DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N–0447]

Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: On November 10, 1997, the Food and Drug Administration (FDA), in consultation with the Office for Protection from Research Risks (OPRR) at the National Institutes of Health, requested written comments relating to the proposed republication of the list that identifies certain research activities involving human subjects that may be reviewed by the Institutional Review Board (IRB) through the expedited review procedure authorized in 21 CFR 56.110. The comment period closed on March 10, 1998. FDA and OPRR received a combined total of 108 comments. After a review of the comments, FDA and OPRR are now simultaneously publishing identical revised lists of categories of research activities that may be reviewed by the IRB through the expedited review procedure.

EFFECTIVE DATE: The revised list is effective November 9, 1998.

FOR FURTHER INFORMATION CONTACT: Paul W. Goebel, Jr., Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1685.

SUPPLEMENTARY INFORMATION: The FDA regulations for protection of human subjects can be found under part 50 (21 CFR part 50), and the regulations for the IRB's can be found under part 56 (21 CFR part 56). The regulations require, with limited exceptions, obtaining and documenting legally effective informed consent for all human subjects of research on FDA regulated products and review of research involving human subjects by an IRB.

Section 56.110 provides for expedited IRB review procedures for certain categories of research involving no more than minimal risk, and for minor changes in previously approved research during the period for which approval is authorized. The list that is referenced in § 56.110(a) was originally published in the **Federal Register** of January 27, 1981 (46 FR 8980), as a notice of a list of research activities that could be reviewed by the IRB through the expedited review procedures set forth in the FDA's regulations. OPRR has a separate codification that references the Expedited Review List for matters under the Department of Health and Human Services' (HHS) jurisdiction (45 CFR part 46). The HHS list was published in the **Federal Register** on January 26, 1981 (46 FR 8392). The FDA and HHS lists published in 1981 differ slightly, in that item nine on the HHS list, concerning research on individual or group behavior, pertains only to 45 CFR 46.110. Because behavioral research is not specifically regulated by FDA, that category was not included in the list published by FDA.

The comments received in response to the November 10, 1997 (62 FR 60607), proposal by FDA and OPRR to revise the 1981 expedited review list overwhelmingly supported the proposed revision of the list. Three comments indicated that there should be no expedited review available at all. These comments misunderstood the purpose of expedited review, expressing concern that allowing expedited IRB review also removes the requirement for informed consent of study subjects. FDA and OPRR disagree with these three comments and believe that expedited review is an appropriate part of the IRB review process. In addition, deleting the expedited review process would require a regulatory change to section 110 of the Federal Policy, which is beyond the scope of this revision. However, in response to these comments paragraph (E) has been added to the Applicability section I of this document to make it clear that the standard requirements for informed consent must be met regardless of the type of review—expedited or convened—utilized by the IRB.

The following discussion summarizes the 108 comments received and the resulting changes. In response to over 40 comments expressing concern that the general principles that apply to all research categories could be easily misinterpreted, the introductory paragraph to the 1981 list has been reformatted into six general principles that apply to the entire list. The parenthetical in the introductory sentence to the 1981 list ''(carried out through standard methods)'' has been deleted in response to comments that this phrase served no particular purpose in the 1981 list.

The reformatted general principles are set forth in paragraphs (A) through (G). Paragraph (C) makes it clear that the IRB must consider, for all categories, whether identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. At the time of the publication of the 1981 list, FDA routinely considered only the medical risk to subjects in determining whether a study imparted greater than minimal risk. Since that time, the scope of research projects that are under FDA purview has expanded to include activities that could place the subjects at risk for the harms listed in paragraph (C). Therefore, the IRB's reviewing studies of FDA regulated products may need to consider the listed nonmedical harms. For certain studies subject to regulation under 45 CFR part 46, these concerns have always been implicit in determining whether an activity is a minimal risk activity. The words ''insurability'' and ''be stigmatizing'' have been added to the new list to help ensure that the IRB's consider these potential risks during their review.

Two comments point out that classified research must be reviewed by the IRB at a convened meeting. FDA and OPRR agree and have added paragraph (D), which prohibits expedited review for classified research involving human subjects. This is in accordance with the March 27, 1997, Presidential memorandum that proposed the elimination of an expedited review procedure for all classified research involving human subjects.

Paragraph (E) serves as a reminder to the IRB's that informed consent and expedited review are two totally separate issues. This responds to concerns that allowing an increase in the scope of research eligible for expedited review would result in more waivers of informed consent. Research reviewed under the expedited review procedure is not necessarily eligible for waiver or alteration of informed consent. All research, regardless of whether it meets the conditions for expedited IRB review, must conform to the applicable requirements for obtaining and documenting informed consent. Informed consent must be obtained and documented unless the research meets one of the conditions for waiving, excepting, or otherwise altering the informed consent requirements that are set forth in 45 CFR 46.116 and 46.117, and §§ 50.23, 50.24, and 56.109(c).

The list of research eligible for expedited review continues to fall into nine categories. Category one,

enumerated as category nine on the 1981 list, addresses the availability of expedited review for marketed drugs and devices. This category now contains citations to the investigational drug and device regulations and provides when expedited review of research on marketed drugs (including biologics) would not be appropriate. This modification was in response to five comments that raised questions about these issues. FDA and OPRR on their own initiative have added wording to set out in greater detail the conditions that must be met in order for an IRB to review research with a medical device using expedited procedures.

Over 45 comments suggested certain changes to proposed category two, formerly category four in the 1981 list, addressing the collection of blood. The suggested changes include addition of many specific conditions, including limits on the amount withdrawn, collection procedures, and limits on the physical condition of the subjects. In response to these suggestions, the category has been reorganized to set general limits that the specific procedure must meet. The procedures for the collection of blood now include finger stick, heel stick, ear stick, and venipuncture. The four proposed subcategories were recombined as two separate subcategories. The critical issues to be considered include weight, physical condition, and amount of blood to be collected. The first subcategory (a) concerns healthy nonpregnant adults. The second subcategory (b) concerns all other adults and children. For this second subcategory, the IRB will need to make certain judgments including: Consideration for the age, weight, and health of the subjects in light of the amount of blood to be collected, the frequency with which it will be collected, and the collection procedure. The final sentence of subcategory (b) reads: ''For these subjects, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kg in an 8-week period and collection may not occur more than 2 times per week.'' While an expedited review of research involving pregnant women is permissible under the revised section, this last sentence makes it clear that the amount of blood that can be drawn is subject to limitations greater than those on healthy nonpregnant adults. Also in response to public comment, the proposed phrase ''medically vulnerable adults'' has been deleted.

More than 24 comments were received regarding category three, which was previously categories one and two in the 1981 list, addressing the collection of biological specimens. Some of the comments requested inclusion of specific procedures, such as throat cultures and pap smears. Some of the comments requested the category be rephrased as a general limit, setting out as examples the types of specimens and conditions for collection. In response to these comments, new category three has been reorganized to limit the manner of collection to noninvasive means. The list of specific types of biological specimens is now included as examples of the types of procedures that could fall within this category.

Categories four and five on the proposed list have been combined into one new category, category five, addressing research involving materials collected or which will be collected solely for nonresearch purposes. This new category five was formed in response to comments that raised questions about why the two categories separated out existing and prospectively collected materials. The term ''nonresearch purposes'' was maintained in new category five to describe the origins of the research materials.

An explanatory note has been added to categories five and seven to clarify that some research described in these categories may be exempt from the IRB review under 45 CFR 46.101 of the HHS regulations for the protection of human subjects. Thus, the listing of those categories refers only to nonexempt research.

Category six on the list proposed in November 1997 has become category four on the revised list and addresses the collection of data through noninvasive procedures. In response to several comments that raised concerns about the use of anesthesia and sedation with magnetic resonance imaging procedures, expedited review will not be allowed for any procedure employing anesthesia or sedation. In response to more than 24 comments, the general term ''noninvasive procedures'' now applies to all procedures in this category. The specific procedures to which expedited review was limited in proposed category six, are included in new category four as examples of the types of procedures that could qualify for expedited review. FDA and OPRR, on their own initiative, added wording to clarify that studies intended to evaluate the safety and effectiveness of medical devices or using medical devices that are not cleared or approved for marketing by FDA are generally not eligible for expedited review.

Category seven on the proposed list is now category six on the revised list and deals with the collection of data from voice, video, digital, or image recordings. In the proposal, the IRB was to consider certain risks to the subjects in this category before granting expedited review. In response to several comments that inquired why only this type of research should receive this consideration, it was incorporated as a guiding principle in the Applicability section I of this document and is no longer simply specific to this category.

Category eight on the proposed list is now category seven on the revised list. This category was added to the 1981 list with the proposal and concerns research on individual or group characteristics or behavior. At the time of the publication of the 1981 list, this category was not included in the FDA list because FDA routinely considered only the medical risk to subjects in determining whether a study imparted greater than minimal risk. Since that time, the scope of research projects that are under FDA purview has expanded to include activities that are listed in new category seven. Therefore, studies related to FDA-regulated products might employ such methodology.

Over 30 comments requested this category be simplified and rephrased so that researchers and IRB's could more readily determine whether their study is eligible for expedited review. In response, the following changes have been made. The condition that the research does not involve ''stress'' has been deleted; the subsections in the proposed list have been combined to eliminate the distinction between research involving adults and research involving children; research on oral history has been included in response to six comments; and specific research and research techniques have been noted. The category has been reorganized to include research involving motivation, identity, language, communication, cultural beliefs or practices, and social behavior as examples of research on individual or group characteristics or behavior. Methods of conducting such research are now separately listed and have been expanded to include oral history, program evaluation, human factors evaluation, and quality assurance methodologies. As in new category six, the qualification that requires consideration of certain kinds of risks to subjects has been deleted from this category, as it is now a general guiding principle, (C), which applies to the entire list.

Category nine on the proposed list, research previously approved by the convened IRB, received more than 50 comments explicitly applauding this category. It has now been divided into new categories eight and nine. New

category eight identifies three situations in which research that is greater than minimal risk and has been initially reviewed by the convened IRB, could undergo subsequent continuing review by the expedited review procedure. The new category nine concerns continuing review of research that is not greater than minimal risk, but had to undergo initial review by a convened IRB because it did not meet the criteria of categories two through seven on this list.

Certain other minimal changes have been made for editorial purposes or to clarify certain words that were used in the proposed list. Accordingly, the list of categories of research which may be reviewed by the IRB through an expedited review procedure is amended as set forth:

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure [1]

Applicability

(A) Research activites that (1) present no more than mimimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required.

(Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children,[2] considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylatic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. *45 CFR 46.101(b)(4).* This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group,

[1] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

[2] Children are defined in the HHS regulations as ''persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.'' 45 CFR 46.402(a).

program evaluation, human factors evaluation, or quality assurance methodologies.

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. *45 CFR 46.101(b)(2) and (b)(3).* This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) Where no subjects have been enrolled and no additional risks have been identified; or

(c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Dated: November 2, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–29748 Filed 11–6–98; 8:45 am]

BILLING CODE 4160–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[Document Identifier: HCFA–0670]

Agency Information Collection Activities: Proposed Collection; Comment Request

AGENCY: Health Care Financing Administration, HHS.

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services, is publishing the following summary of proposed collections for public comment. Interested persons are invited to send comments regarding this burden estimate or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

Type of Information Collection Request: Extension of a currently approved collection; *Title of Information Collection:* Team Composition and Workload Report and Supporting Regulations in 42 CFR 493.1–493.2001; *Form No.:* HCFA–0670 (OMB# 0938–0583); *Use:* This form requests resource utilization information on Medicare and Medicaid providers, suppliers, and CLIA laboratories. The data is used to determine Federal reimbursement for all participating health care facilities that accept Medicare and Medicaid beneficiaries.; *Frequency:* As needed; *Affected Public:* State, Local, and Tribal Government, Business or other for-profit, and Not-for-profit institutions; *Number of Respondents:* 53; *Total Annual Responses:* 449,252; *Total Annual Hours:* 71,667.

To obtain copies of the supporting statement and any related forms for the proposed paperwork collections referenced above, access HCFA's Web Site address at http://www.hcfa.gov/regs/prdact95.htm, or E-mail your request, including your address, phone number, OMB number, and HCFA document identifier, to Paperwork@hcfa.gov, or call the Reports Clearance Office on (410) 786–1326. Written comments and recommendations for the proposed information collections must be mailed within 60 days of this notice directly to the HCFA Paperwork Clearance Officer designated at the following address: HCFA, Office of Information Services, Security and Standards Group, Division of HCFA Enterprise Standards, Attention: Louis Blank, Room N2–14–26, 7500 Security Boulevard, Baltimore, Maryland 21244–1850.

Dated: November 2, 1998.

John P. Burke III,

HCFA Reports Clearance Officer, HCFA Office of Information Services, Security and Standards Group, Division of HCFA Enterprise Standards.

[FR Doc. 98–29959 Filed 11–6–98; 8:45 am]

BILLING CODE 4120–03–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[Document Identifier: HCFA–R–250]

Agency Information Collection Activities: Proposed Collection; Comment Request

AGENCY: Health Care Financing Administration.

In compliance with the requirement of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Health Care Financing Administration (HCFA), Department of Health and Human Services, is publishing the following summary of proposed collections for public comment. Interested persons are invited to send comments regarding this burden estimate or any other aspect of this collection of information, including any of the following subjects: (1) The necessity and utility of the proposed information collection for the proper performance of the agency's functions; (2) the accuracy of the estimated burden; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) the use of automated collection techniques or other forms of information technology to minimize the information collection burden.

Type of Information Collection Request: Extension of a currently approved collection.

Title of Information Collection: Skilled Nursing Facility (SNF) Resident Assessment MDS Data and Supporting Regulations in 42 CFR 413.343 and 424.32.

Form No.: HCFA–R–250 (OMB# 0938–0739).

Use: Skilled Nursing Facilities (SNF's) are required to submit Resident Assessment Data as described at 42 CFR, 483.20 in the manner necessary to administer the payment rate methodology described in 42 CFR, 413.337. Pursuant to sections 4204(b) and 4214(d) of OBRA 1987, the current requirements related to the submission and retention of resident assessment data for the 5th, 30th and 60th days following admission, necessary to administer the payment rate methodology described in 413.337, is subject to the Paperwork Reduction Act.

Frequency: Monthly.

Affected Public: Business or other for-profit, and Not-for-profit.

Number of Respondents: 17,000.

Total Annual Responses: 204,000.

Total Annual Hours: 3,865,885.

To obtain copies of the supporting statement and any related forms for the