What IRBs Could Learn from Corporate Boards

BY RICHARD S. SAVER

Institutional Review Boards (IRBs) continue to endure a painful crisis period. Many IRBs lack sufficient resources and expertise and strain under the weight of ever-increasing workloads and a more complex research environment. Yet insufficient attention has been paid to how IRBs perform relative to other oversight bodies. One unappreciated reference point for better understanding IRBs is the corporate board of directors. The experience of corporate boards offers a fresh perspective for assessing IRBs’ institutional strengths and limitations and for thinking about the proper direction of IRB reform.

As with the current period of IRB crisis, these are turbulent times for corporate governance. The alleged oversight failures of corporate directors feature prominently in the current round of business scandals at public corporations such as Enron and WorldCom. Renewed attention has focused on board dynamics and improving the monitoring effectiveness of corporate boards. What could IRBs learn from these parallel corporate board developments? IRBs and corporate boards have drawbacks as monitoring bodies for very similar reasons. A number of disparate factors influence board performance, and qualitatively improving board operations is no easy task. Accordingly, those calling for reform of the IRB system would benefit by paying greater attention to the corporate board experience. For example, corporate board developments suggest that one popular IRB reform proposal—increasing the number of IRB community members—should be viewed with some degree of caution. Unless accompanied by more comprehensive changes, adding more community members to an IRB will likely have limited impact on the IRB’s performance. In addition, the corporate board perspective warns against pushing IRBs to take on a more direct role in reviewing researcher and institutional financial conflicts of interest.

Shared Monitoring Limitations

As complex oversight institutions, IRBs assume many duties, including ethics consultation, education, and peer review. Yet the basic function required of all IRBs is to monitor clinical trials to protect the safety and welfare of research subjects. IRBs’ monitoring activities include initial review of protocols, requiring modifications to initial research plans, continuing review at designated intervals of research projects already underway, and consideration of subject or investigator complaints and adverse event reports as they may arise. IRBs also can exercise monitoring authority by establishing record-keeping requirements and internal policies for investigators to follow. Additionally, IRBs can...
engage in periodic audits of trial activities, as well as threaten to sanction non-compliant investigators with rejection or termination of protocols.

Corporate boards, elected by the shareholders, perform a critical monitoring function as well. The typical board of directors hires, fires, and assesses the ongoing performance of senior management; sets compensation incentives; oversees the accounting, auditing, and financial reporting activities of the corporation; and takes other actions to represent the interests of shareholders.

**Information and Time Constraints.** Despite the many other obvious differences between IRBs and corporate boards, both display remarkably similar weaknesses as monitoring bodies. First, IRB members and corporate directors face significant time constraints. Although monitoring the complex affairs of a large corporation would seemingly demand ongoing vigilance, boards of publicly held corporations meet an average of only eight times a year and directors spend the equivalent of only fifteen working days a year on board matters. Similarly, the part-time nature of IRB service has not kept up with IRB members' drastically increasing workloads. Informational deficits likewise hamper both types of boards. Corporate directors very often lack access to credible, independent sources of information. Senior officers have immediate access to corporate information that the board may not because the officers, not the board, conduct and implement the firm's daily affairs. The officers often can exercise great discretion in whether and how they report this information to the board. Moreover, senior executives typically control board meeting dates, influence the board's agenda, and can cue information to favor current management's position.

IRBs experience the same problem, as IRB members in part look to the investigator or sponsor with more immediate access to information from the clinical trenches to self-identify emerging risks, benefits, and adverse events associated with a protocol. This is particularly true when the research involves a highly specialized, narrow clinical field, or the drug or device under study is so novel that even clinical members of the IRB may have little familiarity with it. In addition, the typical IRB may operate unaware of credible information from other sources, such as another IRB's decision to reject a protocol, or concerns raised by a data safety monitoring board with access to data that the local IRB does not have. More important, IRBs all too often focus on paper review of informed consent documentation, or depend on investigators to self-report any protocol problems, without utilizing as effective fashion alternative and complementary audit procedures such as direct observation, interviews with research subjects, and review of how potential subjects are identified for possible recruitment in the first place. All of these activities would provide an IRB with a more complete picture of what actually happens with research subjects.

**Factions, Conformity, and Groupthink.** Another factor confounding monitoring effectiveness is that IRBs and corporate boards comprise a mix of inside and outside factions. Corporate boards include inside directors who the firm directly employs, as well as outside directors employed by other companies. Inside directors drawn from the internal management ranks must report to the chief executive officer (CEO) and thus may be averse to challenging current management or likely share the same biases of the current corporate officers. Inside directors wield significant influence in board deliberations and can obstruct efforts by outside directors to probe and monitor more vigorously. An inside/outside mix in board composition similarly complicates IRB operations. Nonaffiliated members drawn from the community are supposed to represent layperson views, provide a check against bias in favor of experimentation, and counter pressures to approve research projects lucrative for the institution. However, only a token number of nonaffiliated members serve on most IRBs. Nonaffiliated members can easily find their concerns dismissed or marginalized, and they report having frequent negative experiences in interacting with institutional researchers on the IRB.

Additionally, corporate directors and IRB members can become entangled in a complex web of personal associations and bonds with the very actors they are supposed to monitor. A director who confronts a fellow senior executive over a proposed transaction risks ostracism from the elite group invited to work in the boardroom. Similarly, it can be socially uncomfortable for an academic IRB member to vote to disapprove the protocol of a fellow researcher within the institution. Moreover, highly cohesive groups often develop the "groupthink" bias. This bias discounts critical examination of alternatives and urges consensus among members, even if suboptimal and inaccurate decisions result. Corporate governance theorists warn that directors are at risk for groupthink problems because traditional boardroom culture favors consensus and collegiality over conflict, and directors face enormous pressures to conform to the group.

The major conditions identified as creating high levels of conformity in corporate boardrooms include: decision-making involving uncertainty and ambiguity; strong social identification and interdependence between group members; and face-to-face meetings that inhibit dissent. These complicating conditions apply equally well to IRB
members. First, IRB decisions involve considerable uncertainty and ambiguity. For example, in applying the vague regulatory criteria for protocol review, IRBs reviewing the same protocol often disagree about informed consent requirements and whether the protocol should be approved. Second, most IRB members at medical institutions are clinical researchers who socially identify with each other and no doubt expect to be treated with the deference accorded one’s peers. Third, IRB members meet face-to-face when deciding whether to approve protocols. Members who want to dissent from the group or request that the IRB spend more time on a matter must do so openly, making it more uncomfortable for those who do not follow the deferential, collegial norm.

12 Insularity. Another shared feature is that IRBs and corporate boards are both remarkably insular institutions, with few external constraints or rewards pushing them to monitor more effectively. As most IRB members serve as unpaid volunteers, economic incentives for greater monitoring are virtually nonexistent. While corporate directors receive direct payment for their services, the compensation does not necessarily establish clear incentives for effective monitoring, as a director’s compensation has traditionally been unrelated to the individual director’s oversight performance.

Apart from positive rewards, corporate directors and IRB members face limited penalties for subpar performance. In theory, the threat of legal sanctions should be an incentive for individuals serving on these boards to exert greater monitoring effort. Yet director decisions challenged by shareholders as breaching the duty of care ordinarily receive the protection of a doctrine known as the business judgment rule, which insulates many board decisions from creating liability so long as they are rational, made in good faith, and free of conflict of interest. This, combined with insurance and indemnification protections, as well as procedural obstacles to shareholder lawsuits against directors, means that the actual risk of director liability is so low that it plays at best only a modest role in shaping board conduct. Liability exposure for IRB members for inattentive monitoring also is quite limited. There are hardly any reported cases of plaintiffs successfully suing IRB members for research subject harms. While some predict an increase in the frequency of IRB-related litigation, any such upswing is still in its very beginning stages. Plaintiffs will still have to overcome thorny issues of causation, damages, and unclear duties in the novel context of medical research in order to succeed. Considering the volume of clinical trials underway, IRB members generally face limited litigation risk at present.

Increasing the Number of Community Members

Because of the many parallels between IRBs and corporate boards, the experience of corporate boards can help in evaluating proposed IRB changes. Increasing the number of nonaffiliated members serving on IRBs stands out as a central, recurring theme in many current reform proposals. Both the Institute of Medicine and the National Bioethics Advisory Commission (NBAC) have urged IRBs to expand the ranks of nonaffiliated members so that they comprise at least 25% of the membership slots on each IRB. In theory, increasing the number of community members offers many advantages: greater attention to layperson viewpoints; stronger links between the IRB and the larger community; and a wider and qualitatively different level of scrutiny than internal peer review that should encourage investigators to take more care in design of protocols.

The corporate board perspective, however, cautions that there are limits to how much numerical changes in the insider/outsider mix of IRB members can realistically affect IRB operations without additional changes. The corporate board analog to the IRB’s nonaffiliated member is the outside director, an individual not employed by the corporation. The assumption is that the outside director will be less beholden to the CEO and better able to inject alternative viewpoints into business deliberations. Yet there have been mixed results from corporate governance reforms adding more outside directors. Repeated corporate governance failures at companies with a sizable number of outside directors have demonstrated time and again that the label of outside director does not necessarily mean that a particular director will be an effective monitor. Some degree of financial independence from management may be a necessary condition for effective monitoring, but this is hardly sufficient. Recent cases demonstrate that social interdependence between outside directors and management, notwithstanding the lack of financial conflicts for the directors involved, raises serious doubts about a board’s ability to act independently.

Moreover, a number of additional factors affect a director’s monitoring ability, wholly apart from the director’s nominal outside status, such as the length of time served on the board, the overall size of the board, and the relative strength and tenure of the CEO within the organization. Thus, the experience of corporate boards teaches that trying to change board conduct through the addition of more “outsiders” is no easy task. Boards are unwieldy, convoluted bodies. Empirical research indicates that the composition of the board does not correspond neatly with improved performance outcomes; instead, the effects of board composition are more complicated, subtle, and indirect.

This suggests that simply increas-
ing the number of community members on an IRB will have an attenuated impact at best. Community members are not going to be good monitors just because they are non-affiliated with the institution. They can still find themselves worn down by lengthy tenure on the IRB, lack of proper training, social interdependence with fellow IRB members, information and time constraints, and an IRB too unwieldy in size for individual members to make effective contributions.

Indeed, unless the appointment process changes for community members, simply adding more of them may not change IRB dynamics a great deal. Outside directors on corporate boards can disappoint as vigilant monitors because they typically exhibit strong degrees of loyalty to the CEO, likely due to the fact that directors are aware they owe their board seats to the CEO’s behind-the-scenes efforts. New corporate board reforms try to minimize such pressures by requiring that committees composed exclusively of independent directors nominate candidates for the board seats. IRBs might want to explore similar appointment reforms. At present, nonaffiliated IRB members often join the IRB at the invitation of the existing IRB chair or on the recommendation of an IRB member. Thus, nonaffiliated members typically join an IRB encumbered by social ties and likely feelings of indebtedness to the other IRB members or other institutional officials. This no doubt makes it quite daunting for the non-affiliated members to radially change the status quo by leading the IRB into a more active monitoring posture.

Finally, corporate governance reformers have come to understand that, in order to reap the benefits of an increased outsider presence on the board, changing board procedural rules is as important as changing board composition. Revised New York Stock Exchange and National Association of Securities Dealers listing requirements now require that the outside directors of publicly traded firms meet at regularly scheduled executive sessions, without the inside directors present. Meanwhile, the Sarbanes-Oxley Act, enacted in response to the Enron scandal, requires that a corporation’s critically important audit committee be comprised entirely of outside directors. In other words, an apparent lesson to be learned from recent corporate board reforms is that the outsiders on a board require sufficient opportunities to act independently and flex their muscle. Accordingly, rather than just adding more nonaffiliated members in the meeting room, a more important step may be to change an IRB’s procedural rules to treat the nonaffiliated members as a quasidistinct organ, capable of autonomous deliberation and action. Nonaffiliated IRB members might be required periodically to deliberate and discuss in closed sessions, without the chilling presence of inside scientist members. Alternatively, it may be necessary to split the IRB itself into two distinct groups, with certain critical oversight functions assigned to the outside faction alone.

Enhanced IRB Review of Financial Conflicts of Interest

Many institutions, in part to comply with federal agencies’ conflict of interest rules, have established distinct conflict of interest committees (COICs) to deal with recurring issues of financial conflicts of interest for institutions and investigators. Despite the use of COICs, current trends are pushing IRBs to do much more about financial conflicts of interest in medical research. The NBAC recommended that IRBs investigate financial arrangements as part of regular protocol review, while numerous academic commentators call for more direct involvement of IRBs in monitoring financial conflicts. In addition, new guidance from the Department of Health and Human Services envisions considerable expansion of IRBs’ traditional limited role in financial conflicts monitoring. Even at institutions that make use of COICs, the new guidance gives IRBs considerable discretion and encouragement to address financial conflicts in their own protocol reviews, supplementary to and wholly apart from COIC analysis of the financial ties.

The corporate board experience cautions that tasking IRBs with an increased role in this area may prove disappointing. Empirical studies of corporate board action in monitoring financial conflicts, such as in setting the CEO’s compensation, indicate that a critical mass of independent directors in the boardroom corresponds with, and may be a necessary condition for, effective board action. Indeed, the evidence is mixed at best as to whether even boards with more outside directors adequately police financial conflicts. In the recent Enron debacle, a board comprised overwhelmingly of outside directors nonetheless performed dismally in monitoring financial conflicts of interest for key senior executives within the company. Financial conflicts monitoring puts great personal strain on corporate directors, as they run the risk of appearing to be disloyal to or untrusting of fellow peers when challenging a manager or director over a financial conflict. Because social interdependence can seriously inhibit effective oversight of financial conflicts, a strong, viable independent faction on the board seems necessary to do this type of monitoring. Moreover, effective oversight requires that a corporate board develop pockets of expertise and sufficient resource capacity in this area by including directors experienced in reviewing compensation packages and similar matters.

The corporate board experience with financial conflicts of interest does not bode well for IRBs. As currently comprised, IRBs have few
nonaffiliated members. Meanwhile, financial ties to industry already compromise the potential objectivity of many of the affiliated members, as estimates are that nearly half of all medical school faculty IRB members have served as consultants to pharmaceutical and medical device companies.\textsuperscript{43} Moreover, serious, credible financial conflicts review will require that IRB members have a sophisticated understanding of complex economic arrangements—such as licensing rights, stock options, and royalty-based payments—that increasingly help fund clinical research. IRB members must have this knowledge in order to assess the relative intensity of potential financial conflicts. Yet many IRBs simply do not have this expertise to draw upon from their typical membership.

The corporate board perspective suggests that it makes much more sense to leave the lion’s share of financial conflicts monitoring not to IRBs, but to wholly separate institutional conflict of interest committees. As part of the IRB review of informed consent procedures, IRBs will want to review financial ties to consider what research subjects should be told about financial conflicts, but it seems unwise to expect IRBs to be effective in doing much more. Indeed, the corporate board experience serves as a warning about the need to avoid too many mandates and diffuse agendas, as this can make IRB work conflicted, frustrating, directionless, and lead to dysfunctional organizational dynamics. Analyses of corporate boards reveal that it is important to respect board capacity and recognize that boards need sources of support, pockets of expertise, defined goals, and open communication flows to function well. Moreover, the overall effectiveness of corporate boards often has been undercut by the imposition of additional monitoring obligations.\textsuperscript{46} These considerations suggest that giving IRBs greater responsibility for monitoring financial conflicts could make their work more strained, burden their nonaffiliated members, and lead to dysfunctional behavior.

Conclusion

There are valuable insights from the world of corporate boards that can be applied to thinking about IRB reform.\textsuperscript{47} IRBs and corporate boards are expected to function as very complex oversight bodies, yet neither are designed to perform this task effectively. Recognizing that IRBs share many problematic features seen in corporate boards should make clear that simple solutions for changing IRB dynamics and performance are difficult to prescribe. The corporate board experience indicates that powerful forces can impede reform efforts to improve the board’s oversight activities. Certain board behaviors are hard to control and are resistant to quick-fix changes, given the fundamental insularity and autonomy of these institutions.

The corporate board perspective does not mean that we must be complacent about current IRB operations or regard reform initiatives as unwelcome. However, in developing reform proposals, greater consideration should be given to the organizational dynamics and functional constraints that IRBs share with corporate boards. Further comparative analysis could prove useful to enrich our understanding of IRBs’ capabilities and envisioning possible alternative futures for IRBs. For example, the effects of mandatory limited tenures for corporate directors, the ability of the corporate board to hire its own expert staff of advisors, or how corporate boards make effective use of independent audit committees would be possible further areas of study of considerable interest to the IRB community.

Perhaps most important, the corporate board experience reminds us to reconsider IRBs in a fresh, different light. As with corporate boards, an IRB’s ultimate success is dependent upon organizational ability, neutrality, expertise, culture, and training. IRB reform proposals that simply assign more tasks when IRB members run the risk of work overload, potential bias, conformity pressures, or gaps in expertise will likely disappoint. Whatever direction IRB reform takes, careful attention to the corporate board perspective offers a more nuanced, balanced understanding of an IRB’s capacity and limits as an oversight institution.

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References


20. See ref. 8, Dallas 1996.


25. See ref. 12, Mello et al. 2003.


31. See ref. 9, Lin 1996.

32. See ref. 4, Forbes et al. 1999.

33. See ref. 4, Johnson et al. 1996.


35. See ref. 27, Porter 1986.


37. 13 USC Section 78J-1.


42. See ref. 8, Dallas 1996.

43. See ref. 9, Lin 1996.

44. See ref. 2, Senate Permanent Subcommittee on Investigations of the Subcommittee on Governmental Affairs 2002.


Balancing Privacy Protections with Efficient Research: Institutional Review Boards and the Use of Certificates of Confidentiality

In recent years, Institutional Review Boards (IRBs) have focused with increasing intensity on privacy interests and data protection in their review of human subject research. Proper storage and use of individually identifiable research data have long been required by federal regulations and ethical codes, but recent legislative activity—including the enactment of the Health Insurance Portability and Accountability Act (HIPAA)—has heightened awareness of the need to protect health information. These stringent protections and increased scrutiny reflect a societal conviction that health data, including those collected for research purposes, are among the most sensitive types of personal information.

Yet, despite the value of these comprehensive new protections, there are important definitional limitations to their application in the research context. Identifiable research data that are not considered Protected Health Information (PHI) are not protected under HIPAA. In addition, data collected and used outside of a covered entity, or data that are subpoenaed for law enforcement purposes, fall outside of the legal protections of the HIPAA Privacy Rule. Absent additional safeguards, the potential for improper disclosure of sensitive research information may still place subjects at risk for social stigmatization, discrimination, or criminal prosecution.

This article will analyze the role of IRBs in mandating the use of Certificates of Confidentiality as one such additional safeguard to protect subject privacy. Certificates of Confidentiality provide protection against compelled disclosure of individually identifiable research data. As such, they offer nearly absolute privacy protection to subjects of biomedical, behavioral, clinical, or other research. The benefits of the protection accrue both to subject and researcher and include: 1) reduced risk to subject privacy; 2) improved data quality through provision of more accurate information; and 3) promotion of research on sensitive topics such as drug abuse, sexual behavior, or violence.

Along with these benefits, however, come certain procedural constraints that militate against their widespread use. Certificates of Confidentiality are a discretionary measure: their protection does not automatically adhere to studies that cross a specific risk threshold, but must instead be obtained through an application process. For studies where confidentiality risks are substantial, IRBs may require the investigator to obtain a Certificate as a condition of protocol approval. The application process can take several months to complete and constitutes an administrative burden for the researcher; it may also delay the initiation of research. Moreover, it is often unclear whether research data actually warrant the Certificate, and IRB requirements to obtain the protection may appear heavy-handed or arbitrary.

Because of these procedural constraints, IRBs should require confidentiality certificate protection as a condition of protocol approval only after a rigorous assessment of the factors that impact subject privacy risk. This paper proposes a framework to aid IRBs in carrying out this deliberative process. Under this framework, confidentiality certificate protection should be mandatory only when the IRB has determined that: 1) the risks of compulsory disclosure are greater than minimal; 2) the research could not otherwise be carried out; and 3) existing legal safeguards do not provide adequate data protection. If these standards are systematically applied, IRBs can ensure an adequate measure of respect for subjects’ privacy and confidentiality consistent with an efficient system of human subject research.

The Scope of Protection

Certificates of Confidentiality are designed to prevent consequential harms associated with compulsory legal disclosure of identifiable research data. However, the scope of the coverage has evolved significantly over time. First established under the Comprehensive Drug

Abuse Prevention and Control Act in 1970, the initial protection was limited to identifiable research data on the use and effects of illegal drugs. Legislation in 1974 expanded confidentiality certificate coverage to mental health research in general, including studies on use of alcohol and other psychoactive drugs. Currently, the Public Health Service Act authorizes the Secretary of the Department of Health and Human Services (DHHS) to issue confidentiality certificates to protect any research, whether funded by DHHS or not, where confidentiality is deemed essential for producing valid and reliable information.

Although Certificates of Confidentiality provide comprehensive privacy protections, they also carry limitations that researchers and IRBs should recognize. By definition, the protection from court-ordered disclosure applies only to identifiable data. There have been several cases in which courts have granted subpoenas for confidential research data with the caveat that the data be provided in de-identified form. In these cases, an appropriate compromise between subjects’ privacy rights and the truth-finding function of the courts was reached. However, depending upon the volume of data in question, the process of de-identification may place an onerous burden on the researcher and his or her institution.

In addition, Certificates of Confidentiality allow researchers to shield subjects’ identities from compelled disclosure, but do not require them to do so. As such, they cannot defend against voluntary disclosure of identifiable research data. There is a small body of evidence indicating that some investigators are unfamiliar with confidentiality certificate protection altogether, while others may not fully understand its scope. It should not be assumed that investigators who obtain Certificates of Confidentiality are prepared to respond to subpoena requests. Nor can Certificates of Confidentiality reduce privacy risks deriving from some other aspect of the study design, such as inadequate data security measures. IRBs have a central role to play in educating researchers about the purpose and scope of the protection and in ensuring that the broader confidentiality requirements outlined in the Common Rule are met.

IRB Assessment of Confidentiality Risks

The prospective assessment of research risks is a core IRB function, identified in the Belmont Report and federal regulations as critical to the protection of the rights and welfare of human subjects. It has been noted, however, that IRBs may be poorly equipped to evaluate the complex legal and ethical dimensions of privacy and confidentiality rights. Unlike Privacy Boards, which must at least possess “appropriate professional competency as necessary to review the effect of the research protocol on the individual’s privacy rights and related interests,” IRBs are not required to include privacy experts among their members. Risks to privacy and confidentiality often carry important legal implications for subjects, researchers, and institutions. IRBs are in need of guidance on how to anticipate and respond to these types of challenges.

Federal regulations, guidance, and training documents offer little assistance to IRBs in how to measure and evaluate the risk of privacy-related harms that can occur in human subject research. Both the Common Rule and Food and Drug Administration (FDA) regulations charge IRBs with ensuring “adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data,” but neither establishes criteria to assess the adequacy of protection. The National Institutes of Health (NIH) Computer-Based Training Course for IRB Members notes that “more elaborate [confidentiality] procedures may be indicated in studies in which data are collected on sensitive matters,” but it does not propose an explicit standard for IRBs to use in adjudicating the need for extra protection. In contrast to biological harms—which may be more easily quantified and supported by known models of causation—it is often difficult to predict the risk to subject privacy interests.

One approach to this problem has been the use of a “sensitivity” typology for research data: certain categories of data are classified as sensitive and may therefore be eligible for extra privacy protections. This strategy is advocated by the NIH, which provides a list of research domains that might be eligible for confidentiality certificate protection. Common categories of sensitive data include information about:

- Mental health;
- Socially aberrant behavior (e.g., child abuse, criminal behavior, violence);
- Alcohol or other drug use;
- Reproductive behavior and health (e.g., infertility, pregnancy, egg or sperm donation, abortion);
- Sexual orientation, attitudes, practices, and functions;
- Sexually transmitted diseases, including HIV/AIDS;
- Genetic information or tissue samples; and
- Medical or other personal characteristics that, if released, might be damaging to an individual’s financial
standing, employability, or reputation within the community or might lead to social stigmatization or discrimination.\textsuperscript{33}

These categories offer a useful compilation of the types of data that are regarded by the public as especially sensitive. However, they do not provide an operational framework for IRBs to use to determine when Certificates of Confidentiality should be required. The categories are highly inclusive, potentially covering many studies that do not warrant extra protection. Conversely, the same categories may exclude information that some find to be sensitive and feel should be protected. In affirming this view, a DHHS Task Force on the Privacy of Private-Sector Health Records stated

it is appealing to classify information according to sensitivity, [but the Task Force] questions whether this is the most effective approach to protecting data that may potentially cause harm to an individual . . . . In addition, the definition of what constitutes a sensitive medical record may differ from decade to decade and individual to individual.\textsuperscript{24}

A more nuanced and rigorous methodology is therefore necessary to ensure appropriate and effective use of Certificates of Confidentiality.

Recommendations for a Deliberative Framework

In their review of human subject research, IRBs must strike an appropriate balance between the rights and interests of individual subjects and the potentially competing interests of other individuals and society generally. The nature and degree of protection that should be accorded to subjects’ interests in privacy and confidentiality can range widely and are among the most significant questions to be addressed in the review process. The following recommendations are intended to guide IRBs in determining whether Certificate of Confidentiality protection should be required.

\textbf{Recommendation 1: Structured Risk Assessment.} IRBs should adopt a structured approach to assessing privacy risks, including the systematic evaluation of:

1) the magnitude of potential harms caused by compulsory disclosure; 2) the probability of compulsory disclosure; and 3) whether the risk of compulsory disclosure is greater than minimal.

At its most basic level, risk assessment involves identifying the magnitude of possible harms and then ascribing a probability to each of them.\textsuperscript{35} With regard to Certificates of Confidentiality, this raises two immediate concerns for IRBs: how to identify the magnitude of confidentiality-related harms, and how to assign likelihood to their occurrence. Ideally, these concerns could be addressed within an objective framework informed by empirical data on the frequency and degree of previous confidentiality harms in research. IRBs could then anticipate the magnitude of future harms according to factors such as the amount of damage caused, the duration of the harm, the permanency of its consequences, and the extent to which it had the potential to alter or affect subjects’ lifestyle.\textsuperscript{36} In this ideal scenario, IRBs could also use existing data to derive a reasonable estimate of the probability that such harms would re-occur.

Unfortunately, little, if any, empirical research has been done to evaluate the magnitude or frequency of harms resulting from compelled disclosure of identifiable research data. Instead, investigators and IRBs are required to draw inferences from a rather spotty historical record. One of the few studies to investigate the use of Certificates of Confidentiality found that “None of our respondents described an attempt by third parties to access data that were thwarted by the COC, and it is not clear whether, or how often, litigation might have been initiated in the absence of a COC.”\textsuperscript{27} In addition, there has been only one documented court case in which a Certificate of Confidentiality was used to prevent disclosure of identifiable research data.\textsuperscript{28} In this case, the New York State Court of Appeals upheld the Certificate of Confidentiality protection, but only by a narrow four to three margin. This paucity of data limits the utility of an objective approach, requiring IRBs to rely heavily on subjective risk estimates.

That IRBs should be required to make subjective judgments when identifying the magnitude and probability of confidentiality-related harms does not constitute an insurmountable hurdle, however. IRBs should take a systematic approach to subjective evaluation of risks through consistent application of a common methodology, such as a numerical ranking scale. This suggestion has been made elsewhere by Eric Meslin regarding a global assessment of research-related risks; however, Meslin’s approach could be specified to guide judgments about risks relating to compulsory disclosure of identifiable subject data.\textsuperscript{29} In cases where an empirically-based objective approach is limited or impossible, the magnitude of potential harms should be ranked according to members’ subjective perception of the severity of the harm (e.g., on a scale of one to ten). Subjective probability estimates should also be ranked in similar fashion. This process ensures that discrepancies between mem-
bers will not be overlooked and promotes a more rigorous, comprehensive analysis of risk.\textsuperscript{30} Once the assessment is completed, what level of confidentiality risk should be tolerated by IRBs? Both the Common Rule and Privacy Rule articulate a definition for minimal risk research that can be utilized as a practical standard for assessing the need for confidentiality certificate protection.\textsuperscript{31} Under this definition, privacy risks comparable to those encountered in daily life or during the performance of routine physical or psychological examinations or tests are categorized as minimal and warrant a lesser degree of scrutiny. Conversely, privacy risks that cross this threshold demand closer analysis and will generally require additional protective measures. This definition does not create a precise boundary between minimal and greater than minimal privacy risks, but it does establish a workable one. Most subjects and IRBs should be aware of the types of sensitive personal information that are shared through routine social transactions and the context in which such transactions occur. As Freedman and colleagues have noted, “if we are unsure whether [particular risks] belong within the set of common risks then they don’t.”\textsuperscript{34}

Two case examples demonstrate the practical application of the risk assessment model outlined above. These cases are intended to be illustrative rather than paradigmatic; ultimately, risk assessment must be tailored to the specific context of each individual research proposal.

Case 1: The IRB reviews a protocol designed to assess the safety and efficacy of a new chemotherapy agent in patients with breast cancer. The therapeutic study will be conducted at a university medical center and subjects will be recruited from throughout the United States. At various points during the study, subjects’ urine will be collected to screen for a variety of exclusionary criteria, including illicit drug use. Data will be recorded in identifiable form and will be included in subjects’ medical records.

This study plans to collect sensitive information about subjects’ use of illicit drugs, which should certainly alert IRB members to the possible need for a Certificate of Confidentiality. The magnitude of potential harms associated with compelled disclosure of a positive test result—including loss of employment or criminal prosecution—is also great. However, the probability that such harms will occur is low. In the context of a therapeutic trial, expectations of privacy for patients’ medical information (including protection from subpoena) are supported by existing federal, state, and local law, as well as institutional policy and professional codes of conduct. The hospital may also employ legal staff who could assist in quashing a subpoena. Finally, the overall privacy risk associated with participation does not exceed the minimal threshold. Routine physical and psychological examinations address many sensitive matters, including drug use, which would harm patients if publicly disclosed.\textsuperscript{33} Drug testing is also regularly carried out in various domains of daily life: for example, many employers require job applicants to submit to a drug test before they can be hired. Due to these factors, the IRB could choose to approve the research without requiring a Certificate of Confidentiality.

Case 2: Investigators plan to study the effectiveness of a needle exchange program on disease transmission among intravenous drug users (IDUs). Subjects will be recruited from homeless shelters and through word-of-mouth advertising. Among other procedures, subjects will be asked to complete a self-report survey on drug use and will undergo a urinalysis. The study is nontherapeutic, although subjects will be assisted in gaining access to rehabilitation programs.

The sensitivity of the information in Case 2 is comparable to that in Case 1, as is the magnitude of potential harms. However, the privacy risks associated with participation in Case 2 are substantially different. The subject population consists primarily of homeless IDUs, a vulnerable group that engages regularly in illegal activity (the purchase and use of drugs) and may be a target for law enforcement. Consequently, these individuals face a greatly increased probability of compelled disclosure. In addition, because of the non-therapeutic nature of the research, existing legal protections for the research data are virtually nonexistent. These circumstances raise the risk of participation above those encountered in daily life, thus providing a compelling rationale for the IRB to require that a Certificate of Confidentiality be obtained before the research can begin.

Recommendation 2: Research Feasibility. IRBs should assess whether the research can be practically carried out without confidentiality certificate protection.

It was in response to research feasibility concerns that Congress established confidentiality certificate protection in 1970.\textsuperscript{34} Prior to this date, drug users would not provide information about their illegal activities to researchers due to the perceived risks of incrimination.\textsuperscript{35} Subjects’ unwillingness to participate effectively stymied efforts to research an important health policy issue.

The IRB’s primary concern when assessing feasibility is a utilitarian one: are confidentiality protections suffi-
cient to attract a large enough pool of subjects who will provide accurate, quality information? Depending upon the study design, the concept of “large enough” will be defined differently. In quantitative research with a formal hypothesis, the required sample size should be clearly identified by a power calculation. Other research paradigms use different sample size criteria, but still require adequate numbers of subjects to ensure a rich and complete set of data. In either case, determining the adequacy of proposed confidentiality procedures requires IRBs to make complex judgments about the experiences and beliefs that potential subjects will draw upon when considering participation. Studies that solicit subjects whose social position is marginal (such as undocumented immigrants or criminals), or that request especially sensitive data, may be more likely to encounter recruitment difficulty in the absence of extraordinary privacy protections. IRBs should draw upon their own members’ knowledge and experience when evaluating whether this difficulty will compromise the feasibility of the research; if the relevant expertise does not exist within the IRB, it may be necessary to consult with outside experts. IRBs also need to question investigators about their own experience with the proposed subject population to identify whether Certificates of Confidentiality have been necessary in the past. Prior recruitment patterns may not predict future results with absolute certainty, but they can contribute substantially to IRB deliberations.

It is important to emphasize that a determination of research feasibility should not obscure an IRB’s concomitant obligation to ensure that subject confidentiality is protected more generally. For example, there might be subjects who would willingly consent to participate in a study with extremely high privacy risks even without a Certificate of Confidentiality in place—such a study would therefore satisfy the feasibility criterion. However, IRBs still must ensure that the social value of the research they review, and the nature and extent of the benefits they expect to accrue, are in reasonable relation to the risks associated with participation. The combination of high privacy risks and insufficient protection might therefore preclude IRB approval of the hypothetical study described above.

- **Recommendation 3: Existing Protections.** IRBs should evaluate existing legal protections, as well as the types of information eligible for these protections, when considering whether Certificates of Confidentiality should be required.

Although Certificates of Confidentiality offer a powerful protection for study data, they are not the only means to safeguard subjects’ privacy interests. Health information has been the focus of intense scholarly and legislative activity in recent years, culminating in the new federal privacy protections under HIPAA. Federally funded drug or alcohol treatment centers must maintain the confidentiality of patient records in accordance with strict federal rules. Privacy protections are also legislated at the state level through medical and other professional practice acts, hospital and institutional licensure laws, and, in some cases, comprehensive medical information statutes. Other disease-specific state laws create a loose web of privacy protection for conditions such as HIV infection or AIDS. The majority of states acknowledge a common law duty of confidentiality applying to certain health care professionals. Under this duty, if a patient discloses personal information to a health care professional with an expectation of privacy, the professional may be liable if the information is later disclosed without the patient’s consent.

A small number of states have passed laws protecting researchers from unjustified subpoenas. For example, New Hampshire protects data “obtained for the purposes of medical or scientific research by the commissioner [of Health and Human Services] or by any person, organization or agency authorized by the Commissioner to obtain such data.” Minnesota and Michigan have similar laws regarding health research. While these protections are not universal or absolute (for example, nonmedical data are generally not protected and federal courts may choose to override state laws), they do constitute an important tool for IRBs to consider in their evaluation of proposed research. Such protections could significantly reduce the privacy risks to subjects and could eliminate the need for extraordinary confidentiality measures.

**Conclusion**

Research subjects have the right to expect, and IRBs have the obligation to provide, assurances that identifiable research data will be confidential and secure. The success of the research enterprise depends in large part on the integrity of information and the confidence of the public that private information will be vigorously protected. Due to the protection they afford, Certificates of Confidentiality are an important mechanism to help achieve this objective. However, their use must be supported by a rigorous IRB assessment of research design
and privacy risks. The framework outlined in this paper is intended to systematize this deliberative process and to ensure that IRB requirements for extra confidentiality protections are appropriately justified.

Acknowledgments

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References

   2.  45 CFR 164.512.
   3.  45 CFR 160.103; 45 CFR 164.512.
   4.  Public Health Service Act 301(d) 1988.
   5.  The exceptions to this protection are few and reasonably well defined. They include: audit by federal research sponsors; FDA audit of studies involving Investigational New Drug or Investigational Device Exemptions; and requested disclosure by the subject. Studies with Certificate of Confidentiality protection may be exempt from disease reporting requirements, per NIH policy. See Mason JO. Memorandum, "Certificates of Confidentiality—Disease Reporting." August 9, 1991. http://grants.nih.gov/grants/policy/coo/cd_policy.htm.
   7.  The NIH issues the majority of Certificates of Confidentiality. However, other DHHS agencies, including the FDA and CDC, are also authorized to grant the protection.
   11.  42 CFR Part 2a; 42 USC 241(d).
   18.  45 CFR 164.512; The regulations require only "the professional competence . . . to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice" (45 CFR 46.107).
   20.  45 CFR 56.111(a)(7).
   22.  Although Certificates of Confidentiality are issued by many different agencies within DHHS, the NIH has taken the lead in providing information resources about the protections they offer and promoting their use. These resources are compiled online in the NIH Certificates of Confidentiality Kiosk. http://grants1.nih.gov/grants/policy/coo/index.htm.
   30.  It should be noted that the subjective ranking scale approach is intended as a next step—rather than a final solution—in the process of facilitating IRB review in this area. Further empirical research is clearly needed to help categorize confidentiality-related harms more precisely.
   31.  The Common Rule defines minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.104). A similar definition is used to describe privacy risks in the Privacy Rule (45 CFR 164.512).
   32.  See ref. 25, Freedman et al. 1993, p.16.
   36.  45 CFR Parts 160 and 164.
   37.  42 USC 290dd-2(c); 42 CFR 21.2-2.67. These protections apply only to specialized substance abuse treatment facilities and to specialized units within general medical facilities, but not to substance abuse information in general medical records.
Informed Consent: Practices and Views of Investigators in a Multinational Clinical Trial

The attitudes and practices of investigators who engage in the process of obtaining informed consent from research subjects are central both to understanding how informed consent is obtained and to developing methods to improve the process. Although studies have examined attitudes of investigators toward informed consent, few have specifically examined their consent practices. In this study, we surveyed a multinational sample of investigators to determine how much time they dedicate to the consent process, what aspects of the clinical trials they emphasize during the consent process, and what they think about the effectiveness of that process. We also evaluated how they assess subject understanding of the clinical trial and what they do when subjects fail to understand. Finally, we evaluated other factors that are potential barriers to enrolling individuals in clinical trials.

Study Design and Methods

We surveyed principal investigators in ESPRIT (Evaluation of Subcutaneous Proteolikin® in a Randomized International Trial), a multinational, open-label, randomized, Phase III trial evaluating the effectiveness of subcutaneous interleukin-2 (IL-2) in reducing HIV progression over a five-year period. The U.S. National Institute of Allergy and Infectious Diseases (NIAID) is the sponsor of ESPRIT, which takes place in 25 countries, most in Europe and North America.

Subjects are HIV-positive, 18 years or older, have a CD4+ cell count ≥ 300/mm³, and are randomized in a 1:1 ratio to receive IL-2 in addition to standard combination antiretroviral therapy or combination antiretroviral therapy without IL-2. Common side effects, including flu-like syndrome, are associated with IL-2, as is the potential for more serious, life-threatening side effects. The goal of ESPRIT is to compare the effectiveness of IL-2 plus antiretroviral therapy to antiretroviral therapy alone in reducing the rate of disease progression, including death, over five years. The protocol team provided investigators at each site with sample informed consent materials. These materials varied based on recommendations of the reviewing Institutional Review Board (IRB) or Research Ethics Committee (REC), within certain limits set by NIAID.

We developed the survey instrument in conjunction with the National Opinion Research Center (NORC) at the University of Chicago. The instrument was pretested in interviews with five principal investigators from different countries represented in the study. The final instrument consisted of 56 questions, 49 of which were multiple choice. Questions covered the following domains: 1) attitudes, experiences, and satisfaction with the informed consent process and document; 2) experiences enrolling subjects in ESPRIT; and 3) demographic characteristics of the investigators.

We sent self-administered, confidential questionnaires to principal investigators who had enrolled five or more subjects in ESPRIT. The cover letter stated that return of the questionnaire would indicate consent to participate. Investigators who did not respond were sent a reminder and an additional questionnaire. Completed questionnaires were sent to the University of Minnesota ESPRIT Coordinating Center where data were double entered and analyzed.

Data analysis involved the use of descriptive statistics. Dichotomous variables including sex, clinical research experience (involvement in more than the sample median of 13 studies over the past five years vs. 13 or fewer studies), IRB or REC membership, region (European vs. non-European countries), and medical specialty (Infectious Disease vs. other specialties) were examined for associations with six outcomes using logistic regres-
Table 1.
Investigator Demographics (n = 117)

<table>
<thead>
<tr>
<th>Region (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>49.6</td>
</tr>
<tr>
<td>North America</td>
<td>18.0</td>
</tr>
<tr>
<td>South America</td>
<td>12.8</td>
</tr>
<tr>
<td>Australia</td>
<td>12.0</td>
</tr>
<tr>
<td>Asia</td>
<td>6.0</td>
</tr>
<tr>
<td>Gender (M %)</td>
<td>70.9</td>
</tr>
<tr>
<td>Age*</td>
<td>44 (41-50)</td>
</tr>
<tr>
<td>Number of studies over past five years*</td>
<td>13 (6.5-20)</td>
</tr>
<tr>
<td>Number of ESPRIT studies over past five years*</td>
<td>10 (5-20)</td>
</tr>
<tr>
<td>Number of Infectious Disease subjects enrolled*</td>
<td>11 (7-20)</td>
</tr>
<tr>
<td>Infection Disease Specialist (%)</td>
<td>53.0</td>
</tr>
<tr>
<td>IRB or REC member (%)</td>
<td>21.4</td>
</tr>
</tbody>
</table>

*Expressed as median (interquartile range).

Table 2.
Investigators’ Reported Practices Regarding the Consent Process

<table>
<thead>
<tr>
<th>% (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average of more than 30 minutes discussion prior to signing consent form</td>
</tr>
<tr>
<td>Subjects were given their own copy of the consent materials</td>
</tr>
<tr>
<td>Subjects had opportunity to read consent materials before coming to clinic to sign the consent form</td>
</tr>
<tr>
<td>Method used to assess understanding*</td>
</tr>
<tr>
<td>Formal</td>
</tr>
<tr>
<td>Informal</td>
</tr>
<tr>
<td>Clinical judgment</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

* Percentages do not sum to 100 because eight investigators did not respond to this question.

Respondent Characteristics

Of 139 eligible investigators, 117 (73.6%) from 23 countries returned questionnaires by June 2003. Approximately half were from Europe and 71% were male. On average, respondents worked on 16.9 studies over the past five years. Over a fifth have served on IRBs or RECs (Table 1). Most of the investigators (83.8%) served as the primary physician for one or more of the ESPRIT subjects at their site.

Practices and Attitudes

In Informing Potential Subjects.
When asked who spends the most time explaining to potential subjects the purpose, risks, and benefits of the ESPRIT study, 40.2% of investigators identified themselves, followed by nurses (17.1%), other physician investigators (12.8%), and study coordinators (8.5%). An additional 11.1% of investigators self-identified as the person who obtains subjects’ signatures on the informed consent form, even though they do not spend the most time explaining the study.

Just over 84% of investigators said informing subjects was the primary purpose of the informed consent materials, while 12.2% said the primary purpose was to satisfy regulatory requirements. Sixty-nine percent of investigators said discussion is more effective than written materials in informing individuals about a clinical trial; 29.2% responded that both are equally effective. The majority of investigators (65.0%) said they and their teams spent more than half an hour discussing the study with potential subjects, and all but one gave potential subjects their own copy of consent materials to keep (Table 2). At 58.1% of the study sites, potential subjects were given over a week after the informed consent discussion to decide whether to sign the consent form, thereby enrolling in the trial, whereas at 9.4% of the sites individuals were given less than a day to consider the information and make an enrollment decision.

Just over 44% of investigators reported that in their discussions with potential subjects they placed greatest emphasis on the purpose of the study; 26.5% said they gave greater emphasis to the study’s potential benefits, and 20.5% said greatest emphasis was given to potential risks. Fifty-seven percent of investigators said that both common and serious risks were equally important to
Figure 1.
Investigators' Views on How Much Detail Should Be Given in the ESPRIT Consent Materials Regarding Different Aspects of the Study

<table>
<thead>
<tr>
<th>Topic</th>
<th>no detail</th>
<th>minimal amount</th>
<th>moderate amount</th>
<th>great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose of the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation requirements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability of IL-2 after</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meaning of randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensation for injuries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Explain to potential subjects, while 41.0% chose “common but not serious” risks as the most important risks to explain. Ninety percent of investigators said they would have included the small risk of death from IL-2 had they written the consent materials themselves (the risk of death was included in the standard consent form sent to all sites). However, only 46.2% reported discussing the risk of death with potential subjects.

Forty-seven percent of investigators (61.1% of those who responded to an open-ended question about the most difficult topic to explain to subjects) identified side effects or risks as the most difficult part of the study to explain. A number of them found explaining side effects to potential subjects particularly difficult because enrollees had to be relatively healthy and IL-2 is commonly associated with flu-like symptoms, as well as a number of potentially serious side effects. Fifteen percent of all respondents agreed that either randomization or why a patient should enroll in a randomized trial was the most difficult aspect of the study to explain.

Just over 36% of investigators reported placing a great deal of emphasis in their discussions with potential subjects on the fact that half of trial subjects would not receive IL-2. Fewer (44.4%) said they placed a great deal of emphasis on the fact that random assignment is not based on what the investigator thinks is best for the subject individually, and one third (34.2%) on the fact that subjects randomized to the control group would be followed for five years without IL-2.

According to the percentage of investigators who thought subjects should receive a great deal of information about a certain topic, the meaning of randomization rated sixth out of eight topics (Figure 1).

Assessing Understanding and Enrolling Subjects. The most common method investigators used to assess potential subjects’ understanding of ESPRIT was an informal approach such as asking, “Do you understand what I’ve told you?” (65.8%) (Table 2). All of the respondents believed that in general, potential subjects at their sites understood the study, with half (52.1%) reporting that potential subjects generally understood the study very well. If a potential subject did not demonstrate understanding after reasonable efforts at explanation, 80.3% of respondents said they would not enroll the individuals, while 15.4% said it would depend on the circumstances.

Sixty-five percent of investigators encountered at least one potential subject who was eligible for ESPRIT and wanted to enroll, but whom they thought should not enroll. Of these investigators, 71.0% explained their hes-
itation, with 40.0% of them expressing concern about possible noncompliance with protocol requirements, based on facts about the individual's past compliance, past or present drug and alcohol abuse, or mental health status. Almost as common were concerns about physical health (32.8%), followed by concerns about mental health or social situations, including a history of substance abuse (31.4%). When the 65.0% of respondents who reported encountering individuals who should not be enrolled were asked, “What do you do in this situation?” 50.0% said they do not let the individuals enroll in the study, 38.1% said they try to talk the individuals out of enrolling, 17.1% reported soliciting the opinion of another investigator, and one person said he or she allows the individuals to enroll.

Investigator Characteristics and Practices.
Multivariate analysis showed no significant association between investigator practices and region, gender, medical subspecialty, or IRB/REC experience. The only factor that was predictive of investigators’ behavior was past research experience. Investigators who had been involved in more than the sample median of 13 studies over the past five years were significantly less likely to give potential subjects more than a week to consider the information. Twenty-one percent of 57 investigators with experience in more than 13 studies gave potential subjects more than a week, whereas 40.7 percent of 54 investigators involved in 13 or fewer studies over the past five years were more likely to give subjects more than a week (odds ratio 0.34, 95% confidence interval 0.13 to 0.89). The more experienced group was also significantly more likely to report that in their discussions with potential subjects, they gave little or no emphasis to the fact that randomization is not based on what the investigator or another physician thinks is best for the subject. Fourteen of 57 investigators involved in more than 13 studies over the past five years (24.6%) reported placing little or no emphasis on this idea, whereas seven of 54 involved in 13 or fewer studies (13.0%) reported placing little or no emphasis on the idea (4.27, 1.20 to 15.22). Investigators with more research experience were also more likely to consider enrolling subjects who lacked understanding about the clinical trial (P = 0.06).

Discussion
To our knowledge, this is the first published account of the informed consent practices of a multinational sample of investigators. We were able to meaningfully compare investigators’ practices because those surveyed were working on the same study in different countries around the world. Investigators from different geographical regions appear to conduct the informed consent process in a similar manner. They reported dedicating a considerable amount of time to the informed consent process and viewed the process as effective. In their view, potential subjects understood the information presented to them. Thus, investigators did not view lack of understanding as a major barrier to enrolling subjects in ESPRIT.

Attitudes of ESPRIT investigators toward informed consent seemed more positive than those of physicians in previous studies, who viewed consent as an impediment or intrusion into their relationships with patients being recruited to participate in clinical trials. It is generally accepted that the primary purpose of informed consent is to enable potential subjects to make an informed choice about whether to enroll in a trial, and the vast majority of investigators we surveyed recognized this purpose. Their responses suggest that they understand the need for informed consent and believe they conduct the process effectively.

We discovered some divergence between aspects of the study that investigators agreed were important to disclose and what they reported focusing on in their discussion with potential subjects. Although nearly 90% said they would have included the rare risk of death from IL-2 in the written consent materials (which was included), only 46% reported discussing the risk of death with potential subjects. Yet almost all of the investigators said discussion is more effective than or equally as effective as written materials in informing potential subjects about the potential risks and benefits of trial participation. Perhaps investigators were uncomfortable with any discussion about death or with the prospect that discussing the risk of death would result in fewer enrollees. It’s also possible they thought the matter was not important to discuss, or that it was sufficient to include the risk of death in the consent form without further discussion. For whatever reasons, investigators who acknowledged that it is important for potential subjects to know about the risk of death still avoided discussing the matter. Similarly, many investigators responded that it was difficult to explain the potentially non-lethal, serious side effects to potential subjects. Investigators may have found talking about death and other serious side effects to be stressful or uncomfortable because enrollees had to be relatively healthy, and most were asymptomatic.
Previous studies have shown that randomization is one of the hardest aspects of study design for subjects to understand. Yet, of eight topics given to investigators in this study, more respondents said potential subjects should receive a great deal of information about each of five other topics than said potential subjects should receive a great deal of information about randomization. Further, most investigators did not emphasize the idea that randomization means subjects’ treatment is not chosen by a physician determining what is best for each individual subject. Why they failed to place greater emphasis on randomization is unknown. Perhaps they believe this complex topic is too difficult for potential subjects to understand. Alternatively, they might place less emphasis on discussing randomization because they are uncomfortable explaining the topic, they think it is not an important topic, or they are afraid that potential subjects will decline to enroll because they don’t want to be randomized to the noninvestigational arm of the study.

In contrast to earlier studies, a majority of investigators said they would not enroll individuals who they thought did not understand the details of the study. This was not a major issue for ESPRIT investigators because they generally thought that potential subjects had a good understanding of the study. Indeed, while we expected to find that lack of understanding about randomization would be the most common reason for refusing to enroll individuals, investigators indicated that the primary reason was concern about subject noncompliance with the protocol. When subjects fail to comply with a trial’s protocol, the study’s scientific validity may be compromised. This puts other subjects who have benefited from effective treatments derived from the study at a disadvantage. Moreover, noncompliance with scheduled study visits, safety labs, or other aspects of the trial could be harmful to the individual subject. A key feature of ESPRIT is its five-year duration, which made participant compliance particularly important. A number of investigators based their concern about noncompliance on the psychosocial history of potential subjects, including past psychological, social, or substance abuse issues. Making medical treatment decisions on the basis of these and other factors is not uncommon, though whether it is justified in both the clinical and research context requires more inquiry.

Unexpectedly, investigators with more research experience gave potential subjects less time to consider information and emphasized randomization less. Experienced investigators may believe that spending additional time and effort to explain complex topics is futile and unnecessary. Their practices might also reflect confidence in managing enrolled subjects without additional time explaining the study.

Our study had a number of limitations. The survey focused on the consent materials and process used in ESPRIT. Investigator responses might differ if asked about the informed consent materials and process for a different study or in general. It is also possible that self-reported practice differs from actual practice and that investigators’ assessments of factors such as subject understanding were inaccurate. The survey instrument was in English, which might have made it difficult for some respondents whose primary language is other than English to fully comprehend the questions. Further, while there is a wide range of geographical diversity in this study, the majority of respondents work in developed nations. Thus, the views presented may not be representative of the views of investigators in developing nations.

In general, investigators in this study viewed the informed consent process as important and effective. Future studies should examine strategies for explaining randomization; observed, rather than self-reported, informed consent practices of investigators; the ethics of refusing enrollment to potential subjects based on worries about noncompliance; and the effects of variation in the consent process on potential subjects’ follow-up regarding enrollment.

Disclaimer

The opinions expressed are the authors’ own. They do not reflect any position or policy of the National Institutes of Health, the U.S. Public Health Service, or the Department of Health and Human Services.

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Human Subjects Protection

The IRBs at the National Institute of Allergy and Infectious Disease and the National Opinion Research Center approved this study.

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References


3. See ref. 1, Taylor et al. 1987; see ref. 2.


ANOTATIONS

Resnik DB. Eliminating the daily life risks standard from the definition of minimal risk. Journal of Medical Ethics 2005;31:135-38. • Resnik shows that defining what constitutes minimal risk involving human subjects research is difficult because federal research regulations do not provide clear guidance. Consequently, IRBs have difficulty applying the "daily life risks standard" required by the regulations in determining whether risks associated with a study are minimal. The variability that results in defining minimal risk is problematic because the concept of minimal risk is a threshold for requiring whether certain studies require informed consent and whether certain vulnerable populations can participate in research. In order to clarify the concept of minimal risk, Resnik proposes eliminating the "daily life risks standard" from the definition and defining minimal risk as "the risks associated with routine physical or psychological exams." He contends this definition is more likely than the current regulatory standard to promote fairness in subject selection and consistency across IRBs in determining whether studies constitute minimal risk.

Sugarman J, Lavori PW, Boeger M, Cain C, Edson, R, Morrison V, Yeh SS. Evaluating the quality of informed consent. Clinical Trials 2005;2:34-41. • The authors developed and tested an instrument to measure the quality of informed consent. After recruiting participants from a parent clinical trial, Sugarman et al. conducted interviews using what they call the Brief Informed Consent Evaluation Protocol (BICEP). Based on the results of the interviews, they developed two summary scores, the Informed Consent Aggregate Score (ICAS) and the Therapeutic Misconception Aggregate Score (TMAS). Ninety-nine percent of respondents reported they were completely or somewhat satisfied with the informed consent process. Although 89% said the parent study addressed a research question, a third of participants mentioned a direct benefit from participation and 8% said the study was directed at an outcome that would benefit them. Moreover, nearly half of respondents apparently did not have a clear understanding of the voluntariness of continued participation. The authors suggest comparing findings from studies using BICEP with studies using other approaches in assessing the informed consent process to ensure that informed consent is meaningful.
A Multi-Faceted History

Readers of IRB have some sense of the history of human experimentation in the twentieth century. For many, it is a chronological recounting of infamous milestones beginning with the atrocities of Nazi Germany and progressing through stories and scandals—Walter Reed's yellow fever experiments, the so-called Tuskegee Syphilis Study, Willowbrook, Jewish Chronic Disease Hospital, and so on. This is a mostly contemporary history that we can recite from memory like the received truth it has become.

Like so many other things, there is more than one way to see the history of human experimentation. The editors and contributors of Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century want us to think more broadly about that history. As the title implies, the collection of eight chapters in this edited volume focuses on the thesis that what motivated biomedical research in the mid-twentieth century was making (presumably good) use of the bodies of research subjects in the interest of science. That much will be easily recognized by most readers. But the editors frame the history in a longer view. In their coauthored chapter, they claim that the story was not so much one of serving the interests of biomedical science, but a more thoroughgoing relationship among researchers, the state, and the subjects of research:

For by the beginning of the twentieth century, the boundary between science and the state was becoming progressively blurred as medical men and scientists were absorbed into the wider machinery of the state in ever-increasing numbers.

On this view the relationship is more complicated than merely those directly involved in medical research. The broader context of medical research includes the state and its interests, and the question is how far those interests can be pushed at the price of researchers, their research, and most importantly the subjects themselves. The argument in Useful Bodies is that the relationship was hardly one-sided but more hand-in-glove—state interests and researcher interests both fared well in the process, and it is easy to understand why it grew. This consistent thread throughout the chapters allows them separately and together to tell a story of those who performed research, on what kinds of subjects, and for what reasons.

The book's eight chapters are divided into three sections: What is an experiment? Who experiments? Whose body? The sections are useful reminders about the three-part axis around which the editors try to develop the story. They do this in chapters that examine research on germ warfare, neurosyphilis, radiation experiments of various kinds, and hepatitis.

Readers will recognize the examination of how the story of Willowbrook is told and retold and will be introduced to lesser known cases such as biological warfare research on populations in the United Kingdom after World War II.

The chapters are of consistently high quality and each is interesting to read on its own, while fitting well into the overall structure. I am not a historian, but as staff director of the White House Advisory Committee on Human Radiation Experiments, I had the privilege to be immersed in the review of human subject research conducted during the Cold War. This period of the American experience is well-described in the three chapters dealing with that history, and I read them with renewed interest and appreciation.¹

What we learn from a collection of this scope and caliber is that this is a history with many facets. The editors and authors point out that we tend to think about the evolution of protections in terms of consent and the relationship of medical research to clinical care, arguing that this view is not only limited but probably wrong. They propose that a fuller appreciation requires looking at the underlying motives for and implications of justifying research based on its usefulness and the need to use people in the process. It is easy to understand how ethics gets subsumed when human beings become useful cogs in the machinery of experimentation in the interest of the state. I'm persuaded that both are aspects of what is clearly a multidimensional story from which we can profitably learn.

This is a history book that acknowledges the ethical issues that arose in and around the stories that are told, but it isn't a book about the ethics of research. The deeper history it offers is interesting and important to anyone who cares about the ethics of research on human subjects not only as academic information, but as an aid to a more complete understanding. That can only help as we face all the complicated research relationships the twenty-first century is sure to hold.

¹. In the interest of full disclosure, one of the chapters in the book is co-authored by Gilbert Whitemore and Miriam Boleyn-Fitzgerald, both of whom were staff to the White House Advisory Committee.

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Autonomy and Contraception

In “Contraception in Research: A Policy Suggestion” (March-April 2005), Schonfeld and Gordon note that “Respect for persons is violated when investigators insist on an invasive form of contraception (like oral contraception) without regard for the woman’s values, goals, or priorities.” I was, therefore, very surprised at the discussion (or lack thereof) of what constitutes a “reliable form of contraception.” The list given was presented without reference and did not include fertility-awareness-based methods for which numerous studies have shown method efficacy rates comparable or better than the “reliable” methods listed.1 How is autonomy respected when a woman who has successfully used one of these proven methods for years is told she cannot enroll unless she switches to another method?

All methods depend on user compliance, and high failure rates have been reported for the “reliable” methods listed (e.g., up to 70% in adolescents using condoms).2 In addition, there is evidence that failure rates with some methods may be higher in the first six months of use,3 calling into question the wisdom of requiring initiation of a new method coincident with entering a study. Finally, while the notion has face validity, I know of no study that demonstrates improved effectiveness for combinations of the listed methods, as implied in the recommendations for category C and D drugs.

If we are truly to take the autonomy of women seriously, reliable methods must be more carefully defined, and proven natural family planning methods should be included.

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