Protection of Human Subjects: Informed Consent; Institutional Review Boards

0910-0755

SUPPORTING STATEMENT

Terms of Clearance: The burden associated with 21 CFR § 50.25 (Elements of Informed Consent) and 21 CFR § 50.27 (Documentation of Informed Consent) is limited to the burden of development and approval by an institutional review board (IRB) of a site-specific informed consent document, and the documentation of informed consent. OMB does not grant approval for the content of individual consent forms that are reviewed and approved by IRBs and subsequently presented to research participants.

A. Justification

The information in Title 21 Code of Federal Regulations (21 CFR) parts 50 and 56 is used by FDA to determine whether clinical investigators and IRBs are providing adequate protections to human subjects participating in FDA-regulated clinical research.

1. Circumstances Making the Collection of Information Necessary

   21 CFR Part 50 (Part 50)[1] – Protection of Human Subjects:

   Part 50 applies to all clinical investigations regulated by FDA under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA. Those products include foods, including dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with part 50 is intended to protect the rights and safety of subjects involved in investigations filed with the FDA pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the FD&C Act and sections 351 and 354-360F of the Public Health Service Act.

   Certain limited provisions in part 50, subpart B (informed consent of human subjects) are approved under OMB control number 0910-0755. Those sections are:

50.24	Exception from Informed Consent Requirements for Emergency Research
50.25	Elements of Informed Consent
50.27	Documentation of Informed Consent

   21 CFR Part 56 (Part 56)[2] – Institutional Review Boards:

[1] See the regulatory text at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=50.
[2] See the regulatory text at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=56.

Part 56 contains the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations regulated by FDA under sections 505(i) and 520(g) of the FD&C Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA. Compliance with part 56 is intended to protect the rights and welfare of human subjects involved in such investigations.

Certain provisions in part 56 (IRBs) are approved under OMB control number 0910-0755. Those sections are:

56.109(e)	IRB Written Notification to Approve or Disapprove Research
56.109(f)	IRB Continuing Review
56.113	Suspension or Termination of IRB Approval of Research
56.120(a)	IRB Response to Lesser Administrative Actions for Noncompliance
56.123	Reinstatement of an IRB or Institution

This notice also contains two collections of information not included in a previous information collection notice:

56.109(d)	Written statement about research when documentation of informed consent is waived
56.109(g)	IRB written statements to the sponsor about required public disclosures related to emergency research under 50.24

2. Purpose and Use of the Information Collection

The regulations in parts 50 and 56 are designed to protect human subjects participating in FDA-regulated clinical research. Except under certain conditions, no clinical investigator may involve a human being as a subject in FDA-regulated research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

- 21 CFR § 50.25 (Elements of Informed Consent), and 21 CFR § 50.27 (Documentation of Informed Consent)

Informed consent provides the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether the subject should participate in the research. The elements of informed consent provided in § 50.25 help ensure that human subjects thoroughly understand all aspects of the clinical trial relevant to the subject's decision to participate.

Documentation of informed consent provided in § 50.27 records this understanding by means of a written, signed, and dated informed consent form. The provisions in §§ 50.25 and 50.27, and the information collected, help show that human subjects are fully informed and protected from undue influence or coercion when deciding to participate in FDA-regulated research.

- 21 CFR § 50.24 (Exception from Informed Consent Requirements for Emergency Research)

Emergency research may present an exception to informed consent. For this exception, the IRB has the burden of finding and documenting that certain conditions are met. In § 50.24(a), those conditions include:

(1) a human subject is in a life-threatening situation with no available proven treatment,
(2) obtaining informed consent is not feasible,
(3) participation holds out the prospect of a direct benefit to the subject,
(4) the research cannot practicably be carried out without the waiver,
(5) within the therapeutic window the investigator is committed to attempting contact with a legally authorized representative,
(6) the IRB has reviewed and approved informed consent procedures and an informed consent document, and
(7) additional protections of the rights and welfare of the subject are provided.

Also, the IRB has the burden of having in place procedures for informing at the earliest feasible opportunity each subject, or if the subject remains incapacitated, the subject's legally authorized representative or a family member, of 1) the subject's participation and 2) information about the study contained in the informed consent document (§ 50.24(b)). If an IRB determines an investigation cannot be approved because it does not meet regulatory or ethical concerns, the IRB has the burden of documenting its findings and providing those findings promptly to the investigator and sponsor (§ 50.24(e)).

In § 50.24, strict safeguards are in place to balance the risks and benefits to the patient. Documenting the IRB's actions and findings when determining whether to approve emergency research helps to show that the IRB has fulfilled its responsibilities to protect the rights and welfare of human research subjects.

- 21 CFR § 56.109 (IRB review of research)

  - 21 CFR § 56.109(d) (Written statement about research for which documentation of consent has been waived)

    In § 56.109(d), if an IRB has waived documentation of consent for research that (1) presents no more than minimal risk of harm to subjects and (2) involves no procedures for which consent is normally required outside of the research context, the IRB may nevertheless require the investigator to provide a written statement about the

research to the subjects. This statement is a safeguard to protect the rights and welfare of study subjects.

- 21 CFR § 56.109(e) (IRB Written Notification to Approve or Disapprove Research)

When reviewing clinical research studies regulated by FDA, IRBs are required to create and maintain records describing their operations, and make the records available for FDA inspection when requested. In § 56.109(e), an IRB's decision whether to approve or disapprove a proposed research activity or of modifications required to secure IRB approval must be documented and shared in writing with the investigator and institution. This written notification must include a statement of the reasons for the IRB's determination. The amount of time an IRB spends on reviewing research and documenting the IRB's determination will vary depending on the nature and complexity of the research.

- 21 CFR § 56.109(f) (IRB Continuing Review)

In § 56.109(f), at least once a year or more frequently depending on the degree of risk posed by the research, the IRB must conduct continuing review of the research to protect the rights and safety of the human subjects. The amount of time an IRB spends on the continuing review of a particular study will vary depending on the nature and complexity of the research, the amount and type of new information presented to the IRB, and whether the investigator is seeking approval of substantive changes to the research protocol or informed consent document. For many studies, continuing review can be fairly straightforward, and the IRB should be able to complete its deliberations and approve the research within a brief period of time.

- 21 CFR § 56.109(g) (IRB statement to sponsor about information that has been publicly disclosed)

In § 56.109(g), an IRB is required to provide the sponsor of a study involving an exception from informed consent for emergency research under 21 CFR 50.24 with a written statement about information that has been publicly disclosed to the communities in which the investigation will be conducted and from which the subjects will be drawn. Public disclosure prior to initiation of the investigation would include the plans for the investigation and its risks and expected benefits. (See 21 CFR 50.24(a)(7)(ii).) There must also be public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results. (See 21 CFR 50.24(a)(7)(iii).)

The purpose of the IRB's written statements is to make the sponsor aware that public disclosure has occurred, and also so that the sponsor can provide copies of the information that has been disclosed to FDA, as required by 21 CFR 312.54(a). The

sponsor submissions under part 312 are currently approved under OMB Control Numbers 0910-0014.

- 21 CFR § 56.113 (Suspension or Termination of IRB Approval of Research)

If an IRB discovers that research the IRB approved is not being conducted according to the IRB's requirements or the research is associated with unexpected serious harm to subjects, the IRB can suspend or terminate its approval. The IRB has the burden of providing a statement of the reasons for the suspension or termination of research, and reporting promptly to the investigator, appropriate institutional officials, and the FDA.

- Administrative Actions for Noncompliance

    - 21 CFR § 56.120(a) (IRB Response to Lesser Administrative Actions for Noncompliance)

    When an IRB or institution violates the regulations and places human subjects at risk, FDA issues a noncompliance letter to the IRB or institution in accordance with§ 56.120(a). The IRB or institution has the burden of responding to the noncompliance letter describing the corrective actions that will be taken by the IRB or institution.

    - 21 CFR § 56.123 (Reinstatement of an IRB or Institution)

    When an IRB or institution refuses or repeatedly fails to comply with any of the applicable FDA regulations and the noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation, the IRB is subject to disqualification by FDA. A disqualified IRB or institution may seek reinstatement by providing to FDA a written submission explaining the corrective action and providing adequate assurance that the IRB or institution will operate in compliance with the regulatory standards. In 2016, FDA disqualified one IRB pursuant to § 56.121. To date, no IRB or institution has applied for reinstatement or been reinstated under § 56.123.

The recordkeeping requirements approved under OMB Control Number 0910-0130 for 21 CFR § 56.115 (IRB Records) are related to the IRB information collections discussed above. When an IRB reviews FDA-regulated clinical research studies, the IRB must create and maintain records about their operations and make those records available to FDA upon request during an FDA inspection.

The record collections approved under OMB Control Number 0910-0130 include:

- written procedures describing the structure and membership of the IRB and the methods that the IRB will use in performing its functions;
- the research protocols, informed consent documents, progress reports, and reports of injuries to subjects submitted by investigators to the IRB;

- minutes of meetings showing attendance, votes and decisions made by the IRB, the number of votes on each decision for, against, and abstaining, the basis for requiring changes in or disapproving research;
- records of continuing review activities;
- copies of all correspondence between investigators and the IRB;
- statement of significant new findings provided to subjects of the research; and
- a list of IRB members by name, showing each member's earned degrees, representative capacity, and experience in sufficient detail to describe each member's contributions to the IRB's deliberations, and any employment relationship between each member and the IRB's institution.

This information is used by the FDA in conducting audit inspections of IRBs to determine whether IRBs and clinical investigators are providing adequate protections to human subjects participating in FDA-regulated clinical research.

3. Use of Improved Information Technology and Burden Reduction

The Food and Drug Administration Modernization Act of 1997 (FDAMA) mandates that FDA develop and update its information management infrastructure to allow the paperless receipt and processing of investigational new drug applications and new drug applications. Among other actions, FDA followed up with a final rule for submission of labeling in electronic format for human prescription drugs and biologics (published December 11, 2003).

In addition to rulemaking, FDA issued several guidance documents describing how to make voluntary electronic submissions to FDA. One such document is about general considerations for electronic submissions, titled "Providing Regulatory Submissions in Electronic Format – General Considerations." The general considerations guidance document includes a description of the types of electronic file formats FDA is able to accept for processing, reviewing, and archiving electronic documents. This guidance document, along with other issued related guidance documents, can be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances.

Section 745A(b) of the FD&C Act, added by section 1136 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), provides statutory authority to require eCopies after issuance of final guidance (see Public Law No: 112-144). FDA's implementing guidance describes how device companies should replace one paper copy of a device application with an eCopy and identify the required format and technical requirements of the eCopy. The eCopy requirement does not require or request any information that is not already submitted to the FDA and/or covered under the existing ICR, and therefore does not change the cost or hour burden.

4. Efforts to Identify Duplication and Use of Similar Information

There is no duplication resulting from these requirements.

5. Impact on Small Businesses or Other Small Entities

A substantial majority of IRB reviews are conducted at large institutions such as universities, medical schools, and research and teaching hospitals. The documentation requirements require only minimum documentation necessary for a committee to function in accord with good management practices, for FDA to conduct its inspections and to ensure the integrity and accuracy of information submitted to FDA in support of marketing permits.

Likewise, a substantial majority of clinical investigators conducting FDA-regulated research conduct those studies at large institutions such as universities, medical schools, and research and teaching hospitals. Most of the information collection burden for clinical investigators who conduct FDA-regulated studies with human subjects is covered under existing approved OMB Control Numbers. For example, recordkeeping requirements for investigators in 21 CFR § 812.140 (Investigational Device Exemptions) is approved under OMB Control Number 0910-0078. The information collected under the Investigational New Drug regulations is currently approved under OMB control number 0910-0014.

For those small businesses or entities affected, FDA helps minimize the burden for the information collection through various means. FDA developed and widely distributes a series of guidance documents to assist IRBs, clinical investigators and others concerned with the protection of research subjects to conform to the requirements in FDA regulations.

FDA continually offers assistance to any IRB or investigator seeking information through Agency guidance documents, outreach, and participation in publicized open workshops. Also, certain FDA offices are available to discuss regulatory requirements and provide clarification and direction to small businesses and entities. For example, the Center for Devices and Radiological Health (CDRH) has offices charged with providing technical and other nonfinancial assistance to small firms expressly to aid them in complying with the requirements of the FD&C Act and FDA regulations. CDRH staff are available to respond to questions through an advertised toll free telephone number to facilitate communication from small businesses or entities.

6. Consequences of Collecting the Information Less Frequently

IRB continuing review is required annually. (21 CFR 56.109(f)) Less frequent review would compromise the protection of research subjects. The obligation to protect human subjects is an ongoing responsibility and not a one-time effort. Changes in research protocols, new scientific or medical findings or innovations, as well as preliminary results of ongoing research, may change the degree of risk to subjects or the subjects' willingness to continue participating in the research. Therefore, IRB review is required to be conducted at least annually to protect the rights and welfare of the human research subjects throughout the research project.

Documentation of informed consent occurs at the time of consent. Less frequent information collection is not feasible and would put at risk human subjects participating in FDA-regulated research.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

   There are no special circumstances for this collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

   In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of July 19, 2016 (81 FR 46935). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

   FDA will not provide any payments or gifts to respondents of this information collection.

10. Assurance of Confidentiality Provided to Respondents

    The documentation obtained during IRB and investigator inspections rarely contains any sensitive or confidential information that has not been submitted to FDA (e.g., copies of research protocols which may be considered confidential and contain trade secret information). The material is kept confidential in accordance with 18 U.S.C. 1905, 21 U.S.C. 331(j), and 21 U.S.C. 520(c), as well as sections 301(j) and 520(c) of the FD&C Act.

11. Justification for Sensitive Questions

    The documentation maintained and collected does not contain questions of a sensitive nature, such as, sexual behavior and attitudes, religious beliefs, and other matters that are commonly considered private. Such data are more commonly contained in behavioral research, which FDA does not regulate. The identity of study subjects is rarely collected. Such sensitive information is treated as confidential and not released to third parties unless required by law or requested by Congress.

12. Estimates of Annualized Burden Hours and Costs

    12 a. Annualized Reporting Burden Estimate

    The burdens are estimated from experience with prior similar activities and from information retrieved from various FDA databases and the Office for Human Research Protections (OHRP) IRB Registration database.[3]
    In 2009, FDA issued regulations requiring IRBs that oversee FDA-regulated research to register on an internet-based system maintained by OHRP. U.S. IRBs that review research involving FDA-regulated products are required to register using the the OHRP database. (21 CFR 56.106(a)) Non-U.S. IRBs may voluntarily register. There are approximately 2,520 registered IRBs in OHRP's database that indicate they review FDA-regulated research.

[3] http://ohrp.cit.nih.gov/search/search.aspx?styp=bsc

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
56.109(d) Written statement about minimal risk research when documentation of informed consent is waived	2,520	2	5,040	0.5 (30 minutes)	2,520
56.109(e) IRB written notification to approve or disapprove research; 56.109(f) Continuing review; 50.25 Elements of informed consent; and 50.27 Documentation of informed consent	2,520	40	100,800	1	100,800
50.24 Exception from informed consent requirements for emergency research	8	3	24	1	24
56.113 Suspension or termination of IRB approval of research	2,520	1	2,520	0.5 (30 minutes)	1,260
56.120(a) IRB response to lesser administrative actions for noncompliance	7	1	7	10	70
56.123 Reinstatement of an IRB or an institution	1	1	1	5	5
Total					104,679

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

In § 56.109(d), if an IRB has waived documentation of consent for research that (1) presents no more than minimal risk of harm to subjects and (2) involves no procedures for which consent is normally required outside of the research context, the IRB may nevertheless require the investigator to provide a written statement about the research to the subjects. We estimate that each IRB will review about 2 minimal risk FDA-regulated studies each year. Because the studies are minimal risk, the review can be fairly straightforward, and the written statement for the subjects would be brief. We estimate that IRB review of each written statement could be completed in less than 30 minutes (0.5 hours); for an estimated total annual burden of 2,520 hours (2 x 2,520 = 5,040; 5,040 x 0.5 hours = 2, 520).

The burden for each of the sections in 21 CFR 56.109(e) and (f), and 50.25 and 50.27, have been considered as one estimated burden. FDA estimates that there are approximately 2,520 respondents, with 40 responses per respondent. The average burden of response is one hour. FDA estimates that approximately 100,800 hours of person-time are required to meet the requirements of the applicable provisions in the regulations.

An IRB may approve emergency research without requiring the informed consent of all research subjects provided the IRB finds and documents that certain criteria are met as required in § 50.24. We estimate that about eight IRBs per year receive a request to review emergency research under § 50.24. We estimate, of the eight yearly requests for IRB review under § 50.24, a particular IRB will take about an hour during each of three separate fully convened IRB meetings to review the request under § 50.24 (one meeting occurring after community consultation). The total annual reporting burden for IRB review of emergency research under § 50.24 is estimated at 24 hours.

The information requested in the regulations for exception from the general requirements for informed consent in 21 CFR 50.23, paragraphs (a) through (c), and (e), is currently approved under OMB control number 0910-0586. The information requested in the investigational new drug (IND, 21 CFR 312) regulations concerning exception from informed consent for emergency research under § 50.24 is currently approved under OMB control number 0910-0014.

In § 56.113, an IRB has the authority to suspend or terminate the IRB's approval of research. We estimate that an IRB will suspend or terminate research about one time per year. FDA estimates that there are approximately 2,520 respondents. We estimate about 30 minutes for the IRB to report its action to the investigator, institutional officials, and FDA, with an estimated total annual burden of 1,260 hours.

When an IRB or institution violates the regulations, FDA issues to the IRB or institution a noncompliance letter in accordance with § 56.120(a). The IRB or institution must respond to the noncompliance letter describing the corrective actions that will be taken by the IRB or institution. FDA estimates about seven IRBs or institutions will be issued a noncompliance letter annually. We estimate that an IRB's or institution's response will take about 10 hours to prepare, with an estimated total annual burden of 70 hours.

To date, only one IRB or institution has been disqualified by FDA under § 56.121. No IRB or institution has been reinstated or requested reinstatement under § 56.123. For this reason, we estimate the annual reporting burden for one respondent only. We estimate a five hour burden per response, with an estimated total annual burden of five hours.

[See Table 1.]

12b. Annualized Third Party Disclosure Burden Estimate

FDA estimates the burden of this third party disclosure burden as follows:

Table 2.--Estimated Annual Third-Party Disclosure Burden

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
56.109(g) IRB written statement about public disclosures to sponsor of emergency research under 50.24	8	2	16	1	16

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

In § 56.109(g), IRBs are required to prepare and submit to the sponsor two written statements describing public disclosure related to research involving an exception from informed consent for emergency research under § 50.24: one prior to initiation of the research and one following the study's completion. We estimate that about eight IRBs per year receive a request to review emergency research under § 50.24. We estimate that it will take an IRB approximately one hour to prepare each written statement, for a total of 2 hours per study. The total annual third party disclosure burden for IRBs to fulfill this requirement is estimated at 16 hours. [See Table 2.]

12c. Annualized Cost Burden Estimate

FDA estimates an average industry wage rate of $75 per hour (averaged from wages for upper management, middle management, and clerical support, plus overhead and personnel benefits) for preparing and submitting the information requested. Using the averaged wage rate of $75 per hour, and multiplied times the combined total number of hours in the two tables above (104,679 + 16 = 104,695), the total cost burden to respondents is approximately $7,852,125.

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

Periodically FDA investigators conduct bioresearch monitoring inspections of IRBs. Before conducting these inspections, FDA staff ensures that the IRBs are registered with FDA. The annual cost to the government to check this information is negligible.

15. Explanation for Program Changes or Adjustments

This is a request for extension of an existing data collection.

FDA estimates that the total annual burden hours have decreased from 243,070 to 104,695, due primarily to a reduction in the estimated number of respondents because of more accurate information about the number of IRBs that review research involving FDA-regulated products. Based on the number of active IRBs in OHRP's registration system that indicate they review FDA-regulated research, the number of respondents has been reduced from 6,000 to 2,520. [See also Section 12a., above.]

16. Plans for Tabulation and Publication and Project Time Schedule

The records maintained under these regulations are not expected to be published.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

This request does not seek approval to exempt display of the OMB approval date on any documents that are associated with this reporting requirement.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.