



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

May 18, 2009

SUBJECT: Science and Ethics Review of Protocol LNX-002 for a Human Study of Biting-Fly Repellent Performance

FROM: John M. Carley
Human Research Ethics Review Officer

Kevin Sweeney, Senior Entomologist
Science Reviewer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Carroll, S. (2009) Efficacy Test of KBR 2023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) with Biting Flies Under Field Conditions: Efficacy Test Protocol LNX-002, dated March 23, 2009. Unpublished document prepared by Carroll-Loye Biological Research. 216 p.

We have reviewed the referenced protocol for a field test of biting fly repellency from both scientific and ethics perspectives. This review assesses the scientific aspects of the proposed research in terms of the recommendations of the draft EPA Guidelines 810.3700 and of the EPA Human Studies Review Board, and the ethical aspects of the proposed research in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the EPA Human Studies Review Board.

A. Completeness of Protocol Submission

The submitted protocol was reviewed for completeness against the required elements listed in 40 CFR §26.1125. EPA's checklist is appended to this review as Attachment 5. The only missing required element was identification in the minutes of the reviewing IRB of the

specific changes called for in the consent forms, and the basis for them. This deficiency does not compromise a review of the protocol.

In addition to the protocol itself (pp. 1-30) and the associated informed consent documents as approved by the Independent Investigational Review Board, Inc., (IIRB) (pp. 34-52), the following supporting documents were considered in this review:

- PI Annotations to protocol (pp. 31-33)
- Documentation of changes by CLBR and IIRB to consent forms (pp. 53-60)
- Data Recording Forms (pp. 61-70)
- Test product labels and MSDSs (pp. 71-82)
- Toxicology Profile of KBR 3023 (pp. 83-84)
- HSR Training records for investigators (pp. 85-86)
- Index of CLBR↔IIRB Correspondence (pp. 88-89)
- Protocol (3/1/8/09) and supporting materials as originally submitted to IIRB (pp. 90-173)
- IIRB (3/23/09) request for additional documentation (p. 174)
- CLBR response, including revised protocol of 3/23/09 (pp. 175-209)
- IIRB Approval letter of 3/24/09 (pp. 211-212)
- IIRB Minutes of 3/24/09 meeting (pp. 215-216)

Two required elements were submitted separately:

- IIRB Membership Roster (1/6/09)
- IIRB Policies and Procedures (10/27/08)

B. Summary Assessment of Ethical Aspects of the Proposed Research

This section summarizes the ethical aspects of the proposed research. Supporting details are in Attachment 1.

- 1. Societal Value of Proposed Research:** This study will test the field efficacy against biting flies of two conditionally registered formulations containing the active ingredient Picaridin (KBR 3023) at 20% concentration. EPA requires efficacy testing of these specific formulations to support continued registration of the products. Direct testing of the duration of efficacy is important because consumers, who rely on repellents to avoid insect bites, cannot readily assess the efficacy of a product independent of EPA's approval. There is potential benefit to society in demonstrating field effectiveness of picaridin repellents at this concentration, which users may prefer to other repellent products because of their cosmetic or other qualities.
- 2. Subject Selection:** Subjects will be recruited from a "Volunteer Database" of previous subjects and others who have asked to be added to the database. The database is racially diverse, 75% in the age range from 20-40 and 25% in the range 40-55. The youth and high education levels of candidates in the database reflect the

university community where the laboratory is located. Explicit factors exclude as subjects children, pregnant or lactating women, those in poor health or physical condition, or those unable to speak and read English. The sample will thus not be fully representative of the population of potential repellent users. There is no indication that any subjects will be from populations vulnerable to coercion or undue influence.

Two “experienced” subjects will serve as untreated controls to verify ambient biting pressure from mosquitoes in the field. The protocol specifies additional inclusion criteria for these experienced subjects, and they will see a different consent form from that used for treated subjects.

- 3. Risks to Subjects:** The protocol and consent form discuss risks of five kinds: risks from exposure to the test materials; risks from exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. All practical steps to minimize subject risks have been taken.

The test material is accurately characterized in the Informed Consent Form as an eye irritant, harmful if swallowed—consistent with the required hazard statements on the registered product label.

Because of the generally low acute and chronic hazard profile of the material, the design of the research to minimize exposure, and the training of subjects to remove landing flies before they have time to probe or bite, the probability of the identified risks is accurately characterized as “extremely small”.

- 4. Benefits:** There are no direct benefits to subjects. This is made clear in the protocol and Informed Consent. If the testing shows good field efficacy the direct beneficiary of the research is likely to be the sponsor. Assuming eventual regulatory approval, indirect beneficiaries may also include repellent users who prefer these products to other repellents.
- 5. Risk/Benefit Balance:** No practical opportunities to further reduce risk to subjects while maintaining the robustness of the scientific design have been overlooked. The residual risk to subjects is very low, and reasonable in light of the potential benefits of the data to future repellent users.
- 6. Independent Ethics Review:** The Independent Investigational Review Board, Inc., of Plantation FL has reviewed and approved the protocol and informed consent materials. The IIRB, Inc., is independent of the investigators and sponsors. Satisfactory documentation of IIRB procedures and membership was provided.
- 7. Informed Consent:** The protocol contains a complete and satisfactory description of the process by which potential subjects, both treated and untreated, will be recruited and informed and for seeking their written consent to participate. A copy of the Informed Consent Form showing approval by the IIRB is included in the protocol.

Separate Informed Consent Forms are provided for use for and are appropriate for the untreated control subjects and repellent-treated subjects.

- 8. Respect for Subjects:** Methods proposed for managing information about prospective and enrolled subjects will protect their privacy from compromise. Subject names and other personal information are linked on only one form to their arbitrary “subject number”; in all other data collection forms subjects are identified only by their assigned number.

Subjects—treated and untreated—will be free to withdraw at any time, and will be reminded of this at several points. Subjects who withdraw will be compensated for time spent up to the point of withdrawal; alternate subjects who are not needed for the field trial will be compensated for their inconvenience. Medical care for research-related injuries will be provided at no cost to the subjects.

C. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. Because the test will be conducted in California, the provisions of the California Code of Regulations, Title 3, §6710 apply as well. A point-by-point evaluation of how the requirements of 40 CFR 26 Subparts K and L and the criteria for protocol evaluation recommended by the HSRB are addressed is appended as Attachment 1.

No deficiencies requiring correction relative to 40 CFR 26, subparts K and L, or to FIFRA §12(a)(2)(P) were identified in this review. We defer to reviewers in the California Department of Pesticide Regulation to assess compliance with applicable California state requirements.

One drafting error in the protocol should be corrected. In section 4.7.7 (lines 828-829) the entry “More than one biting insect attempts to bite during any exposure period” should be moved from its current placement under the heading “All subjects” to a position under the heading “Individual subjects.” As it stands, if two flies attempted to bite two different subjects in the same exposure period, the whole test would be stopped.

40 CFR 26 Subpart L, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

The protocol requires that subjects be at least 18 years old and excludes female subjects who are pregnant or lactating. Thus §26.1703 would not forbid EPA to rely on a study executed according to this protocol.

D. Summary Assessment of Scientific Aspects of the Proposed Research

The study will test the field efficacy as a biting fly repellent of two conditionally registered repellent products containing picaridin (KBR 3023). The objective of the study is to quantify the efficacy of the formulations to prevent biting fly landings in the field.

Biting pressure will be monitored for five minutes every 30 minutes during the test by two untreated subjects. One landing is required in five minutes for the test to continue. Biting flies landing on untreated subjects will be aspirated by the attending technicians to prevent biting and for later identification. Treated subjects will work in pairs to facilitate observations, and will expose treated skin for 1 minute at 15 minute intervals until they experience a confirmed landing with intent to bite (LIBe) or until the end of the test period—whichever comes first.

- 1. Study design:** The objective is to test the field repellent efficacy of the conditionally registered KBR 3023 formulations against biting flies. This objective can be met by the study as proposed.
- 2. Statistical design:** The sample size of 10 treated subjects per test material is larger than is required by EPA guidelines—large enough to ensure robust averages across subjects, but small enough to be economical. Two untreated subjects are proposed to establish and confirm ambient biting pressure; no statistical comparisons to the untreated controls are proposed. No positive control or negative vehicle control is proposed. Because the test materials differ, efficacy testing will not be entirely blinded, but technicians recording results will not know which formulation has been applied to each subject. Repellency will be reported as “Complete Protection Time”, calculated as the mean time across all treated subjects from application of the repellent to the first confirmed landing with intent to bite (LIBe). Time of LIBes will be reported with a precision of 30-minute intervals, with standard deviation and 95% confidence interval, as called for by EPA’s guidelines. Results will also be subjected to Kaplan-Meier survival analysis.
- 3. How and to what will human subjects be exposed?** A standardized “typical consumer dose,” determined in the dose determination phase of the earlier study LNX-001 and reported in MRID 47506401, expressed as volume per unit area, is scaled to the measured surface area of each subject’s limb and applied by a technician to the subject’s forearm or lower leg. The repellent will remain in place for 8 to 14 hours during the field test. In addition, subjects in the field will be exposed to potential bites by wild mosquitoes, and (with very low probability) to arthropod-borne diseases.
- 4. Endpoints and Measures:** Complete protection time (CPT) will be measured as the mean time from initial application of a typical consumer dose until the first confirmed

LIBe, and will be presented with standard deviation and 95% confidence interval. Subjects will be trained to remove landing flies before they have time to bite. In the field subjects will work in pairs, checking each other as well as themselves. All reported LIBes will be verified by a research technician.

E. Compliance with applicable Scientific standards

This protocol adequately addresses the following elements according to applicable scientific standards:

- Scientific objectives
- Experimental design for achieving objectives
- Methods for estimating dose of test material
- Quantification of efficacy of the test materials
- Data collection, compilation and summary of test results
- Discussion of the statistical power of the study.
- Justification for sample size in dosimetry and repellency phases
- Rationale for use of two untreated negative control subjects to monitor biting pressure.

This protocol does not adequately address the following elements:

- Justification for biting pressure. Low biting pressure could lead to right censored data.
- Justification for sampling once for five minutes every 30 minutes instead of for one minute every 15 minutes.

Attachments:

1. Summary Review of Carroll-Loye Protocol LNX-002 dated 3/23/2009
2. §26.1111 Criteria for IRB approval of research
3. §26.1116 General requirements for informed consent
4. §26.1117 Documentation of informed consent
5. §26.1125 Criteria for Completeness of Proposals for Human Research

EPA Protocol Review: LNX-002

Title: Efficacy Test Protocol #LNX-002: Efficacy Test of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray) with Biting Flies under Field Conditions

Date: 23 March 2009

Principal Investigator and any sub-investigators:
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1. Societal Value of Proposed Research**(a) What is the stated purpose of the proposed research?**

“The objective of this study is to determine the duration and efficacy of the Test Material(s) in repelling biting flies . . . when applied at a typical consumer dose. . . . The study will primarily target black flies, but may substitute or include other flies [no-see-um flies, horse or deer flies, or stable flies] depending on seasonal availability in nature.”

“Efficacy and duration will be measured as Complete Protection Time, or CPT, defined herein as the time between application of test material and the First Confirmed Probing called ‘Landing with Intent to Bite’ or ‘LIBe’, defined as when a biting fly lands on the treated test skin of a subject and ceases locomotion. A ‘First Confirmed LIBe’ is that which is followed by another within 30 minutes.” (p. 5)

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

“The US Centers for Disease Control (CDC) has acknowledged the existence of substantial consumer interest in new and effective insect repellent products, including the choice of a variety of formulations, delivery systems, and concentrations of active ingredient. Of the three DEET-alternatives currently considered by CDC to have public

health value, Picaridin probably has the highest broad-spectrum efficacy. However, few Picaridin products are currently available to US consumers. US EPA has requested new, US-based efficacy data as a condition of registration for the test products. The purpose of this study is to provide those efficacy data. The information will also be used in product labeling.” (p. 6)

(c) How would the study be used by EPA?

EPA will consider the study in defining acceptable label claims for repellent efficacy for the test materials.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

The concentration of KBR 3023 in this product is higher than that in other registered repellents containing it, so EPA requires product-specific efficacy data to support its registration. No previous field testing of these products against biting flies has been conducted.

(e) Could the question be answered without newly exposing human subjects? If so, how? If not, why not?

“Human subjects are . . . the target system for the test material, and sufficiently reliable models for repellency testing have not been developed.” (p. 6)

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

“The objective of this study is to determine the duration and efficacy of the Test Material(s) in repelling biting flies . . . when applied at a typical consumer dose.” (p. 5)

No explicit hypothesis is stated.

(b) Can the study as proposed achieve that objective or test this hypothesis?

The objective quoted above can be achieved by the study as proposed.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

“In efficacy testing, we will use 10 subjects per treatment and 2 untreated control subjects per field trial.” (p. 17) The rationale for this sample size appears on pp. 17-

19. A sample size of 10 reflects a compromise between cost and precision; it is larger than the minimum of 6 required by EPA's 1999 guideline, and promises to provide an acceptably robust measure of average complete protection time at reasonable cost.

“Our chosen sample size of 10 subjects will improve precision in estimating test material performance. This sample, which is larger than that traditionally required by US EPA, is implemented at considerable expense to the study sponsor, but is consistent with suggestions from HSRB advisors to EPA. The resulting data set will provide values suitable for any additional statistical characterizations of repellent performance that EPA may wish to employ in developing labeling language for the Test Materials.” (p. 27)

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

“In efficacy testing, we will use . . . 2 untreated control subjects per field trial.” (p. 17) “There are no controls by which the formulation matrices without the repellent active ingredient are tested.” (p. 19) There are no positive controls. Use of two untreated controls to confirm continued pest pressure throughout the field testing is appropriate for the study design. Omission of matrix and positive controls is appropriate for the study design. No direct comparisons of treated and untreated subjects are contemplated.

(d) How is the study blinded?

“Because the treated condition will be evident to experimenters and subjects, neither group will be effectively blinded. However, within the treated group, the two treatments will be indistinguishable to test subjects and technicians based on their physical properties. Accordingly, the two treatments will be coded ‘A’ or ‘B’ by a technician. That technician will dispense the Test Materials so labeled for efficacy test treatments. That technician will not be involved in judging LIBe events during efficacy data collection.

“The treatment code key will be recorded in hardcopy by the technician and maintained in a locked file drawer to which only he/she has the key. As a backup, the key will also be recorded in a password protected computer file. For backup access, two technicians will be charged with memorizing and privately maintaining the password offsite from the laboratory. Technicians will be charged not to reveal the code or the specific identity of Test Materials at any time during application or data collection, unless needed for medical or legal reasons. The Study Director will retrieve the code key from the technician(s) after the conclusion of data collection.” (pp. 21-22)

(d) What is the plan for allocating individuals to treatment or control groups?

“All subjects that are not untreated controls will be assigned to the treated group, which will be blocked by gender. The treatments will be allocated in sequence (‘A’, then ‘B’, then ‘A’, etc.). Within each gender, the treatments will be allocated at random excepting minor adjustments needed to constrain the numbers treated with a particular Test Material to 10. The treatment each subject receives and the time of application for each subject will be recorded on a data capture form (Appendix 2). Multiple technicians will make the applications, and each application will take only about three minutes to complete, so that subjects receiving ‘A’, for example, will not be treated on average significantly earlier than those treated with ‘B’.

“Whether arms, legs or both are tested at a given site will depend on the behavior of the biting fly population employed. That decision will be made by the Study Director based on reconnaissance of the field sites prior to data collection. Treatments will be balanced between arms and legs if both limbs are used.” (pp. 20-21)

(e) Can the data be statistically analyzed?

Yes. At the field site ten individual values for CPT will be obtained for each test material and averaged.

(f) What is the plan for statistical analysis of the data?

“Statistics will be computed with SAS’s JMP software, Version 5.0.1.2 (SAS Institute, Cary, NC).

“The hypothesis that the test material will significantly reduce the number of biting flies LIBing on treated versus untreated skin is not the objective of this study. The objective is to compute, for each test material, a reasonable estimate of mean and standard deviation for the duration between application and repellency breakdown sufficient such that two biting flies LIBe on a subject within a one-hour period (“Complete Protection Time” or CPT). That pattern is here assessed at a resolution of 30 minutes. The untreated limbs serve to monitor whether the ambient biting pressure remains at or above the EPA standard.

“For each control, we will record the number of LIBes occurring within a 5- minute exposure at the beginning of each interval.

“For each treated subject, we will measure (data form Appendix 2):

- Exposure delay (min) – time between application and first exposure
- Minutes in field to First Confirmed LIBe (FCLIBe) or end
- Complete Protection Time (CPT) – time between application and FCLIB

“CPT is measured as a single time value for each subject. Based on the requirements for such estimates in the EPA draft repellent efficacy testing guidelines (1999);

OPPTS 810.3700), we will calculate mean CPT across all 10 subjects, with standard deviation and 95% confidence interval information.

“Data will be normalized as possible to enhance the value of confidence interval calculations. Ambient LIBing pressure as measured by untreated subjects will be presented tabulated by individual and exposure period. Mean LIBing pressure will be calculated as the number of LIBes received per untreated control subject and per period and span of exposure.

“To examine the temporal pattern of failure further, we will employ Kaplan-Meier survival analyses by subject. Kaplan-Meier survival analysis accommodates some data censoring in the event that any subjects withdraw before failure. In addition, we will estimate the Kaplan-Meier median, and the time until 25% failure, for each test product. In the presence of a high frequency of censoring, median (and mean) values will be underestimated.” (pp. 26-27)

(g) Are proposed statistical methods appropriate to answer the research question?

Yes.

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

Yes. It will produce a data set more robust than most on which past decisions by EPA concerning acceptable claims of repellency have been based. However, the basis for biting pressure is not clear. This low biting pressure and sampling twice per hour instead of four times per hour for the duration of the study might lead to right censored data sets or a data set with an inadequate number of data points.

2.2 How and to what will human subjects be exposed?

(a) What is the rationale for the choice of test material and formulation?

The test materials are conditionally registered by EPA as Reg No. 39967-50 (Cream) and 39967-53 (Spray). Product specific efficacy testing of this material was required by EPA as a condition for the products' continued registration.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

A “typical consumer dose” of each of the two test materials applied to arms and to legs was previously determined by this investigator in study LNX-001, reported in MRID 47506401. The appropriate standard unit dose will be used for all treated subjects in LNX-002. One limb (forearm or lower leg) of each subject will be treated; exposure to the repellent will be continuous throughout the period of the efficacy test.

Subjects will also be exposed for five of every 30 minutes during field testing to “either biting midges (*Leptoconops carteri*) or black flies (*Simulium* cf. *Vittatum*.)” (p. 23)

(c) What duration of exposure is proposed?

The day of field testing will last for 8-16 or more hours, including travel time. The data collection form (pp 65-66) is set up to accommodate reports over a period of 14 hours, but could be used to record efficacy over a longer test period.

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

“For each control, we will record the number of LIBes occurring within a 5- minute exposure at the beginning of each interval.

“For each treated subject, we will measure (data form Appendix 2):

- Exposure delay (min) – time between application and first exposure
- Minutes in field to First Confirmed LIBe (FCLIBe) or end
- Complete Protection Time (CPT) – time between application and FCLIB”

(p. 27)

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Alternate subjects will be enrolled to ensure adequate sample size
- Subjects will be trained to recognize a “LIBe”
- Subjects will work in pairs, checking each other as well as themselves
- LIBes will be verified by a research technician

(c) What QA methods are proposed?

“Protocol Review and Comments must take place before data collection commences. In-Life Inspection must include observing the measurement and recording of key variables by subjects and technicians. In addition, the Final Report will be audited for completeness and accuracy. A QAU Statement will address compliance and noncompliance or any omissions in auditing. Findings from the In-Life Inspection and the Final Report, as well as the QAU Statement will be transmitted to both the Study Director and to the Sponsor Monitor.” (pp. 27-28)

Reports of QAU findings should be incorporated into the final report.

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

“We will calculate mean CPT across all 10 subjects, with standard deviation and 95% confidence interval information.” (p. 27)

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern? How was it identified?

The population of ultimate concern consists of people who would purchase and use insect repellents. Little information is available to characterize this population, but it is presumed that users of insect repellents are highly diverse in age, gender, physical size, general health, attractiveness to biting insects, and other characteristics. The population from which subjects are recruited appears to be chosen largely on the basis of convenience, and is not screened for past or likely future use of repellents.

(b) From what populations will subjects be recruited?

“For reasons of practicality and control, we work with people associated with the community in which our business is located (Davis, CA). Davis is a university dominated community, and so the population demography differs somewhat from non-university communities. Compared to the Population of Concern (the US population - all potential repellent users), our sampling frame tends to under-represent blacks and over-represent Asians. It is also young, well educated, and slanted towards Life Science researchers and students.

“Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers. The size and composition of the database varies over time as new individuals volunteer and old volunteers move out of the Davis area, but is now typically over 100 individuals, with the following average ethnic (self-identified) and gender distribution (averaged over 3 years):

Male	52%
Female	48%
Caucasian	74%
Asian	12%
Hispanic	7%
African-American	4%
Arabic	3%

“In general, about three-quarters of the subjects are age 20-40, with the remainder between 40 and 55. Final composition is not determined until enrollment is completed. The relevant demographics of the participants will be reported.” (p. 12)

(c) Are expected participants representative of the population of concern? If not, why not?

“There are few published studies of repellent affects on biting flies, in contrast to mosquitoes, thus considerations of how attributes of the arthropod or the repellent test design affect repellent performance are best 388 inferred from studies of mosquito repellents. Carroll (2006) reviewed the factors that influence the performance of insect repellents and concluded that there is no ready *a priori* means of predicting an individual’s attractiveness to a particular mosquito population. Likewise, there are few clear patterns permitting us to predict which individuals might be at relatively greater risk from participating in this study. Pregnant and lactating women are excluded on general medical principals, and persons over 55 are excluded due to slightly elevated health risks from West Nile Fever (above), even though the likelihood of contracting the causal agent during a biting fly repellent test is very low.

“We conclude that this study’s deviations from the ideal frame will not influence the representativeness of the results, or their generalizability to the greater population. In addition, because our Volunteer Database cohort is comprised by individuals who regularly spend time in outdoor settings (and thereby may have relatively frequent encounters with biting arthropods), this group is probably appropriate for insect repellent users in general.” (pp. 12-13)

By excluding children, pregnant or lactating women, non-English speakers, and those in poor physical condition, among others, the exclusion criteria will mean that participants will not be representative of at least some segments of the population of concern.

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

Inclusion: age 18-55, written consent, speak and read English. (p. 14)

Additional inclusion criteria specific to the two untreated subjects: “To qualify for candidacy as a subject who exposes untreated skin, an individual must be regarded as competent to do so by the Principal Investigator, must have participated in at least five prior Carroll-Loye repellent efficacy trials, or have participated in at least three such trials and have a least two years of experience as a college life sciences major, or be professionally employed in vector control services.” (p. 14)

Exclusion: hypersensitivity to biting fly bites; phobic of biting insects; allergic to repellents or common cosmetics; sensitive to any of the test product ingredients; poor physical condition; unwillingness to submit to brief query about personal condition; use of insect repellent within one day before field test; unwillingness to abstain from alcohol, smoking, and perfumed products; pregnant or lactating; unable to see biting flies on skin or to remove landing flies; student or employee of Study Director; unaccustomed to outdoor activity. (pp. 15-16)

These criteria for inclusion and exclusion are appropriate.

(b) What, if any, is the relationship between the investigator and the subjects?

Subjects are recruited from “the community in which [the Investigator’s] business is located Over time, we have developed a Volunteer Database of individuals who have expressed interest in participating in future repellency tests, provided contact information, and asked us to contact them. Initial recruiting is from this database, then from word-of-mouth of volunteers.” (p. 12)

Students and employees of the Study Director are excluded from participation (p. 15)

(c) If any potential subjects are from a vulnerable population, what is the justification for including them?

No subjects from a vulnerable population are proposed.

(d) What process is proposed for recruiting and informing potential subjects?

The recruiting/informing process to be used is described in the protocol on pp. 15-16.

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

Students and employees of the Study Director are excluded from participation. (p. 15)
No subjects are potentially subject to coercion or undue influence.

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

“[E]ach research study participant will receive a cash payment of \$20 per hour. . . . If you are designated as an ‘alternate subject’ you will be paid for the hours you spent being trained, plus you will receive a payment of \$50 to compensate you for being inconvenienced.” (p. 41, 50)

(b) Is proposed remuneration so high as to be an undue inducement?

No.

- (c) **Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?**

No.

- (d) **How and when would subjects be paid?**

“Payment will be made at the end of each visit or whenever you withdraw from the study.” (p. 41, 50)

4. Risks to Subjects

4.1 Risk characterization

- (a) **Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test materials?**

“A complete toxicology package required for the registration of an insecticide including acute and subchronic neurotoxicity and metabolism studies was conducted. . . . KBR 3023 and its formulated products have low acute toxicity by oral, dermal, or inhalation routes of exposure. They were not irritating to the skin nor sensitizers in the animal studies. A slight to moderate ocular irritation was observed in the animal studies.” (p. 83)

The cream formulation bears the signal word “Warning” because the product causes “substantial but temporary eye injury.” (p. 68)

- (b) **What is the nature of the risks to subjects of the proposed research?**

The protocol discusses risks of five kinds: risks from exposure to the test materials; risks from exposure to biting arthropods; risks from exposure to disease vectors; risks of physical stress in the test environment; and risks of stress from learning the results of a pregnancy test. Each class of risk and the steps taken to minimize it is discussed in pp. 6-9.

The same classes of risk are characterized in the informed consent documents on pp. 38-40 and 47-49.

- (c) **What is the probability of each risk associated with the research? How was this probability estimated?**

No numerical probability is estimated. Potential treated subjects are told (with respect to the risks of mosquito bites and of contracting an arthropod-borne disease) “since you are wearing repellent and/or other protective measures, and are carefully watching for mosquitoes that land and try to bite, you are probably at no more risk

than you would experience when engaged in normal outdoor activities in a similar rural area at the same time of year.” (p. 47)

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

- The risk of a skin reaction to an insect bite is reduced by excluding candidate subjects who are aware of having a history of such reaction.
- Candidates with known allergic reactions to insect repellents and common cosmetics are excluded.
- Subjects will be trained to quickly remove any insects that land and attempt to bite them.
- Subjects will be instructed to cover any exposed skin immediately if more than one fly attempts to bite during any exposure period.
- Subjects will expose small areas of treated skin for only ten minutes per hour. Other parts of the body will be protected with provided gloves, headnets and full body suits made of Tyvek, through which insects do not bite.
- At the end of each five-minute exposure period subjects will move away from the area with biting fly activity. Partners will assist each other to cover the treated area.
- Subjects will be teamed with a partner for joint observation; experienced technical personnel will be present at all times to assist.
- Only 2 untreated controls are used to confirm biting pressure.
- Exposure of untreated controls for no more than ten minutes per hour; in each exposure interval exposed skin may be covered immediately following the first LIBe.
- First Aid materials will be available on-site
- Epi-Pens will be on-site to treat anaphylactic allergic reactions.
- No control with formulation matrix exclusive of active repellent ingredients.
- A physician who has read the protocol and discussed the research with the Study Director will be on call on the day of field testing.

(b) How do proposed dose/exposure levels compare to established NOELs/NOAELs for the test materials?

Margins of exposure are calculated in the table below. The standard dose rates for both formulations on arms and legs were established in the dose determination phase of the completed study LNX-001. The average skin area of the limbs of subjects in the dose determination trials was calculated from the data reported in MRID 47506401, pp. 33-34 and 38. The specific gravity was reported on p. 11 as 0.98 for the cream formulation and 0.96 for the spray formulation.

The highest exposure would result from treatment on the lower leg with the cream formulation. At the proposed dose rate of $2.36 \mu\text{l}/\text{cm}^2$, and based on the average skin area of the legs of the subjects in dose determination testing for this product, each

subject treated with the cream formulation on the legs will receive a dose of about 2.7 ml of repellent, equivalent to 2750 mg of repellent. Since the concentration of the products is 20%, this is the equivalent of 550 mg picaridin. Assuming a 70 kg adult this is a dose of approximately 7.86 mg/kg.

The NOAEL for acute dermal toxicity in the rat for picaridin is 5000 mg/kg bodyweight, picaridin is less readily absorbed by human skin than by rat skin, and we do not expect the inert ingredients to affect the systemic dermal toxicity. Thus the estimated margin of exposure for picaridin acute dermal toxicity when the cream formulation is applied to subjects' legs is not less than and may be substantially greater than 5000/7.86 or 636. MOEs are higher for applications to subjects' arms, and for applications of the 20% spray formulation to either arms or legs.

Calculation of Margins of Exposure

	Cream 20%		Spray 20%	
	Arms	Legs	Arms	Legs
Standard dose rate ($\mu\text{l}/\text{cm}^2$)	2.51	2.36	0.97	0.83
Average skin area (cm^2)	500	1142	500	1142
Average product dose (μl)	1255	2695	485	948
Average product dose (mg)	1281	2750	505	987
Average picaridin dose (mg)	256	550	101	197
Picaridin dose in mg/kg	3.66	7.86	1.44	2.82
Margin of Exposure (MOE)	1367	636	3464	1772

(c) What stopping rules are proposed in the protocol?

“Stop Rules

All subjects

- Consented duration reached
- Test site becomes unsafe for subjects for any reason
- Biting/foraging pressure falls below threshold needed to challenge the test materials
- Biting/foraging pressure rises to levels unacceptable in terms of subject comfort or safety
- More than one biting insect attempts to bite during any exposure period
- Sustained wind speed exceeds 10 mph

Individual subjects

- Subject asks to withdraw
- Subject proves unattractive to target species

Subject's treated limb receives Confirming LIBe.
 Medical management is invoked for the subject (§1.3.6)" (p. 24)

The fifth entry under the "All subjects" heading (i.e., "more than one biting insect attempts . . .") should be moved under the "Individual subjects" heading. As it stands, if two flies attempted to bite two different subjects in the same exposure period, the whole test should be stopped.

(d) How does the protocol provide for medical management of potential illness or injury to subjects?

"If you are injured as a result of being in this study, a consulting physician who is aware of the study will be contacted immediately by telephone. Medical treatment will be available from a health care facility." (p. 50)

(e) How does the protocol provide for safety monitoring?

"Subjects are clearly and repeatedly informed that they may remove themselves for any reason from the study at any time, without penalty to their compensation. All subjects are asked to contact the Study Director and a physician of their own choice at any time should they develop a rash (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day.

"On the test day, staff will immediately communicate all subject concerns about health, safety, or comfort to the Study Director for assessment. The Study Director will also assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing, or any subject reports any discomfort in treated areas. Subjects are instructed to inform the Study Director (i.e., the 'Principal Investigator'), or any other staff member if at any time during the study a subject suffers a skin reaction, such as redness, edema, itching or pain, or feels ill. Such subjects will be immediately withdrawn from testing and insect exposure, and medical management will be implemented. When a subject completes the study or is removed for any reason, treated skin areas will be gently washed with clean water and mild soap, rinsed with a 35% ethanol in water solution, then gently dried with a towel to remove test materials.

"When medical management is implemented, the Study Director will contact the On-Call physician for the study and comply with the physician's instructions. On the day of testing, a physician who has read the protocol and discussed the research with the Study Director will be on call. Contact information for the nearest medical facilities and maps from the test site to the facilities will be prepared and on file before the day of testing. In unlikely event of a Type 1 allergic reaction (anaphylaxis), we will contact 9-1-1 by cellular or satellite telephone and cooperate as instructed with emergency personnel. Epi-Pens will be on-site. At least one qualified researcher will remain with the other test subjects if other researchers depart with an injured or ill subject. We will be prepared to instruct emergency personnel on how to reach our site via multiple routes. In addition, we will personally transport affected persons to the

nearest hospital if so advised by emergency personnel. There is sufficient redundancy in personnel that in such a case subjects remaining at the study site will still receive appropriate technical, scientific and safety guidance.

“Subjects may also request access to standard first aid materials (such as bandages, antiseptics, and mild topical and oral antihistamines) and request qualified first aid assistance at any time.

“As part of Medical Management, the Study Director will record all benign and adverse health observations.” (pp. 9-10)

(f) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

“Contact a physician and the Principal Investigator if you develop a rash within 48 hours after the day of testing.” (p. 38)

“To provide additional information about your disease risk during the field test, we will check mosquitoes that land on you and other subjects for the presence of West Nile and similar viruses. That information will be available within one week of the test, and we will inform you both verbally and in writing if any disease organisms were found. Even if you are not aware of receiving any mosquito bites during the field test, if you experience any of the symptoms described above [flu-like symptoms (unusual tiredness or unusually severe headaches, body aches, fever), swollen glands or a rash on the trunk] in the month following the field test you should contact a medical practitioner and inform the Principal Investigator.” (p. 39)

(g) How and by whom will medical care for research-related injuries to subjects be paid for?

“Carroll-Loye Biological Research will cover the costs of such medical treatment that are not covered by your own insurance or by a third party. If necessary, Carroll-Loye Biological Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study.” (p. 40)

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

“There are no immediate benefits to you from your participation.” (p. 41, 49)

(b) What benefits to society are anticipated from the information likely to be gained through the research?

“Against the slight risks are balanced substantial and reasonably likely benefits. For the general public, insect-borne disease is of growing significance in the United States and around the world where U.S. citizens are active. Moreover, discomfort associated with nuisance biting restricts many work and pleasure activities. Because EPA registration requires efficacy data, a test such as that proposed here is the only path toward further product development, greater availability, and greater consumer acceptance of new repellent formulations in the United States.” (p. 10)

“[B]y serving as a participant you may assist in making new insect repellent products available to consumers.” (p. 41, 49)

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

“The sponsor will benefit by obtaining accurate measures of efficacy and fully compliant labels for product marketing.” (p. 10)

Assuming eventual regulatory approval, indirect beneficiaries would include repellent users who prefer the new formulations to previously available repellents.

(d) What is the likelihood that each identified societal benefits would be realized?

The testing is likely to demonstrate that the new formulations are effective, and thus the sponsor is likely to realize a direct benefit from the research. Realization of other societal benefits will depend on consumer acceptance of the new formulations.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol systematically reduces risks to subjects without reducing the robustness of the scientific design. No reasonable opportunities to further reduce subject risk have been overlooked. The resulting residual risk to subjects is very low—as low as or lower than the risk to anyone engaged in outdoor activity where biting flies are active. The potential benefits to repellent users from a wider variety of effective repellents with different cosmetic characteristics are likely to be realized, and make the residual risks to subjects in this proposed research reasonable.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Independent Investigational Review Board, Plantation FL

(b) Is this IRB independent of the investigators and sponsors of the research? Yes

(c) Is this IRB registered with OHRP? Yes

(d) Is this IRB accredited? If so, by whom?

Not reported. IIRB is not listed as accredited on the AAHRPP website.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP?

Not reported. IIRB is not listed as holding an FWA on the OHRP website.

(f) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

Complete records of the IRB review are provided in the protocol submission.

Satisfactory documentation of IIRB, Inc., policies and procedures and of IIRB, Inc., membership was submitted in addition to the protocol.

(g) What standard(s) of ethical conduct would govern the work?

“U.S. EPA Good Laboratory Practice Regulations (40 CFR 160); 40 CFR 26 subparts K, L, and M; FIFRA §12(a)(2)(P); California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710).” (p. 1)

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject? Yes.

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117? Yes.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research? Yes.

(d) What is the literacy rate in English or other languages among the intended research subjects?

100%. English literacy is a requirement for participation.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects? n/a

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

Frequent opportunities to ask questions.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

See pp. 15-16 and Informed Consent Forms.

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Candidates are offered repeated opportunities to decide not to participate; participants are offered repeated opportunities to withdraw. Exclusion factors rule out participation by employees or students of the Study Director. Recruitment of alternate subjects ensures that subjects will not be reluctant to withdraw lest the validity of the investigation be compromised.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

“Carroll-Loye Biological Research will retain records of this study indefinitely. You may access your own records by contacting the Study Director. Representatives from the sponsor (LANXESS Corporation), the U.S. Environmental Protection Agency (EPA), the California Department of Pesticide Regulation and the Independent Investigational Review Board, Inc. (an independent committee that reviewed this study’s ethical aspects to help protect the rights and welfare of study participants) may have access to all non-personal information collected in this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Any information or reports published as a result of this study will not identify you by name, or by any other personal identification.” (pp. 41-42; 50)

“Results of a subject’s [pregnancy] test are only observed by one female CLBR staff technician and never recorded to minimize stress on a female subject testing positive, and

minimize the possibility that other staff or subjects may become aware of the results of that test.” (p. 9)

Subjects are identified by name and subject number on the “Confidential Test Subject Information” form (p. 61). On all other data collection forms only the subject number is used. Recruitment of alternate subjects provides an opportunity for discrete withdrawal without explanation.

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

Subjects are so informed in the recruitment process (pp. 15-16) and in the Informed Consent Form (p. 42; 50):

“You understand that you are free to withdraw from this study at any time, and you agree to inform the Principal Investigator immediately if you intend to withdraw. It is understood that your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of compensation to which you are otherwise entitled. You may withdraw from this study at any time.”

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Subjects who decide not to participate will simply go their way. Subjects identified as alternates, and any who withdraw from the research, will be paid for their time (p. 41; 50). How soon after withdrawing subjects would be able to leave the field study site would depend on how they got there; this is not explained.

**§ 26.1111 Criteria for IRB approval of research
Protocol LNX-002 (3/23/09)**

Criterion	Y/N	Comment/Page Reference
(a)(1)(i) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.	Y	
(a)(1)(ii) Risks to subjects are minimized, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.	N/A	
(a)(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.	Y	
(a)(3) Selection of subjects is equitable, taking into account the purposes of the research and the setting in which it will be conducted, and being particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.	Y	
(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §26.1116.	Y	
(a)(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §26.1117.	Y	
(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.	Y	
(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.	Y	
(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.	N/A	

**§26.1116 General requirements for informed consent
Protocol LNX-002 (3/23/09)**

Criterion		Y/N	Comment/Page Reference
No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative		Y	All subjects will provide legally effective informed consent.
An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence		Y	The procedure described in §§ 3.1 and 3.2 provides sufficient opportunity to consider. . . and minimizes the possibility of coercion or undue influence.
The information that is given to the subject or the representative shall be in language understandable to the subject or the representative		Y	Information is clearly presented in plain English
No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative 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		Y	CF contains no exculpatory language
(a) In seeking informed consent the following information shall be provided to each subject	(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Y	p. 34; 43
	(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	pp. 38-40; 47-49
	(3) A description of any benefits to the subject or to others which may reasonably be expected from the research	Y	p. 41; 49
	(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	Y	p. 41; 49
	(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	pp. 41-42; 50
	(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	Compensation p. 41; 50 Treatment p. 40; 49
	(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Y	p. 41; 49-50
	(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Y	p. 42; 50
(b) When appropriate, one or more of the following elements of information shall also be	(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable	Y	p. 40; 49
	(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	Y	p. 42; 50-51
	(3) Any additional costs to the subject that may result from participation in the research	Y	p. 41; 50
	(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	n/a	
	(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	Y	p. 40; 49
	(6) The approximate number of subjects involved in the study	Y	p. 35; 45
(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.		Y	p. 34; 43

**§26.1117 Documentation of informed consent
Protocol LNX-002 (3/23/09)**

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.	Y	Form pp. 34-42; 43-51 Procedures pp. 15-16
(b)(1) The consent form may be a written consent document that embodies the elements of informed consent required by §26.1116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or	Y	Proposed ICF meets requirements of §26.1116; procedure described in protocol §§ 3.1 and 3.2 provides adequate opportunity to read it before it is signed.
(b)(2) The consent form may be a short form written consent document stating that the elements of informed consent required by §26.1116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.	N/A	

**40 CFR 26.1125 Submission of proposed human research for EPA review
Carroll-Loye LNX-003 (Version of 3/23/2009)**

Any person or institution who intends to conduct or sponsor human research covered by §26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by §26.1115(a), and the following additional information, to the extent not already included:

	Requirement	Y/N	Comments/Page Refs	
All information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of <ul style="list-style-type: none"> • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects. 	Y n/a Y n/a	Original pp. 90-173; Revised pp. 175-209 pp. 34-51	
	(2) Minutes of IRB meetings . . . in sufficient detail to show <ul style="list-style-type: none"> • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; • a written summary of the discussion of controverted issues and their resolution. 	Y Y Y N n/a	pp. 215-216 Specific changes made in CFs not identified; basis for changes not recorded. No controverted issues.	
	(3) Records of continuing review activities.	n/a		
	(4) Copies of all correspondence between the IRB and the investigators.	Y	pp. 90-216	
	(5) <ul style="list-style-type: none"> • A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. 	Y Y	Separate document	
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).	Y	Separate document	
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).	n/a		
The following information, to the extent not already included:	§1125(a) a discussion of:	(1) The potential risks to human subjects	Y	pp. 6-9
		(2) The measures proposed to minimize risks to the human subjects;	Y	pp. 6-10
		(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 10
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	p. 6
		(5) The balance of risks and benefits of the proposed research.	Y	p. 10 (very weak)
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	Original pp. 121-138 As approved pp. 34-51	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	p. 13	
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	pp. 15-16	
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	pp. 90-216	
	§1125(f): Official notification to the sponsor or investigator . . . that research involving human subjects has been reviewed and approved by an IRB.	Y	pp. 211-212	



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