Draft Framework for Developing Best Practices for Recruiting, Screening, and Informing Human Subjects an Obtaining Consent for Occupational Exposure Studies with Pesticides

March 15, 2007

Introduction

One of the fundamental protections for people who participate as subjects in human research is embodied in the requirement that their choice to participate be both fully informed and fully voluntary. EPA's regulation governing the conduct of third-party research involving intentional exposure of human subjects for pesticides contains provisions that require that all subjects provide written informed consent before participating in a covered study. See 40 CFR §§26.1116, 26.1117. These sections, which closely parallel provisions in the Common Rule, also require that informed consent documents contain certain basic information (§26.1116(a) and (b)) and that investigators obtain written documentation of each subject's consent to participate (§26.1117). These provisions, however, contain broad directions which must be interpreted and applied in the context of specific research proposals to achieve their intent.

Two industry task forces–the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force (AEATF)–are preparing to conduct research to measure exposure received by professional pesticide handlers who mix, load, or apply pesticides in representative agricultural or antimicrobial use scenarios. The Agency believes that investigators undertaking this kind of research need to interpret the general requirements of the regulations and apply them to the specific circumstances associated with this kind of research. To help ensure that people who consider participating in these studies are treated ethically, EPA plans to compile guidance on best practices that investigators could employ to recruit and enroll subjects into this kind of research.

This paper addresses the major elements of ethical recruitment and enrollment and the issues that typically arise during these processes. For each element, EPA discusses broad principles which should be considered in the course of research design. In the future, through a participatory process involving investigators, workers, and other stakeholders, EPA intends to add to the document specific best practices, and to identify publicly available resources that contain additional discussion and guidance relevant to the application of general ethical principles in occupational exposure research.

Overarching Concerns

The remainder of this paper presents a conceptual framework for considering and organizing best practices in occupational exposure studies for pesticides under four broad headings:

- Equitable Subject Selection
- Fully Informed Choice to Participate

- Fully Voluntary Choice to Participate
- Respect for Prospective and Enrolled Subjects

Equitable subject selection

As a condition for approval of proposed research, the IRB must determine that subject selection is equitable. (40 CFR §26.1111(a)(3)). This passage continues:

> In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.

Much of the available guidance on the interpretation and application of this requirement focuses on the potential for inequitable *exclusion* from research of subjects who might benefit from participation in it. This concern is clearly important in the context of medical research which may offer therapeutic benefit to subjects. But in pesticide research with human subjects, participation in the research typically offers the subjects no prospect of direct benefit, so exclusion of potential beneficiaries is unlikely to weigh heavily. In pesticide research the greater concern is usually for the potential for inequitable reliance on subjects from vulnerable populations—especially those who are economically disadvantaged or in a dependent or subordinate relationship to the investigators or others involved with the research.

The essence of equity in selection of research subjects is that the burden of bearing the risks of research be fairly distributed. There are several aspects of fair distribution.

Representativeness of sample

> Research which is more broadly applicable is of greater societal value than other research. The representativeness of the sample is thus directly related to the justification for the research.
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> Ideally, the population selected for research participation would be randomly sampled from the target population to which the study results will be applied. This ideal cannot often be attained, but it should guide the design of recruitment and selection processes in three ways.
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> First, the target population should be identified and characterized demographically. Second, a sampling frame should be defined, and its relation to the target population should be characterized. Differences between the characteristics of the population in the sampling frame and those of the target population—i.e., the extent to which the sampling frame is unrepresentative of the target population to which the study results will be applied—should be justified. Third, the sample should be selected from the sampling frame in a way that preserves its representativeness of the target population. To be

equitably selected, the sample must be selected to serve the scientific purposes of the research, and not for the convenience of the investigators or for other arbitrary reasons.

For example, in a study of agricultural worker exposure to pesticide residues in previously treated orchards, it might make the research easier to conduct if candidates who could not read and understand English fluently were excluded. Because a significant proportion of orchard workers are of limited English language proficiency, such an exclusion would diminish the representativeness of the sample, thereby reducing the applicability—and the societal value—of the resulting data.

Appropriate use of inclusion/exclusion factors

Selection of potential subjects from a sampling frame entails application of appropriate inclusion and exclusion factors to screen candidates. These can serve both to preserve the representativeness of the selected sample and to provide extra protections for potentially vulnerable subjects. In the regulatory sense, "vulnerability" means that some or all of the subjects may be overly susceptible to coercion or undue influence when being enrolled into the research.

EPA's regulations (40 CFR §26.1203) prohibit the use of human subjects in research involving intentional exposure to pesticides, if those subjects are pregnant or nursing women, or children under age 18. Compliance with these prohibitions and protection for potentially vulnerable subjects can both be ensured with appropriate exclusion factors.

Special considerations for vulnerable populations

Special consideration is needed to ensure protection of vulnerable subjects. Many potentially vulnerable populations should simply be excluded from research involving pesticides. The absence of any potential direct benefit and the exposure to potential harm to them makes it fundamentally unethical to consider using prisoners, children, pregnant or nursing women, or mentally disabled people as subjects in research with pesticides. One example of appropriate exclusions is discussed above.

Others, however, who may ethically be included as subjects in pesticide research may also be vulnerable and require special considerations. For example, individuals with limited English language proficiency may appropriately participate in some research, but require translations of recruiting and informed consent materials into language they can understand, and assistance in communicating with investigators in the consent process and during the conduct of the research. Here the "vulnerability" is due to the possibility that potential harms, or the directions to avoid them would not be correctly interpreted/understood.

In studies of occupational exposure to pesticides, subjects are quite appropriately drawn from among those who are occupationally exposed to pesticides. But great care must be taken in recruiting them to ensure that their decisions to participate in the research are made freely, without any coercion or undue influence from their employers or

supervisors or the investigators. One prerequisite to a free choice to participate in occupational exposure studies is a clear understanding of a real alternative to participation.

In some past pesticide studies, subjects have been drawn from among the employees of the sponsor or the students of the investigators of the research. It is very difficult to ensure either that such subjects are representative of the target population or that their choice to participate is made freely and without any undue influence (intended or unintended); thus as a practical matter, the best course is not to involve them as research subjects.

Appropriate recruiting strategy

To ensure that a selected sample is as representative and equitable as possible, the recruiting strategy must be appropriate to the design of the research. Fliers or advertisements or other recruiting efforts may or may not reach the intended audience, depending on where and when they appear. In order that no individual or group bears an undue burden of research, it is important to use a recruiting strategy that will extend the opportunity to participate to a wide population consistent with research design.

Because of the potential for privacy infringement, recruiting procedures that involve one person providing information about another person as a potential subject without his/her permission are discouraged. Information about the study should be provided to potential subjects through flyers, announcements, advertisements or other means initiated by the investigators. Potential subjects may then actively express interest in study participation by contacting the investigator directly.

All recruitment materials—advertisements, flyers, postcards, brochures, press releases, telephone scripts, or postings on the internet—need to be reviewed by the IRB for accuracy in presentation of information that the prospective subject needs to determine his/her eligibility and interest. The IRB review considers content, language, and design.

Fully informed choice to participate.

The second over-arching concern is to ensure that subjects' choices to participate in research are fully informed. The Office for Human Research Protections (OHRP) states that "informed consent is one of the primary requirements underpinning research with human subjects; it reflects the basic principle of respect for persons."

Informed consent is the knowing consent of an individual or his/her legally authorized representative, obtained without undue inducement or any element of force or coercion. Obtaining informed consent doesn't end with a signature on a piece of paper. It is a process in which the subject receives enough information about a study to make an informed decision about initial entry and continuing participation in the research. The process involves reading, understanding and signing an informed consent document as well as discussing the details of study participation with a knowledgeable member of the research team.

By signing the consent form, the project representative—the principal investigator or study coordinator—who obtains consent is documenting that the consent process is complete. The project representative is responsible for ensuring that context and process is conducted to enhance prospective subjects' comprehension of the information and their ability to make free and voluntary choices. The project representative must be knowledgeable about the study, able to present information clearly in plain language, fluent in the preferred language of the prospective subjects, and able to understand and resolve questions.

The subject who signs the consent form acknowledges having read the information in the consent document and having had a chance to discuss it, to ask questions about the study, and to have those questions answered. The subjects' signatures also indicate agreement to participate in the study, and notification that they are free to change their minds at any time and withdraw their consent to participate.

The primary purpose of the informed consent process is to communicate to prospective subjects adequate information, expressed clearly in plain and understandable language, to make an informed decision about participating in the proposed study. This information is outlined in the required elements of consent (40 CFR §26.1116) including:

- The purpose, risks, and benefits of the research.
- The procedures involved and what would be expected of participants.
- That he/she retains the right to decline to participate or to withdraw from the study at any time without penalty.

In addition, the informed consent process should:

- Confirm the prospective subject's understanding of the information provided.
- Answer any questions the prospective subject may have about the study.
- Provide the subject with a copy of the consent form(s).

Essential Elements of a Consent Document

Basic and additional elements of an acceptable informed consent document are specified in regulations at 40 CFR §26.1116(a), (b), and (e). The list below is based on these regulations, but is rearranged for clarity. In case of any perceived conflict between this list and the regulations, the regulations are authoritative.

A consent document for occupational exposure studies for pesticides should include:

- A statement that the subject is being asked to participate in research on a pesticide, and the identity and pesticidal function of the pesticide(s) to which he or she will be exposed.
- Identification of the investigators involved in the study by name, qualifications, and affiliation, and disclosure of any conflicts of interest.
- A plain-language, jargon-free explanation of the purposes of the research.

- An explanation of the eligibility criteria used to identify prospective participants, and the number of subjects being recruited.
- A description of where the research will be conducted and the expected duration of the subject's participation.
- A description of all the procedures that the subject will be asked to follow, identifying any procedures that are experimental.
- A description of the nature and likelihood of any risks or discomforts the subjects might encounter as a result of participation, and of the actions taken to minimize these risks or discomforts.
- a statement about compensation for injury, if any and if medical treatment or other arrangements are available.
- A statement that participation in the research will offer no direct benefit to the subjects.
- A statement about potential benefits to society from the knowledge that may result from this research. This should realistically identify both the nature and magnitude of expected benefits and how they will be distributed—that is, who will receive them. This should not be exaggerated because it would then become a source of undue influence.
- A description of the extent, if any, to which records identifying the subject will be held confidential, explaining the procedures for using and storing data and who will have access to it.
- Information about any payment or other incentive offered to participants, describing what it is and what the subject must do to obtain it. If there is a payment, a statement of the amount, the formula for proration should the subject or investigator chose to discontinue participation, and when and how payment will occur. If no payment or other incentive is offered, a statement that the participant will not be paid to participate in this study. (Note: payments for participation should not be described as "benefits" of the research.)
- Contact information for study personnel and the responsible IRB, in case subjects have questions or concerns about the research, about their participation in it, or about their rights as subjects.
- A statement that the subject's participation is voluntary, and that if the subject decides to participate, they can change their mind and stop their participation at any time without penalty.
- A clear statement of alternatives to participation, specific to the context of the research, should subjects decide not to participate or to withdraw.
- 1116(b)
- The identity of the pesticide and the nature of it's pesticidal function

Capacity to Make Decisions

Like the Common Rule that governs research with human subjects conducted or supported by the federal government, EPA's regulations governing third-party research involving intentional exposure of human subjects to pesticides provide that "no investigator may involve a human being as a subject in research . . . unless the

investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." (40 CFR §26.1116)

But because research involving intentional exposure to pesticides is unlikely to be of direct benefit to subjects, it is equally unlikely that it would ever be ethically appropriate to obtain consent from a representative of a subject rather than from the subject him- or herself.

In short, for these types of studies, it is essential to fully informed consent that the consenting subjects have the capacity to understand the information provided, and to make a free choice to participate or not to participate. If there is any question about the decisional capacity of a prospective subject, that person should not be enrolled in research.

Language of Informed Consent

The regulatory requirement for the language of informed consent documents—and for the entire informed consent process—is that "the information . . . given to the subject . . . shall be in language understandable to the subject." (40 CFR §26.1116)

That means, first, that the language used in the consent documents and throughout the consent process should be selected for the benefit of the potential subjects, not for the convenience of the investigators. If subjects with limited English proficiency are expected to be enrolled, all consent materials should be translated into the language(s) in which prospective subjects are comfortable, and the accuracy of the translation should be confirmed, through back-translation or other means. Translated consent materials must also be approved by an IRB before use. An interpreter fluent in the languages of both the investigators and the prospective subjects may be needed to ensure that the information provided in the process is fully understandable to the subjects.

Understandability also requires that consent materials be written in plain language, avoiding technical jargon. Most authorities recommend writing consent materials at a 6th to 8th grade reading level, using the second person (i.e., addressing the subject as "you.") Understandability of consent materials should be verified before they are used. A helpful web site is: http://www.plainlanguage.gov/howto/index.cfm.

Finally, regulations forbid inclusion in consent materials of "any exculpatory language through which the subject . . . is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence." (40 CFR §26.1116)

Complexity of Consent Materials

It is easy to overwhelm subjects with too much information. The quality of consent materials is not measured by their bulk, but by the accuracy and clarity with which they present what subjects need to know to make a decision to participate. Many details

contained in the protocol itself are unnecessary in good consent materials, and careful editing should exclude them.

One important element, however, that should be described in detail is the procedures involved in the research, from the point of view of the subjects. The goal in developing consent materials should be to discuss all the procedural elements in the research in one place, as much as possible in the sequence they will occur, and in clear, plain language.

Circumstances and Process

The entire consent process and the circumstances in which it takes place are critical components of fully informed and fully voluntary decisions. Most authorities consider the consent process to begin with the potential subject's initial contact with the research—whether through advertisements, flyers, phone calls, or other means. The regulations require investigators to seek consent "only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." (40 CFR §26.1116)

The process should be designed to enhance the prospective subject's comprehension of the information and his or her ability to make a choice. It should take place in an area and in a manner that protects the privacy and integrity of both prospective and selected subjects.

Particular care is needed to ensure that the process is free from any element of coercion or undue pressure when third parties other than the investigators and subjects play a role in the recruiting, informing, and consent processes. If, for example, pesticide handlers are recruited through their employers, care must be taken to ensure they have a free choice not to participate, and that their employers do not influence their decisions, intentionally or unintentionally.

Communicating Risks

Unless prospective subjects understand the risks associated with participation in research, they cannot make a rational decision to participate. Risk should be addressed in consent materials from the point of view of the subjects, rather than from the point of view of the investigators. If the discussion of risk in the informed consent document is the same as the discussion in the protocol, it almost certainly needs revision.

Three aspects of risk need to be addressed in consent materials:

- its qualitative nature. Risks may be physical risks of harm or discomfort; they may also be psychological, social, economic, or legal. For example, a prospective female subject who learns she is pregnant as a result of a pregnancy test associated with eligibility screening may experience psychological harm. If the news of her pregnancy is not communicated to her with care and discretion, she may experience economic or social

harm as well. Risks and harms may also involve others such as family members and future children.

- its likelihood. An informed choice to participate in research depends on a clear understanding of the distinction between likely and unlikely risks. Each risk identified in an informed consent document should also be characterized in terms of its likelihood of occurrence.
- steps taken by the investigators to minimize it. This should include telling potential subjects how injuries or other adverse effects resulting from participation in the research will be managed, what treatment will be available, and who will pay for it.

Communicating Benefits

Occupational exposure studies for pesticides do not offer any direct benefit to participants. This must be clearly stated in consent materials.

Because of the absence of direct benefits, there are likely to be significant asymmetries in the distribution of risks and benefits. The subjects are likely to bear all or nearly all risks, whereas the benefits of the research are likely to accrue to others. An explicit discussion of the nature and distribution of benefits is essential to a fully informed decision by a subject to participate in the research.

Potential societal benefits from the information expected to result from the research should be described to potential subjects. If, for example, a study of pesticide handler exposure is expected to provide information which EPA will use to define the minimum personal protective equipment required for safe handling of pesticides in the relevant exposure scenario, this could affect a potential subject's decision to participate. If the beneficiaries of the research are likely to be pesticide registrants, this, too, should be stated clearly. Care should be taken to not over-state potential benefits.

Compensation must not be described as a benefit to subjects.

Confirming Understanding

It is the responsibility of the research team to confirm subject understanding, and the investigator's signature on a consent form attests to this confirmation. It is not sufficient to obtain signatures on forms worded so as to put the responsibility on the subjects. Statements such as "I understand . . ." in informed consent documents represent an unacceptable transfer of responsibility. As with consent itself, subject understanding is an ongoing process, which needs to be confirmed and enhanced if the project occurs over time.

Fully voluntary choice to participate

Recruitment must be conducted without any element of coercion or undue influence to participate. Potential sources of undue influence are from dependent relationships and from social pressure from peers. Is the consent process adequate to ensure that the subject's

agreement to participate is informed, rational and voluntary? What safeguards could be implemented to improve the consent process? Do candidates have a free and real alternative to participating?

Managing Dependent Relationships

In many occupational exposure studies for pesticides, the subjects—whether they are pesticide handlers or re-entrant workers—are recruited for the research through their employers. In such cases, great care is needed to ensure this does not compromise the voluntariness of the subjects' choices to participate. The employer must have no interest in the research, or in whether an individual chooses to participate in it, and this must be clearly communicated to potential subjects. Subjects must understand that their decision either to participate in research or not to participate will have no impact on their job, their pay, or any other aspect of their relationship to their employer.

In some past studies for pesticides, the employers of the subjects have had a direct interest in the research. Also, some companies that sponsor or conduct exposure studies have recruited subjects from among their own employees. This practice is inconsistent with ensuring that subject choices to participate are entirely voluntary.

In some exposure studies, subjects have been recruited as a crew, through a crew leader or labor contractor. This introduces a clear potential for undue influence, especially because some members of agricultural work crews may be in the U.S. illegally, and thus particularly vulnerable.

Minimizing Peer Pressure

It may be essential to fully voluntary choice to design the circumstances and process for discussing the research, addressing questions about it, and seeking consent of potential subjects so that each candidate has the privacy to act without any pressure from a peer group. Because it is often obvious whether someone is participating in research—as, for example, when participants are all wearing whole-body dosimeters—it is important to ensure privacy for individual choices and discretion concerning reasons for nonparticipation. If each candidate is interviewed and makes a participation decision in private, for example, non-participation could result from application of the exclusion factors by the investigators or from personal choice by the candidate. A well-designed process would leave it entirely up to the individual subject whether to disclose the reason for non-participation.

Real Alternatives to Participation in Research

It is common practice to include in the consent materials for non-therapeutic research such as that conducted with pesticides a statement to the effect that "this study is not associated with any therapeutic treatment, so your only alternative to participation is not to participate." This simple statement is a carryover of habits associated with biomedical research, where alternative treatments may not be available to potential subjects of

research. But such an unexplained statement is inappropriate for occupational exposure studies for pesticides. Potential subjects in occupational studies must be told in some detail what they would do if they decide not to participate in the research, or if they decide later to withdraw from the research. This must be thought through in the course of study design and spelled out in the consent materials, so subjects can understand their options more fully.

For the following example, assume mixer/loaders and aerial applicators are recruited from among the employees of a commercial pesticide application service to participate in a study of agricultural handler exposure. The study coordinators have identified a particular farmer who is a client of the application service, and arranged with him to make his fields available for pesticide treatment in the course of the research. What does it mean to tell an aerial applicator employed by the service that his only alternative to participating in the research is not to participate? What would he do that day if he did not participate in the research? Would he apply the same pesticide to the same field, but with no measurement of his exposure? Would he be reassigned to service another client? Would he get an unscheduled day off? Would he get paid?

To extend the example, what does it mean to tell an aerial applicator that he is free to withdraw from the research at any time? If he decides to withdraw in the middle of the study, will someone else fly the plane? What would he do for the rest of the day? How will the cooperating farmer's field get treated? Would anyone's income—his own, his employer's, perhaps the farmer's—be affected by the pilot's decision to withdraw from the research?

For another example, consider a study of re-entrant agricultural worker exposure, for which subjects were recruited through a crew boss. If one member of the crew chose not to participate in the research, what would that individual do that day?

Respect for potential and enrolled subjects

Fully informed, fully voluntary participation in research is required by the principle of respect for persons. But research subjects are sometimes treated in ways that undermine this principle.

Incentive Payments for Subjects

To assist in subject recruitment, an incentive may be offered. Any incentive should be reasonable, taking into account the burden or inconvenience incurred by study participants. The amount and type of incentive should not unduly influence prospective subjects to participate. Subjects should understand what incentives will be offered before they agree to participate in the study. The terms of the incentive should be described in the consent form. Incentives may also be described in general terms in recruitment materials, but should not be emphasized. All incentives and methods of communication (e.g., fliers) to prospective subjects need to be approved by the IRB before use.

It is particularly important in research on occupational exposures to explain clearly to potential subjects how any incentive payments for their participation in research relates to their normal compensation for doing their job. Will they be paid above and beyond their usual pay? How will their pay be affected if they decide to withdraw from the research?

Privacy and Confidentiality

The protection of a prospective or enrolled subject's privacy must be considered in the design and conduct of research. A perceived invasion of privacy may result in harm to the individual.

A breach of confidentiality may also result in harm to the individual. To maintain confidentiality of research data, the investigator should protect information obtained from the subject to avoid unintentional access by others. Subjects should understand the procedures used to protect confidentiality.

Guidelines for developing procedures to address confidentiality include:

- Limit the personal information recorded to that which is essential to the research;
- Store personally identifiable data securely and limit access;
- Code data as early in the research as possible and dispose of the code linking the data to individual subjects when data have been processed;
- Do not disclose personally identifiable data to anyone other than the research team without the written consent of the subjects. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).

Conclusion / Summary