this balance by minimizing the risks of research and would even engage in self-experimentation when the research was risky.

However, over the course of time, it became clear that relying on such a professional ethic was insufficient protection for patients and other research subjects. There was global recognition of this problem following World War II, during which Nazi doctors conducted egregious experiments on concentration camp prisoners. In no way did professional ethics protect the well-being of these prisoners. Accordingly, in the court case in which some of the Nazi doctors were tried, the judges announced the Nuremberg Code, which is a set of 10 principles guiding research.[6] Of course, most biomedical research is totally different from the Nazi experiments, which led the World Medical Association to develop the Declaration of Helsinki in 1964 that outlined ethical obligations for research.[7] In the United States, revelations regarding unethical research led to the publication of The Belmont Report, which was developed by the US National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. The report outlines three ethical principles: respect for persons, beneficence, and justice.[8] Respect for persons is based on the ethical principle of respect for autonomy and the political principle of liberty (in short, the right to be left alone). In research practice, this implies that subjects give their consent to participate in most research. Beneficence is the obligation to help and to avoid harming others. This translates into the obligation to

minimize research risks and to maximize its benefits. Justice demands fairness. In research, this requires selecting participants fairly as well as protecting those who may be vulnerable.

Nevertheless, announcing ethical principles alone is insufficient to guide research. Rather some explicit practices are required. Currently, it is widely recognized that there are three pillars of protection to help safeguard the rights, interests, and welfare of patients who participate in research: researchers and sponsors; informed consent and oversight. Researchers and sponsors have the primary obligation to protect research participants and to ensure that the results are credible. Ensuring that research is credible includes among other things that the scientific design is sound, the research is conducted responsibly, and that the interventions tested are of good quality. Informed consent is an important protection since it permits patients who are given relevant information about proposed research the opportunity to decide whether participation for them is appropriate given their unique values, priorities, and other opportunities. Finally, oversight provides independent mechanisms to help ensure that the ethical (and regulatory) aspects for research are navigated appropriately. Responsibility for oversight sits with institutions where research is conducted, governmental agencies, IRBs, and Data Monitoring Committees (also known as Data and Safety Monitoring Boards).

The ethical principles and procedures, which have been identified and developed for conventional biomedical research, promise to be important platforms for the burgeoning portfolio of research on and with traditional medicine. Only by attending to these ethical issues will it be possible to properly generate the data needed regarding CIM interventions that are essential to informing the work of practitioners and the choices of patients.

The Challenge of Competing Stakeholders

Nongovernmental and governmental stakeholders can have a major influence over the evaluation and implementation of CIM. These stakeholders have the ability to influence the design and conduct of CIM research.

For instance, the World Health Organization (WHO) is an agency of the United Nations that is charged with directing and coordinating global public health activities. Part of this involves supporting and conducting research activities in multiple areas, including CIM. In 2014, the WHO published its 10-year strategy regarding traditional medicine, outlining a comprehensive strategy to foster the appropriate integration, regulation and supervision of traditional and complementary medicine.[9] Before that, WHO issued guidance specifically focused on clinical trials of herbal products, a key component of much research involving CIM. In this capacity, the WHO has been influential in helping ensure that such research is conducted according to accepted international standards for clinical research.

In the United States, substantial resources are being directed at funding high-quality research on CIM through the National Center for Complementary and Integrated Health (NCCIH), which is part of the National Institutes of Health.[10] Research funded by NCCIH is subject to a set of federal regulations for research, which is overseen by two oversight bodies: the US Office for Human Research Protections (OHRP) and the US Food and Drug Administration (FDA). OHRP is tasked with interpreting and enforcing the US regulations that govern research funded by the US Department of Health and Human Services. The FDA regulates clinical investigations of drugs, devices, and biologics intended for the diagnosis, cure, mitigation, treatment, or prevention of disease. This can include components of CIM research, such as the use of herbal products to treat a disease. As regulators, OHRP and FDA are positioned to directly influence the way IRBs evaluate proposed research involving CIM. The current US regulations do not have specific requirements for research involving CIM. Rather, the regulations prescribe one set of requirements for all human subjects research.[11] In addition to establishing the criteria for approval of research, the regulations also require the IRB to have suitable expertise regarding the research it reviews. This means that IRBs should have members experienced in both conventional and traditional medicine in order to conduct a thorough assessment of CIM research.[12]

The current ethical and regulatory frameworks for clinical research were developed to address research without consideration of the topic of the research. Regulatory frameworks and international research guidance documents do not address CIM, leaving IRBs to figure out whether the review of CIM research requires special rules. WHO, OHRP, and FDA are positioned to influence the way in which IRBs evaluate this research by emphasizing the relevance of current guidance documents, regulations, and ethical principles.

The Challenge of Applying Ethical Standards

IRBs can find common ground among members with diverse perspectives, including conventional and traditional medicine, by incorporating the basic process of principle-based ethical decision making. Principle-based ethical decision making starts with fundamental ethical principles, and from those principles specific rules may be derived. IRBs make determinations by systematically applying those rules to each case. This process of principle-based ethical decision making remains constant regardless of whether the topic of the research is conventional medicine, traditional medicine, or a combination of the two.

As mentioned earlier, the fundamental ethical principles governing human research are respect for persons, beneficence, and justice. These ethical principles are present in most cultures, but are interpreted in a cultural context. For example, most cultures believe in the respect of persons, but the balance between individual versus family autonomy varies among cultures.

Principle-based decision making commonly encounters conflict between principles. For example, the principle of

respect for persons may suggest that it is important to respect children's limited autonomy by limiting their participation in research. Whereas the principle of justice may call to include children in research, so as a group they can fairly share the benefits of research. Philosophers have developed methods that specify how the ethical principles may be balanced and in developing rules that are derived from these specified principles.

The rules followed routinely by IRBs involve assuring informed consent unless informed consent can be ethically waived, establishing sufficient measures to maintain confidentiality and protect privacy, providing additional safeguards for vulnerable populations, minimizing risk, ensuring a favorable relationship between the risks and potential benefits, monitoring aggregate data for new risks, and equitably selecting subjects.[13] The rules that may be difficult to apply with CIM research are those related to the principle of beneficence: Determining risks to subjects are minimized by using procedures consistent with sound research design that do not unnecessarily expose subjects to risks, and determining whether risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of knowledge expected to result.

In evaluating whether risks to subjects are properly minimized, the IRB should consider whether risks to subjects are minimized by using procedures consistent with sound research design, which do not unnecessarily expose subjects to risk. To implement this rule, IRBs should consider whether there are alternative ways to conduct the research that reduces risks to subjects, but allow the research to accomplish its goals. If so, the research procedures should be modified accordingly consistent with sound research design.

In evaluating risks, it is important to consider the probability of risk and the magnitude of the risk as well as whether the probability or magnitude of the risk represents minimal risk (essentially risks commensurate with those posed by the daily life of normal individuals).[14] Establishing the probability of risks may differ when considering conventional and traditional medicine. That is, conventional medicine prefers to establish the nature and probability of risks through blinded clinical trials, whereas traditional medicine usually establishes risks through historical knowledge. Some may mistakenly consider blinded clinical trials necessary to evaluate risks of research. While such data are obviously desirable and if available should be privileged, it is important to consider that often conventional medicine accepts historical data when clinical trial data are unavailable. In the same way, historical knowledge obtained through thousands of years of extensive use can be drawn upon to initially evaluate the risks of research on traditional medicine in lieu of research data.

Another difficulty with the minimization of risks in CIM research is the lack of knowledge regarding the interaction between many traditional and conventional medicines, which may in fact be a relevant question being addressed in the research. At the outset, it is important to recall that interactions that lead to life-threatening conditions are known to exist with items considered generally safe. For example, spinach can interact with warfarin metabolism to produce a potentially lethal complication. Similarly, herbal products can interact with commonly used drugs[15] and anesthetic agents.[16] Depending upon the degree of risk, preclinical studies along with blinded clinical trials to assess the interaction of conventional and traditional medicines are as necessary as they are in studies of drug interactions of conventional medicines.

To evaluate the relationship of risks and potential benefits, IRBs should consider whether risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. Here, IRBs should follow a two-phase process. The first phase is often called "scientific review," whereas the second phase represents ethical review. In the first phase ("scientific review"), the IRB ascertains the risks to subjects in terms of probability and magnitude, the anticipated benefits for the subjects, and the knowledge expected to result. If ascertaining this information requires expertise beyond the IRB's knowledge of conventional or traditional medicine, the IRB should consult others who do. In the second phase of this evaluation ("ethical review") the IRB determines whether the risks are reasonable in relation to the benefits for subjects, if any, and the importance of the knowledge reasonably expected to result.

An effective IRB process to evaluate CIM research follows the same two-phased approach that should be used to evaluate conventional therapies. Independent experts in both conventional and traditional medicine should be asked to provide objective information to the IRB. Then IRB members make an ethical determination of whether the relationship between risks and potential benefits is favorable.

Conclusion

The expansion of the research enterprise to evaluate CIM can pose ethical challenges. These challenges include accommodating differing medical cultures, addressing the interests of competing stakeholders, and conducting meaningful ethical review. Many of these challenges can be addressed through an appreciation of the IRB's fundamental role in protecting human subjects. The IRB's ethical assessment is unchanged between reviews of CIM and conventional medicinal research. There is nothing fundamentally different about traditional medicine that should exempt it from the same scientific assessment used for conventional medicine. Moreover, well designed and conducted research on CIM is essential to ensure the health and safety of patients.

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