Four Paradigms of Clinical Research and Research Oversight

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The understanding of appropriate ethical protections for participants of biomedical research has not been static. It has evolved over time, with the evolution of biomedical research as well as social values. Since World War II, there have been four major paradigms of research and research oversight operative in the United States (Table 1). These paradigms incorporate different values and provide different approaches to research oversight and the protection of research participants.

For hundreds of years, research to test interventions had been sporadic.[1] Little distinction was made between experimentation and therapy. Evidence of the effectiveness, and even safety, of medical interventions was rare.[2] Until the late 19th century, most therapies could properly be considered experimental in the sense that they lacked empirical evidence for their effectiveness. Researchers were usually physicians, motivated to do what they thought best for their patients, and trusted to do the right thing.[3] There were no specific codes of ethics, laws, or regulations governing the conduct of research, but peer judgment and influence served to contain fraud and abuse.[4] For instance, in 1897 Giuseppe Sanarelli, an Italian researcher working on yellow fever, declared he had produced yellow fever by injecting a bacillus into five people.[5] At a 1898 medical meeting William Osler condemned Sanarelli saying, "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."[6]

Systematic biomedical research began to grow as an enterprise after the development of penicillin and the passage of the Food, Drug, and Cosmetic Act in 1938 that required evidence of safety before a product was marketed.[7] Just before World War II, there was dramatic growth in research as an enterprise. Large pharmaceutical companies were starting up, both public and private money was devoted to research, and research became increasingly centralized, coordinated, standardized in method, and publicly supported.

Since right around World War II, understanding of the ethics and oversight of human subjects research has proceeded through four distinct periods or paradigms. Each period embodies different perspectives on research and its dangers and different conceptualizations of the goals of oversight. Each period also advances a different underlying ethical principle guiding the protections of research participants, empowers different institutions to implement the protections, and has its own way of balancing protection of research participants against other important values in biomedical research. At least in the United States, the change from one period to another has frequently been catalyzed by

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Table 1. Four Periods and Paradigms of Research Oversight

	Researcher paternalism	Regulatory protectionism	Participant access	Community partnership
Dates	1940–early 1970s	Early 1970s–mid-1980s	Mid-1980s–mid-1990s	Mid-1990s
Triggering event(s)	World War II	Jewish Chronic Disease Hospital; Beecher's revelations; Tuskegee Syphilis Study	AIDS epidemic; breast cancer movement	Genetic research among Ashkenazi Jews and aboriginal communities; International HIV/AIDS research
Key protection	Researcher judgment	IRB review and individual informed consent	Individual autonomy	Host community collaboration
Conception of subject	Subject—a passive "subject" of research	Vulnerable party	Informed consumer	Participant—active participant in research enterprise
Conception of biomedical research	Sharp distinction between care and research		Clinical research is the best type of clinical care	Continuous with clinical practice
Underlying philosophy	Utilitarianism	Principlism	Individual rights-based theory	Communitarianism
Highlighted ethical principle	Social value	Independent review	Informed consent	Collaborative partnership

crises or scandals. To some degree the periods represent "swings of the regulatory pendulum"[8] but, as will become clear, these swings are not along just one dimension.

Importantly, these periods or paradigms should not be thought of as Kuhnian paradigms with radical, instantaneous paradigm shifts.[9] The transition between paradigms evolved over time, usually due to crises or scandals that forced a reexamination of the existing research oversight paradigm. The ideas that evolve, and are subsequently espoused, have antecedents in the prior paradigm. Furthermore, the dominant ideas and values of a prior paradigm often remain operative and influential in subsequent paradigms. Indeed, distinct paradigms can coexist, and it might be argued that none of the paradigms has been entirely supplanted. Nevertheless, although precise dates cannot be given for each period, there are important changes between periods symbolized and encapsulated in the values of research oversight that become dominant.

Because the different paradigms can overlap, controversies about the oversight system and the ethics of trials are frequently disagreements over what values and which paradigms should be dominant. They may also be disagreements over what types of research studies the particular protections apply to. That is, one paradigm and its protections may clearly apply to intervention studies with controversy over whether they apply to epidemiology, pharmacokinetic, or normal physiology studies. Indeed, some of the more recent paradigms probably apply only to some types of studies.

Paradigm 1: Researcher Paternalism

World War II had a profound impact on Western society, emphasizing the need for people to contribute to the social good. The importance of individual sacrifice for society's benefit was palpable. Indeed, in Britain it was thought that society's very survival depended on such sacrifice, and in the United States there was a strong sense that, if not survival, then certainly the United States's winning of the war depended on such sacrifice. Obviously this was manifest directly in fighting the war, but it also influenced related activities, such as biomedical research. Beginning with the war and extending for nearly three decades, the dominant view was that biomedical research was important for society's benefit and progress against diseases.[10] Individual sacrifice was necessary for research and justified by the tremendous good it would produce for all of society.[11] The war analogy was vivid, visceral, and, with the victory, validated by experience. Frequently, it was implicitly and explicitly invoked to justify clinical research.

Biomedical research during this period has been described as "unashamedly utilitarian."[12] The federal government and the pharmaceutical industry supported intensive research efforts to develop vaccines and antibiotics to help soldiers at risk from infectious diseases. This research frequently involved available and captive populations in prisons, orphanages, homes for the emotionally or developmentally disturbed, and other institutions.[13] Research was justified as a way for such groups to make their contribution to society. Biomedical research was clearly seen as distinct from therapy; participants not necessarily in need of therapy were accepting a personal burden in order to make a contribution to society.

Although utilitarianism is not the only philosophical approach that can justify individual sacrifice for the greater good of society, it is the best developed and accepted. During this period, utilitarianism implicitly or explicitly became the dominant justification for research, and the dominant ethical principle guiding research and research oversight was social value. The ratio of risks and benefits for individual research participants might have been unfavorable—with high risks for the individual. But risks to the individual were thought to be outweighed by the emphasis on social value, the value of the knowledge to be gained for society.

By the late 1960s, clinical research was under attack, and researchers found it necessary to articulate the philosophical justification for research, specifying the benefits of biomedical research for society and the need for individual sacrifice to achieve those benefits. For instance, Hans Jonas attacked the underlying paradigm when he attacked the war image, specifically the idea that research with humans was necessary for society's survival.[14] He also rejected the utilitarian philosophy underlying the research paradigm.

> We may observe that averting a disaster always carries greater weight than promoting a good. Extraordinary danger excuses extraordinary means. . . . Much weaker is the case where it is a matter not of saving but of improving society. Much of medical research falls into this category. As stated before, a permanent death rate from heart failure or cancer does not threaten society. . . . The destination of research is essentially melioristic. It does not serve the preservation of the existing good from which I profit myself and to which I am obligated. Unless the present state is intolerable, the melioristic goal is in a sense gratuitous. . . . [Consequently, t]he surrender of one's body to medical experimentation is entirely outside the enforceable "social contract."[15]

Probably no one was more explicit in defending clinical research against Jonas's view, and willing to state the implicit, than Walsh McDermott, one of the leading figures in postwar American medicine. In 1967, when addressing a colloquium on clinical research, McDermott argued:

> When the needs of society come in head-on conflict with the rights of an individual, someone has to play God. We can avoid this responsibility so long as the power to decide the particular case-in-point is clearly vested in someone else, for example, a duly elected government official. But in clinical investigation, the power to determine this issue of "the individual versus society" is clearly vested in the physician. . . . [A]s a society we enforce the social good over the individual good across a whole spectrum of non-medical activities every day, and many of these activities ultimately affect the health or the life of an individual. . . . I submit that the core of this ethical issue as it arises in clinical investigation lies in [that] to ensure the rights of society, an arbitrary judgment must be made against an individual. . . . [W]e have seen large social payoffs from certain experiments in humans. . . . [W]e could no longer maintain, in strict honesty, that in the study of disease the interests of the individual are invariably paramount. . . . To be sure, by careful attention we can cut down the number of instances in which the problem presents itself to us in its starkest form. But there is no escape from the fact that, if the future good of society is to be

> served, there will be times when the clinical investigator must make an arbitrary judgment with respect to an individual.[16]

Louis Lasagne, chair of Department of Pharmacology and Toxicology at the University of Rochester, agreed that individuals could be sacrificed for the greater social good and noted that the best protection for research participants was the ethical researcher.

> Society frequently tramples on the rights of individuals in the "greater interest." . . . [T]he good of the individual and the good of society are often not identical and sometimes mutually exclusive. I submit that the successful development of such an ethical conscience, combined with professional skill, will protect the patient or experimental subject much more effectively than any laws or regulations. . . . I believe it is inevitable that the many will continue to benefit on occasion from the contributions—sometimes involuntary—of the few. The problem is to know when to say "Halt!"[17]

During this period, the main protection for research participants was the integrity of the researcher and the researcher's judgment. Informed consent was seen as a lesser protection. At the turn of the century, Walter Reed obtained consent for his yellow fever experiments. Over the next 70 years, researchers typically obtained informed consent to research from healthy volunteers. However, consent to research for patients receiving experimental treatments was much more inconsistent. More important than informed consent, it was argued, was the caring, compassionate researcher. Researchers were seen as concerned with the participants' well-being and wanting to protect them. The judgment of researchers regarding the types of research projects they thought were reasonable, as well as what risks and risk–benefit ratios were reasonable, was deemed an appropriate and acceptable safeguard. Individual researchers' judgments about what was reasonable were influenced by what the wider research community deemed acceptable, and that remained an important protection. Nonetheless, the main protection was really researcher paternalism.[18]

This view was widespread. One of the persons most responsible for ending this paradigm—although he did not intend to end it—was Henry Beecher. Through his 1966 article in the *New England Journal of Medicine* delineating 22 cases of abuse of research participants, he catalyzed a transformation that changed the paradigm of research and research oversight.[19] Yet throughout his career, he maintained that the care and integrity of the researcher, rather than informed consent, was the best way to protect research participants. In this sense, he very much supported a kind of researcher paternalism paradigm, although his aim was to emphasize that researchers had to have the right goals in mind.

> The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent. The difficulty of obtaining this is discussed in detail. . . . Secondly, there is the *more reliable safeguard* [for the research participant] provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator. (italics added)[20]

Importantly, the researcher paternalism paradigm for protecting research participants was not an isolated phenomenon; the social values that informed

it influenced other areas of medicine. Paternalism cohered with both the prevailing ethics of clinical care and the legal standards of informed consent for clinical care at that time. During this period, almost everyone agreed that physicians should influence treatment decisions for patients. Although it was accepted that physicians should obtain patients' consent for medical procedures, the amount of information the physician disclosed was based on what the physician community determined was reasonable to tell the patient, the so-called professional standard. For instance, in the landmark *Natanson v. Kline* case, the court held that

> The duty of the physician to disclose . . . is limited to those disclosures which a reasonable medical practitioner would make under the same or similar circumstances.[21]

And, it was accepted that physicians might not tell patients about their cancer or other serious, life-threatening illness out of concern for their best interests.[22] Indeed, the physician was frequently entrusted with deciding what was best for the very sick patient without gaining their informed consent.[23]

Paradigm 2: Regulatory Protectionism

The period of researcher paternalism came to an end in the early 1970s after a series of scandals. The Jewish Chronic Disease Hospital case, Henry Beecher's revelation of many unethical practices in clinical research at leading medical centers, and the Tuskegee Syphilis Study, among others, discredited researchers as concerned protectors of participants' well-being and interests.[24]

What became clear through many of these cases was that researchers were not always judiciously weighing social value over individual risk–benefit assessments when they were in tension; rather researcher paternalism was sometimes a cover for blatantly unethical practices with few social benefits. In the case of both the Jewish Chronic Disease Hospital case and the Tuskegee Syphilis Study, pervasive deception was used to enroll and retain relatively powerless participants.[25] Although deception might not have had an adverse physical impact in the former case, it certainly prevented many African-Americans from getting curative therapy in the Tuskegee case. Furthermore, in some cases, including Tuskegee, the social value of the research was highly questionable.[26] Beecher summarized the problem this way:

> Undoubtedly all sound work has [the good of society] as its ultimate aim, but such high flown expressions are not necessary and have been used within recent memory as cover for outrageous ends.[27]

The cumulative effect of these scandals was to repudiate researchers as effective overseers of the interests of participants and the ethics of research and to question the underlying utilitarian justification for research ethics. These scandals led to a period of intense debate about the scope and limitations of research involving human subjects. Passage of the National Research Act in 1974 and the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research led to a comprehensive reassessment of the ethics of research and the appropriate oversight system.[28] The

result was a regulatory system, codified in 1981 as Title 45 Code of Federal Regulations, Part 46, entitled "Protection of Human Subjects."[29]

The underlying view informing this oversight system was that biomedical research, although valuable and, in some sense, necessary, was inherently dangerous and a threat to the well-being of participants. The goals of therapy and research were distinct. The goal of the oversight system was protectionism—to protect participants from researchers and the inherent risks that they and their research posed. Institutional review board (IRB) review and individual informed consent were thought to be the best mechanisms to protect research participants from the risks and burdens of research. In addition, there were special protections built into the regulations for various groups deemed especially vulnerable to the threat and harms posed by research—prisoners, pregnant women, and children.[30]

A critical aspect of the protections put into place during this period was that decisionmaking authority about research was partially taken away from physician researchers and put into the hands of independent review groups, government regulators, and research participants themselves.[31] IRB review and informed consent did not come out of nowhere. As noted, informed consent for research studies from healthy volunteers had been increasingly standard practice since the turn of the century and was consistently performed with patients at certain institutions. Research review committees had been established at various institutions, such as the Clinical Center of the National Institutes of Health.[32] Nevertheless, there were no uniform rules regarding the content of informed consent or the composition and operation of the independent review committees. Furthermore, under the researcher paternalism paradigm, neither informed consent nor independent review was seen as mandatory, especially in research with patients. As was the case in the Jewish Chronic Disease Hospital case, researchers felt that obtaining consent might upset the participants and therefore it could be suspended. And much research was conducted without any independent review. Thus, a major element of this change in paradigm was to formalize informed consent by requiring signed written informed consent documents, formalize the review process, and, at least for federally funded research, make both informed consent and independent review mandatory.[33]

The underlying ethical philosophy was one of principlism formalized by Beauchamp and Childress in their book *Principles of Biomedical Ethics*[34] and the National Commission's *Belmont Report*,[35] which Beauchamp took a leading role in writing. This approach eschews comprehensive ethical theories in favor of midlevel principles that are shared and can be justified by a variety of ethical theories, particularly utilitarianism and deontology. Three ethical principles: respect for persons, beneficence, and justice, became linked to and justified specific requirements for regulating research: informed consent, determination of a favorable risk–benefit ratio, and fair selection of subjects.[36]

Ironically, although these protections emphasized informed consent and were justified, in part, by appeals to the principle of respect for persons, they remained somewhat paternalistic, although different from the research paternalism of the previous paradigm. For example, regulations prohibited most research with prisoners.[37] This restriction clearly limited prisoner autonomy but was believed to be justified because of the coercive circumstances of prison. Similarly, research with pregnant women was limited. The constraint on the autonomy of women was justified by the need to protect their fetuses.[38]

Once again, the oversight of clinical research was not being reassessed in isolation. At this same time, there was a pervasive social reassessment of the ethical norms governing medical practice as well as particular reevaluation of informed consent. The claim that professional ethics, codes, and oaths established by physicians should serve as normative standards was being attacked. Physician-generated rules for physicians were viewed as inadequate and suspect.[39] Instead, universal ethical principles that were independent of the profession, such as beneficence and autonomy, became the basis for ethical medical practice. As Robert Veatch argued in his book *A Theory of Medical Ethics*:

> What is being questioned is the authority of a professional group to set its own ethical standards and to adjudicate disputes about the conduct of its members. . . . Our conclusion is that a professional ethics grounded in nothing more than agreement, custom, or vote by a group's members can have no ethical bite. No one outside the group would have any reason for conforming to the professional ethical judgments.[40]

Veatch argues for a social contract to replace the profession's ethics. Regardless of his specific alternative, the key point is that general ethical norms are controlling, not norms specified by the profession for itself. This clearly mirrored the change from research oversight based on professional judgment to one that was imposed from outside and derived from three independent ethical principles.

Similarly, in 1972, the *Canterbury v. Spence* ruling delineated a different standard for assessing the amount of information that should be disclosed to patients as part of the informed consent process for medical interventions.[41] The court rejected a professional standard and articulated a patient-centered standard in which the goal was to give patients the power to decide what was in their interest rather than entrusting their interests to physicians.[42]

Mortimer Lipsett, of the National Institutes of Health, in 1982 explicitly recognized that a utilitarian justification of individual sacrifice for the good of society was no longer tenable. In his defense of Phase I oncology studies, he recognized the centrality of individual autonomy in research:

> The larger questions about the ethics of phase I clinical trials of cancer chemotherapies have not been discussed in depth. . . . [I]s this phase I trial an example of the sacrifice of the individual for the good of society? . . . The question is philosophical in nature, and the answers are conditioned by the prevailing morals of society. It is clear that in certain circumstances we mandate individual sacrifice for the good of society. For example, the citizen drafted into the armed services may have to risk his life without prospect of immediate personal gain, although, even here, remote personal gain, such as preservation of home, family, and way of life can be invoked. Although this social contract has been generally accepted, . . . considerations change. A foundation stone of our moral and legal framework is autonomy—the right to personal inviolability, control of one's person, and the exercise of free will in taking risks. . . . In medical research, the imperative for sacrifice is not present, nor is it part of the social contract today. One need only recall the horrors of medical experimentation during World War II to appreciate the brutal extension of the utilitarian philosophy of sacrifice of the individual for a societal purpose.[43]

Period 3: Participant Access

Beginning in the mid 1980s, the oversight system built around protecting potential research participants from researchers and the risks of research began to be attacked. Although the change was heralded by heated emotion and protests, it was not a scandal in which people were being harmed by research but a new health crisis, the AIDS crisis. The fatal nature of the disease and the paucity of effective treatments induced a demand for more research. People with HIV faced the prospect of dying imminently and quickly. To them, trying something unproven, potentially risky, but also potentially beneficial seemed reasonable. They argued that participation in clinical research can be a benefit that individuals should not be denied, rather than a harm to be protected from. Federal regulations to protect research participants were viewed as obstacles rather than safety measures.[44] Protectionism was seen as discriminatory in that it prevented participants from getting experimental interventions that they wanted. Rather than protecting groups from potential exploitation in research, exclusion or limited access to trial participation was seen as exploitative, harmful, and unjust. HIV patients rejected regulatory protections from researchers and research interventions and demanded access to experimental interventions. Activists asserted a right to autonomously decide to try risky but potentially beneficial treatments, a right which they claimed should trump regulatory protectionism and paternalism. Martin Delaney of Project Inform said, "People with life threatening illnesses have rights that supercede those of society to control their behavior."[45] To the AIDS activists, regulations that forced them to die without trying something were more dangerous than researchers with unknown experimental interventions. Just as relying on researcher paternalism often exposed people to excessive risks, HIV activists argued that regulatory protections exposed people to the excessive risk of doing nothing. The justification for regulatory protections in research was challenged as their consequences and costs were exposed.[46]

> The epidemic will not pause for the traditional modes of science; AIDS has forced the acceleration of the procedures and processes of clinical investigation, as well as the mechanisms of regulations. . . . The basic concept of human experimentation has been radically altered—from protecting individuals from research to attempting to ensure individuals access.[47]

The regulatory pendulum began to move.

This period marked not only another major reassessment of research, but substantive changes in the way federal research agencies did business. Research was perceived as not necessarily harmful but as a good and an opportunity for treatment. Concomitantly, researchers were not to be feared as enemies but seen as allies. Moving away from an emphasis on protection against research, there was an increasing demand for access to research. Many advocates and patients argued that more efficient and equitable studies could be done with better patient compliance if community physicians participated in clinical trials. A number of programs were established to allow clinical providers in the community to participate in conducting research, such as the Community Consortium in San Francisco, AMFar's community coalition, and the CPCRA formed by NIAID.[48] The line between research and treatment was

blurred as participation in research was seen as the best and sometimes only way to obtain needed treatment and was being offered by community physicians in community clinics. And, it was argued, the best protection against harm and exploitation was the judgment of individuals about what was in their own best interests and not government regulations or bureaucrats deciding what risks were excessive.

> [R]egulators contend that desperate patients don't know what's good for them, that access to experimental treatments must be controlled by those with the proper scientific training. . . . [M]any feel this argument smacks of "big brother." . . . No one disputes that the multiphase steps of clinical research are a proven way to quantify the effects of a drug. The question is whether those steps should be equally required when seeking to restrain a contagious, world-wide epidemic as when judging a new cold tablet or pain remedy. AIDS is the medical equivalent of war. . . . The question should be, "who gets to decide what risks are acceptable: the bureaucracy in Washington or the patient whose life is on the line?"[49]

Although this trend began with HIV, it was subsequently reinforced by activists associated with other serious diseases for which there also were few effective interventions or cures. Thus, activists for breast cancer, diabetes, Alzheimer's, and other chronic diseases adopted similar pleas for access. Additionally, it was claimed that certain groups of people traditionally underrepresented in research were being denied not only the possible benefits of participation in research, but also the benefits of the application of knowledge gained through research. In the early 1990s, the U.S. National Institutes of Health began to require that those who receive research funding include certain groups of traditionally underrepresented subjects, such as women and ethnic minorities, and later children.[50]

Interestingly, this view began to be supported by organized medicine. Beginning in 1995, the American Medical Associations's Council on Ethical and Judicial Affairs began considering equitable access to research trials across different groups including sociodemographic groups. The Council even explored whether researchers had an obligation to secure funding for participation for those too poor to pay for the various medical interventions required by a trial. Ultimately, the Council rendered a much less innovative opinion. It recognized that "ethical considerations in clinical research have traditionally focused on protecting research subjects" and urged that under the rubric of protectionism groups should not be "categorically excluded, or discouraged, from research protocols."[51] However, the Council fell short of demanding access for participants from these groups.

The underlying ethical principle emphasized in this period was the right to autonomy. Individuals did not need to be protected by regulation; rather they should be entrusted to know their own good and interests and be free to pursue them. After all, as Mill said, the individual knows best what is in his or her best interest and is in the best position to pursue it. Autonomy was invoked as overriding many protections provided by the federal regulations. Activists demanded changes in the oversight system. They succeed in getting a faster FDA approval process as well as a change in the outcomes used to determine effectiveness.

Importantly, this new paradigm directed at participant access had limited applicability. It was most relevant to intervention trials, but not to other types of medical research such as normal physiology studies and other studies that recruited normal volunteers.

Again, this perspective did not arise in isolation from the wider society. It was during Ronald Reagan's presidency that individualism and the free market were championed and government regulation was strongly attacked as interfering with individual freedom. The arguments by the AIDS activists can be seen, at least in part, as an adaptation of this libertarian, individual autonomy view to the domain of research ethics. The words of activists sound like they could have come from libertarians: "If public and individual good are not clearly harmed, then government should not stand in the way. That is the American way."[52]

The pendulum swing to emphasizing the benefits of research and the importance of individual autonomous choice against societal restraints also occurred against the sociopolitical backdrop of a strong and visible gay rights movement, patients' rights movements, and patient and public skepticism about medical and scientific authority.

Period 4: Collaborative Partnership

Beginning in the mid-1990s, the limitations and potential drawbacks of the participant access model began to emerge from three sources. One source was genetics research. With dramatic growth in understanding the human genome and how genes function and cause disease, families and communities were being enrolled in research to attempt to identify genes that caused disease. Increasingly, research implicated not just individuals but extended families and entire communities. Research that targeted Ashkenazi Jews, for example, especially research to identify genes related to mental disorders, and research that targeted aboriginal populations prompted calls for extra protections for communities and for new involvement of communities in the planning, conduct, and dissemination of research.[53] Involvement of communities, it was argued, was the best way to protect them from stigma and other potential harms coming from genetics research. It was observed that the existing federal research regulations focused on individuals and did not mention communities. This seemed to leave communities vulnerable.

Another source of concern that stimulated reevaluation of the benefits and risks of research was what was viewed by some as scandalous—research in developing countries sponsored by developed countries. Research on perinatal HIV transmission in developing countries sponsored by the National Institutes of Health and Centers for Disease Control and Prevention in the late 1990s was attacked for using placebo controls in the trials and for succumbing to what many saw as an ethical double standard.[54] Much debate and commentary ensued, especially about the possibility of exploitation of people in developing countries by researchers from rich, developed countries.[55] One frequently recommended response to the need to protect developing country communities from exploitation was to develop partnerships with the community in which the research was being conducted.[56]

A third source highlighting the limitations of HIV and breast cancer activist demands for greater access to research studies with less regulatory restrictions was the demands of these same HIV and breast cancer advocates to be

integrated into the research enterprise. Advocates and community constituents fought for inclusion at the research table and gradually but increasingly were consulted on the establishment of research priorities, review of protocols, lobbying for funding, and even recruiting participants. Ultimately activism by several groups became less concerned with individual autonomy in deciding about enrollment in a particular study and more focused on community participation in the entire research process, from funding priorities to protocol development to dissemination of results.[57]

At the time of this writing, in 2005, we are in the midst of this trend toward collaborative partnership in the research enterprise. It is far from widely endorsed and solidified. Nevertheless there are important manifestations of attempts to realize this paradigm. For instance, the regulations guiding emergency research promulgated in 1996 require community consultation.[58] Although the purpose and process of community consultation is poorly delineated in the regulations, the inclusion of this requirement is a clear recognition of the need for community partnership, even if how to achieve this remains somewhat undeveloped.

This paradigm may well apply only to a segment of research, epidemiology, and intervention studies. Nevertheless, collaborative partnership constitutes a new paradigm of research and research oversight. This paradigm is based on the recognition that clinical research does not occur in isolation; clinical research is a collaborative, social enterprise. This is obviously true in that it involves a community of scientists. But, more importantly, at least for certain types of research, especially disease specific studies, it also involves a community of participants and medical practitioners, as well as the larger society required to fund the research and also assimilate the results into the health delivery system. The community is a necessary partner for successful research.

In the past, this collaborative partnership was implicit, even hidden. In the current paradigm, collaborative partnership is more explicit and formalized and more extensive. Community involvement is required in the establishment of research priorities through public advocacy as well as participation on advisory boards and funding organizations. The community is involved in oversight of research through growing participation on IRBs and on monitoring boards. Community participation may extend to negotiating benefits from the research, assistance with recruitment, and then integrating results into guidelines, reimbursement policies, and other aspects of the delivery system.

The community partnership paradigm rejects professional paternalism as a protection because the responsibilities and privileges of the researcher occur only within a wider social framework. The community partnership paradigm recognizes that risks and benefits both during and after research are best evaluated by involved communities. In addition, this paradigm deemphasizes individual autonomy and the protections of individual informed consent. Importantly, it does not reject them but places them into a wider context of protections that need to be satisfied prior to seeking the consent of individuals. In this way community partnership is based on a more communitarian model and less on an individual rights model.

Future

Over the past 70 or so years, the paradigm governing clinical research and the protection of research participants has evolved from one based on emphasizing

the social value of research and trust in investigators, to one of stringent protections of research participants from the dangers posed by researchers and research itself, to a rejection of protectionism and a demand for wide access to research opportunities, and finally to the importance of the community in ensuring the relevance and integrity of research practices. It is clear that, at least on the dimension of involvement of ordinary citizens in the clinical research enterprise, there has been great progress and expansion. The early period of research paternalism minimized the involvement of participants and the public whereas the currently operative collaborative partnership paradigm has integrated them as key participants in the entire research enterprise.

Each of these transitions has been catalyzed by scandals, crises, and/or changes in the nature of research practices. Although one paradigm was dominant at any one historical moment, there is certainly overlap. Strains of argument and reasoning from prior paradigms persist. The shift between paradigms is evolutionary rather than one of radical breaks; hence there is continuity between prior and future paradigms, as well as change in the emphasis and the dominant values.

It is unclear how the understanding of clinical research and ethical oversight might evolve in the future. Greater engagement of research participants throughout the process of developing research agendas and protocols, the conduct and dissemination of research, and altering of health policies in relationship to research results is certain to shift the paradigm further. Currently, there is an enormous need for greater focus on how that participation can occur most efficiently and effectively to promote societal good through valuable research while respecting and attending to the rights and well-being of individuals and communities.

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