hours or days instead of the months that can intervene between starting and concluding a research project. The desirable habit of follow-up with a preparedness to react to interval developments in behalf of a patient perhaps sets the stage for what Slatkoff, et al. eventually recognized was a mistaken decision to intervene with patients serving as controls in their study.

Ambiguity and uncertainty are inherent to the nature of primary care, and much of the research that is needed will of necessity grapple with this ambiguity. It seems likely that no amount of anticipation can predict all the variance and unexpected events that will occur during a well-conceived investigation executed in family practice settings. These unexpected events might require responses that readily can be made in the context of a known past and an anticipated future involving patient, clinician, and staff.

So far, much practice-based research has been done without alteration of care and without identification of physician or patient. Data that would have been collected anyway form the substrate for investigation, with the assumption that the consent patients give by seeking care is sufficient and exempts such research from further special procedures. Inevitably, probing beyond descriptions leads to a need for prospective data collection linked to individuals, and more intervention research is needed in family practices. It seems the time has arrived for careful consideration to be given to the mechanisms that should be used to assure research done "among friends" in ongoing relationships is promoted by practical and achievable methods that protect patients who depend upon practices, which are also laboratories.

We suggest that there is a need for further attention to the establishment of standards for the ethical conduct of practice-based research. Not being expert in this area, we suspect such standards will almost certainly replicate much of what has evolved for the rest of medical research. It is possible that on careful reflection, nothing additional will be required. It seems to us, however, that research occurring within the context of an ongoing physician-patient relationship will require some special consideration.

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Planning For The Unknown In Research: Ethical Dilemmas Confronting The Clinician-Investigator

Medical history is replete with examples of ways in which concern about risks and respect for the patient-subject have been allowed to erode in the name of science.[1,2] The recent revelation by the federal government regarding questionable experiments with plutonium on unsuspecting and unconsenting human subjects, particularly in cases where the subjects were considered a captive or disadvantaged class, demonstrates the fragile nature of the moral safeguards supposedly in place for the protection of patients and research subjects. In this issue of *JABFP*, Slatkoff, Curtis, and Coker's thoughtful article highlights at least two difficult problems facing clinician-investigators who enroll their patients in a research study.[3] The first problem focuses on the content of informed consent and the level of knowledge a clinician-investigator should attain about a research project in order to inform the prospective patient-subject fully about uncertainties

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that could materialize during the course of the study. The second addresses conflict of interest issues that confront many clinician-investigators today.

Informed Consent and Unknown Risks

Few ethical and legal issues surrounding the medical profession are as much discussed and as little understood as informed consent. The basic premise of this doctrine is that informed consent must be the willing and uncoerced acceptance of a medical procedure by a patient after adequate disclosure by the physician of the nature of the procedure, its risks and benefits, and the alternatives available with their risks and benefits.[4] Even though considerably less has been written about informed consent in the research setting, there is a clear consensus that a more complete disclosure of information should be required than that required in the clinical setting.[5]

Slatkoff, Curtis, and Coker appear to travel beyond what most institutional review boards (IRBs) and clinician-investigators would feel comfortable with in suggesting that informed consent in research should be based on a comprehension of all ramifications of the procedure in question, including an understanding of the parameters of the unknown risks associated with the study. Focusing too long, however, on the question of unknown risks can quickly cast the clinician-investigator and his or her patient into a sea of confusion. Unknown risks might be considerable in any experimental procedure, and a prospective patient-subject might not have the background to be able to formulate the questions needed for a fully informed consent.

To what extent, then, should a patient be informed about the uncertainties of a study? Is the statement required by Department of Health and Human Services rules and regulations in all government funded research "...that the particular procedure may involve risks to the subject which are currently unforeseeable," sufficient in the situations envisioned by Slatkoff and her colleagues?[6]

The concept of informed consent assumes that the party seeking consent understands the study design, knows whether it is good or bad science, and is prepared to inform the patient-subject fully on the proposed methodologies, the scientific end being sought, and the benefits and risks associated with achieving that end. Does this assumption include unknown risks? Well, yes and no. Yes, if the unknown risks should have been anticipated; that is, they are logically connected or associated with the nature of the study even though unknown at the time. The study set forth in the article in question is a very good example of this connection. There the unknown role of various potential factors, including human papillomavirus (HPV), in the development of cervical intraepithelial neoplasia was the topic of the study, yet HPV was not specifically described in the consent form and, therefore, presumably not discussed with the patients to be enrolled in the study. On the other hand, there are some unknown risks that defy any comprehension or association and fall clearly outside the disclosure requirements of the informed consent process. What is important about this issue is not only the level of competency that should be required of all clinician-investigators who enroll patients in research studies but also the way they go about informing their patients about unknown risks.

Two things are critical here. First, many clinicians and investigators still believe that once a reviewing IRB approves and signs off on the informed consent form, an ethical and legal informed consent is achieved when the form is signed by the patient or patient's surrogate. An informed consent form proves only that consent occurred; it does not prove that consent was informed.[7] It is the process of communication, the explanation of the contents of the document, that satisfies the informed element of consent.

The second thing is dealing with the element of uncertainty that pervades nearly all research studies. Many clinician-investigators fear acknowledging uncertainty to themselves, to their colleagues, and to their patients. As a result, this fear can be carried into the study. For example, many physicians remain unconvinced that they should inform patient-subjects in randomized clinical trials that their therapy will be decided by chance.[5] In Jay Katz's[8] view, the problem posed by uncertainty is not so much how to inform the patient about it but how to keep the existence of uncertainty clearly in mind and not replace it with certainty when one moves from theoretical to practical consideration. Central to this valid premise is the important admonition of the authors that regardless of the nature of uncertainty,

such as unknown risk, the clinician-investigator should be prepared to deal with the problem should it materialize. This preparation includes a clear understanding as to when and how the study will be terminated if the best interests of the patient-subjects are threatened.

Conflict of Interest in Research

The second problem addressed by Slatkoff, Curtis, and Coker interfaces with informed consent and highlights the increasingly important conflict of interest issue facing clinician-investigators today. Without question, the investigator's interest in research has become an important issue from the patient's viewpoint, and Slatkoff and her colleagues should be commended for demonstrating that the problem is always before an investigator, even in a fairly simple and straightforward study.

Generally we think of a conflict of interest arising when clinician-investigators are engaged in research involving a particular drug or medical device, and they receive remuneration from, or own stock in, the company that manufactures the drug or medical device. This area is only one in which a conflict of interest might exist, however. Participating in research offers several benefits to an investigator that are not always beneficial (or obvious) to the patient. It is not unreasonable to suppose that scientific interests, academic reputations, increased prospects for tenure, and institutional pride might not always coincide with the best interests of the patient involved in clinical research.

In response to this difficult issue, the authors mention one possible solution, the establishment of independent data-monitoring committees who are the sole bearers of on-going study results. With such a committee in place, a clinician-investigator could not intervene or terminate a study because of discovery of a superior therapy or significant laboratory findings in epidemiological studies unless authorized to do so by the committee. The desired effect is to alleviate the conflict of interest that some clinician-investigators experience between continuing a study and protecting the best interests of the patient. While establishing an independent data-monitoring committee is an interesting and noteworthy proposition, it has its own problems.

Such a committee, for example, would have no affect on the "real" conflict of interest question. A clinician-investigator cannot assign (and thereby free himself or herself from) the constellation of moral and legal obligations that society imposes on physician-patient relationships or investigator-patient relationships. Given that a patient's best interests not only are basic to the standard of care required of a clinician-investigator from a legal perspective but, more importantly, form the moral core of that relationship, the clinician-investigator will always be charged with the responsibility to intervene in the course of a study if a superior therapy or medical knowledge is uncovered that will prevent the patient from suffering harm. Even if the committee entered into an indemnifying agreement with the investigator, such that the committee would become the primary responsible party much as a principal-agent or master-servant relationship, the clinician-investigator would still remain legally and morally accountable for her or his own acts. In view of this continuing responsibility, it would be quite foolish for any clinician-investigator to surrender the right to terminate a study where the best interests of the patient are at stake. If, however, an investigator does not desire to terminate a study, even though it would benefit the patient to do so, research institutions could have in place proper controls for directing the investigator to do so. This scenario is quite different from being told you cannot intervene on behalf of the patient-subject unless authorized by a committee to do so.

The issues discussed here with respect to clinician-investigators apply to some degree to all medical investigators, because they derive from the underlying ethical obligation to promote the patient's welfare in the best manner possible. To achieve that end today, clinician-investigators must realize that when determining what information about unknown risks should be disclosed, the standards provided in ethical codes and regulations are not particularly instructive. Informed consent to research is a very formal process and involves a complex set of obligations about disclosure of information and education of the patient. To that end, clinician-investigators should strive to develop a comprehensive account of the elements of informed consent for presentation to prospective patient-subjects.

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Designing Research On Health Risk Behaviors: Questioning the Assumptions

The report "Associations with High-Risk Sexual Behavior" in this issue by Steiner and his colleagues[1] raises many issues that invite further discussion and exploration. Certainly, with the rise in rates of persons positive for human immunodeficiency virus (HIV) infection, research on understanding primary prevention of this disease is timely and relevant.

Early attempts at research into the behavioral correlates of population groups with disproportionately high HIV positivity rates initially focused on the information base of the population. Since then, several well-documented studies have reported that information by itself is not sufficient to prompt behavioral change that protects against HIV exposure.[2,3]

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This finding that information is not sufficient to change behavior should come as no surprise. We have, over the years, ample evidence that knowledge of adverse effects of tobacco use, driving while under the influence of alcohol or other drugs, sedentariness, and dietary excessive fat, all of which result in risk to health in the long run, do not predictably motivate persons to change their behavior.

The next question becomes, if information is not enough, what then is needed additionally for individuals to make good decisions about protecting themselves against life-threatening illness?

One of the difficulties of past research in this area is that we have assumed that there is one central reason persons engage in behaviors that jeopardize health. We keep looking for the "magic bullets" that, if discovered, would allow us to design programs which keep populations from taking risks with their health. Unfortunately, the solution is not so simple. There is neither one reason nor one intervention that will address the problem of HIV prevention or the prevention of other diseases when it is within an individual's power to protect his or her health. The reasons African-American men, African-American women, white women, Hispanic women, and others jeopardize their health and expose themselves unnecessarily to HIV are multiple and complex; they are rooted in reasons that can be viewed from three perspectives: the individual perspective, the family or social unit perspective, and a larger societal perspective.

At the individual level, actions about health behavior are influenced by information (both accurate and inaccurate), by the belief that the information pertains to oneself (sense of vulnerability or invulnerability), by the motivation to protect one's health (belief that one's life is worth protecting), and by the freedom and ability to make good choices about health. This latter issue is an area of skill development particularly pertinent for adolescents. Many young persons know the correct information, might or might not believe that it pertains to them, wish to be healthy into adulthood, but lack the interpersonal skills to say "no" to a partner pressing for sexual intercourse without a condom.

At the social unit and family level, the factors that most commonly affect health risk of individuals are peer or group norms (belief and accept-